IN THE SUPREME COURT OF VICTORIA
AT MELBOURNE
COMMON LAW DIVISION
GROUP PROCEEDINGS LIST

Not Restricted

S ECI 2019 02916

PATRICE SARAH TURNER — Plaintiff

v

BAYER AUSTRALIA LTD (ACN 000 138 714) & ORS — Defendants

JUDGE:	KEOGH J
WHERE HELD:	Melbourne
DATE OF HEARING:	11–14, 17–21, 24, 26–28 April, 1–4, 8–12, 23–25, 29–31 May, 1–2, 5–9, 13–16, 19–23, 27–28, 30 June, 21, 28, 31 July, 1–4 August 2023
DATE OF JUDGMENT:	10 December 2024
CASE MAY BE CITED AS:	Turner v Bayer Australia Ltd
MEDIUM NEUTRAL CITATION:	[2024] VSC 760

REPRESENTATIVE ACTION — Implantable medical device — Contraceptive device made from metal alloys and PET fibre — Device designed to incite inflammatory response in fallopian tube to cause development of fibrosis resulting in tubal occlusion and sterilisation — Whether the device had an inherent defect in that it caused ongoing chronic inflammation in a not insignificant number of women, resulting in adverse events of chronic pelvic pain and abnormal uterine bleeding — General causation not established — Plaintiff's symptoms likely caused by adenomyosis — Whether there were risks that the device could migrate, be expulsed, break or fragment, corrode, fatigue, perforate organs and/or leach nickel or other metals resulting in new or increased pain, new or increased menstrual bleeding and/or damage to internal organs — Whether resolution of any adverse event associated with the device was likely to require surgical removal of uterus or fallopian tubes — Some risks established — Degree and magnitude of proven risks.

CONSUMER LAW — Whether devices had a 'defect' within the meaning of s 75AC of the *Trade Practices Act 1974* (Cth) or a 'safety defect' within the meaning of s 9 of the Australian Consumer Law — Significance of supply of devices via gynaecologists — Whether defendants failed to warn doctors or patients of certain risks or potential complications and the gravity of complications — Whether state of scientific or technical knowledge at time of supply not such as to enable defects to be discovered — *Ethicon Sàrl v Gill* (2021) 288 FCR 338 — *Merck Sharp & Dohme (Australia) Pty Ltd v Peterson* (2011) 196 FCR 145 — Adequate warnings and information given about established risks — Goods not defective.

CONSUMER LAW — Whether devices not of 'merchantable quality' within the meaning of s 74D of the *Trade Practices Act 1974* (Cth) or 'acceptable quality' within the meaning of s 54 of the Australian Consumer Law — Expectations of reasonable consumer of medical device — *Medtel Pty Ltd v Courtney* (2003) 130 FCR 182 — Lack of merchantable quality not established.

CONSUMER LAW — Where goods manufactured by foreign defendants in same corporate group and supplied by local corporations — Where foreign defendants had no place of business in Australia but impugned conduct took place in Australia — Whether foreign defendants can be found liable for contraventions of the *Trade Practices Act 1974* (Cth) and the Australian Consumer Law — Whether certain conduct of foreign defendants was 'in trade or commerce' — Whether foreign defendants were carrying on business in Australia.

NEGLIGENCE — Duty of care — Content of duty owed by manufacturers and suppliers to end users of medical devices — Whether defendants were negligent in development, design and marketing of device — Extent of obligation to warn where products supplied through 'learned intermediaries' — Whether product information and warnings insufficient to inform consumers of potential risks — *Wrongs Act 1958* (Vic), s 48 — *Gill v Ethicon Sàrl (No 5)* [2019] FCA 1905 — *Merck Sharp & Dohme (Australia) Pty Ltd v Peterson* (2011) 196 FCR 145 — Plaintiff failed to establish breach of duty owed by defendants.

LIMITATION OF ACTIONS — Whether certain actions statute-barred — Effect of long-stop provisions — *Trade Practices Act 1974* (Cth), ss 74J, 75AO — *Trade Practices Amendment (Personal Injuries and Death) Act (No 2) 2004* (Cth) ss 87F, 87G, 87H — Statutory claims of group members in respect of supply of devices before 13 July 2004 statute-barred — Statutory claims of group members in respect of devices supplied between 13 July 2004 and 28 June 2007 expired.

APPEARANCES:	Counsel	Solicitors
For the Plaintiff	F Forsyth KC and F Ryan SC with E Levine and M Guo	Slater & Gordon
For the Defendants	D Collins KC and B Walker SC with K Brazenor, D Wong and J Teng	Clayton Utz

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GLOSSARY

KEY TERMS	
ASOC	Amended Statement of Claim dated 23 December 2022
CPP	Chronic pelvic pain
AUB	Abnormal uterine bleeding
PET	Polyethylene terephthalate
PIB	Patient information brochure
IFU	Instructions for use
PTM	Physician training manual
FDA	United States Food and Drug Administration
TGA	Australian Therapeutic Goods Administration
ARTG	Australian Register of Therapeutic Goods
NSAI	National Standards Authority of Ireland
ANSM	French National Agency for Medicines and Health Products Safety
PMN	Polymorphonuclear cells
PMA	Post-market approval
PMS	Post-market surveillance
MDR	Medical device report
JER	Joint expert report
DTHR	Delayed-type hypersensitivity reaction
RCT	Randomised controlled trial
PID	Pelvic inflammatory disease
IUD	Intrauterine device
PCOS	Polycystic ovarian syndrome
HSG	Hysterosalpingogram
OCP	Oral contraceptive pill

LEGISLATION	
TPA	*Trade Practices Act 1974* (Cth)
ACL	Australian Consumer Law
TG Act	*Therapeutic Goods Act 1989* (Cth)
Wrongs Act	*Wrongs Act 1958* (Vic)
CCA	*Competition and Consumer Act 2010* (Cth)
Evidence Act	*Evidence Act 2008* (Vic)
TP Amendment Act	*Trade Practices Amendment (Personal Injuries and Death) Act (No 2) 2004* (Cth)

TABLE OF SCHEDULES

HIS HONOUR:

I. INTRODUCTION

1 This proceeding concerns Essure, a permanent contraceptive device that was commercially supplied to women in Australia between 2001 and August 2017 as an alternative to laparoscopic tubal sterilisation.

2 Essure is a spring-like device that consists of inner and outer metal coils with PET fibres located in between. During the implantation procedure, it is hysteroscopically inserted into a woman's fallopian tube. The outer coil is released and expands to press against the inner walls of the fallopian tube, holding the device in place. Features of the device including the PET fibres and expanded outer coil incited a localised inflammatory foreign body response in the fallopian tube in order to cause fibrosis resulting in tubal occlusion and sterilisation.

3 After the birth of her third child, the plaintiff Patrice Turner sought out options for permanent contraception. Essure was one of the options she discussed with her gynaecologist. Turner understood that Essure implantation was a day procedure, was less intrusive and had a faster recovery time than tubal ligation. She chose to proceed with Essure.

4 Turner returned to normal health a few days after the procedure was performed. However, within a few years she began to experience abnormal uterine bleeding ('AUB') and pelvic pain. Turner's menstrual bleeding became much heavier and lasted for longer. She also began to suffer sharp and debilitating pelvic pain, and constant heavy and dull pain in a band around her lower abdomen and back. Turner's symptoms worsened over time.

5 Almost five years after having Essure implanted, Turner consulted a gynaecologist who advised her to have a hysterectomy. By that time Turner was suffering severe pelvic pain and regular heavy menstrual bleeding. After Turner's hysterectomy, the

debilitating symptoms she had been experiencing resolved. Turner was 32 years old when she had hysterectomy surgery.

6 Turner brings this representative proceeding on her own behalf and on behalf of all women who had Essure implanted and allegedly suffered harm as a result. She relies on three causes of action. First, Turner alleges that Essure had a defect within the meaning of s 75AC of the *TPA* and/or a safety defect within the meaning of s 9 of the ACL, giving rise to a cause of action under s 138 of the ACL ('Defect claim'). The defendants raised the statutory 'state of scientific knowledge' defence to the Defect claim. Second, she alleges that Essure was not of merchantable quality within the meaning of s 74D of the *TPA* and/or not of acceptable quality within the meaning of s 54 of the ACL, giving rise to a cause of action under s 271 of the ACL ('Merchantable Quality claim'). Third, Turner alleges that the third defendant, Bayer HealthCare LLC ('Bayer HealthCare') and the fourth defendant, Bayer Essure Inc ('Bayer Essure') were each negligent in the design, development, manufacture, supply and distribution of Essure in Australia. Further, Turner alleges that all of the defendants apart from the second defendant Bayer Aktiengesellschaft ('Bayer AG'), were negligent in failing to provide adequate warnings about the device defects and associated risks to women's health, and in failing to ensure that information disclosing the defects and risks was made available to women who already had Essure implanted ('negligence claims').

7 There were three important features of the case that were critical to the determination of the claims Turner made.

8 Turner alleged, as the first and principal limb of her case, that in a not insignificant number of women Essure caused ongoing chronic inflammation that resulted in chronic pelvic pain ('CPP') and AUB ('inherent defects'). Turner argued that unlike other implanted biomedical devices, Essure was designed to promote an inflammatory response in order to create scar tissue. She alleged there was an inherent risk that Essure would cause ongoing chronic inflammation in some women because of its fundamentally problematic design, and because of certain features of the

fallopian tube environment and adjacent uterus. Turner alleged that in some cases, the corrosion of metal ions and particles from the device would likely cause or contribute to the chronic inflammatory response. Turner relied on expert evidence that ongoing chronic inflammation caused by Essure could result in women experiencing CPP, dysmenorrhea and/or AUB. She said this meant that many healthy young women who chose Essure as a permanent contraceptive option suffered severe symptoms that could only be resolved by major surgery involving removal of the fallopian tubes or uterus ('removal limitation'). The defendants argued that the foreign body response to Essure devices resolved normally and that there was no evidence that Essure could cause ongoing chronic inflammation resulting in CPP, dysmenorrhea or AUB.

9 The following categories of evidence were critical to the determination of whether, as a question of general causation, Essure can cause ongoing chronic inflammation resulting in CPP, dysmenorrhea or AUB. The first is clinical studies which report histologic assessment of fallopian tube tissue from women who had Essure devices surgically removed. Turner argued that the histologic assessments showed ongoing chronic inflammation that would be associated with adverse health outcomes in fallopian tube tissue caused by Essure devices in a not insignificant proportion of women. The defendants argued that the histologic assessments were evidence of a normal foreign body response to Essure, and that in most or all cases the assessments reported the mere presence of certain types of immune cells. The defendants argued the histological studies were not evidence that Essure can cause ongoing chronic inflammation that is pathologic and injurious to health.

10 The second category is corrosion studies. Turner argued that the studies showed that the Essure device corroded in vivo, resulting in significant accumulation of metal ions and particles in adjacent fallopian tube tissue. She argued that the accumulated metal ions and particles were likely to be a cause of ongoing chronic inflammation in some women. The defendants argued that the rate of Essure corrosion in vivo decreased

over time. They accepted there was a risk that metal ions from a device could cause an allergic hypersensitivity reaction in some women, which could be associated with an ongoing inflammatory response. They argued that hypersensitivity reactions were extremely rare, the subject of an adequate warning, and amenable to treatment. The defendants argued that Turner had not established that corrosion occurred at a rate or to a degree that was unsafe, or that corrosion was a likely cause of ongoing chronic inflammation.

11 The third category is evidence of the biological plausibility of mechanisms that Turner argued explained how Essure could cause ongoing chronic inflammation leading to CPP, dysmenorrhea and AUB. Turner relied on what she submitted was compelling scientific opinion evidence of biological causal mechanisms provided by the expert witnesses she called. The defendants submitted that the expert evidence of causal mechanisms relied on by Turner amounted to no more than 'brainstormed' hypotheses which were hotly contested by their own expert witnesses. Further, the defendants argued that even if the biological explanations advanced by Turner were found to be plausible, they were not sufficient to establish that Essure was a cause of CPP and AUB, in the face of contrary evidence including epidemiological studies and the results of extensive testing conducted before and after Essure was placed on the market.

12 The fourth category is epidemiological studies examining the possibility of a relationship between Essure and adverse events including CPP and AUB, using laparoscopic tubal sterilisation as a comparator ('comparative studies'). The outcomes of these comparative studies do not show any increase in the rate of CPP and AUB for women who underwent hysteroscopic sterilisation (principally by use of Essure) compared to women who underwent laparoscopic sterilisation. Turner argued that high quality biostatistical studies of Essure should have but had not been undertaken and that the comparative studies were of inferior design and poor quality, meaning very little weight could be attributed to the available epidemiological evidence.

13 The defendants made two points in response. First, the defendants argued that consistent with the approach taken in legal authority and in scientific analysis, epidemiological evidence was critical to consideration of the possible causal connection between an exposure such as by implantation of Essure and the adverse outcomes under consideration. The defendants submitted that Turner's attempt to prove general causation without relying on epidemiological evidence was novel. Second, the defendants argued that the comparative studies, which examine the experiences of over 100,000 women, show that Essure is not associated with an increase in the incidence of CPP or AUB. The defendants submitted that the most probable explanation is that the rates of CPP and AUB identified in those studies reflect the background rates of those conditions experienced by women of reproductive age. The defendants argued that it logically follows from the outcomes of the comparative studies that Turner had not established an association, let alone a causal relationship, between Essure and CPP or AUB.

14 The fifth category is clinical evidence. The evidence of gynaecologists who had treated women for CPP, dysmenorrhea and AUB did not support a causal connection between Essure and these conditions. There is no evidence that laboratory tests for the presence of pathological chronic inflammation in women who had Essure devices implanted had been administered. The histological assessment in Turner's case did not report the presence of chronic inflammation in her fallopian tubes. Turner's medical records do not indicate that her treaters had a clinical suspicion of pathologic chronic inflammation. Turner's treating surgeon, who was not called to give evidence, diagnosed adenomyosis as the cause of her gynaecological symptoms.

15 The final category is evidence of the prevalence and range of causes of CPP and AUB in women. CPP and AUB commonly affect women of reproductive age. There is a broad range of potential causes of both disorders. Diagnosis is complex and causation is often multifactorial. It is not uncommon that no causal pathology is identified. This context is relevant to Turner's attempt to attribute causation of CPP and AUB to

Essure.

16 For the detailed reasons that follow I have largely accepted the defendants' submissions. I have concluded that the biostatistical evidence weighs heavily against causation, and represents a very significant barrier to Turner proving general causation. The evidence supporting general causation in the histological and corrosion studies, and the expert evidence of biologically plausible causal mechanisms is far from compelling. The clinical evidence does not support general causation. In relation to the first limb of Turner's case, I am not satisfied that she has established that Essure can cause ongoing chronic inflammation in some women resulting in CPP, dysmenorrhea and/or AUB.

17 The second feature of Turner's case was her allegation that, following implantation, there were risks that an Essure device would migrate into the peritoneal cavity; be expulsed from the fallopian tube; break or fragment; corrode; fatigue; perforate the fallopian tube, uterus or other organs such as the bowel; and/or leach nickel or other metals into the body of the recipient ('failure defects'). Turner alleged that eventuation of one or more of these risks could result in new pain or increased pain including dysmenorrhea, new or increased menorrhagia and/or damage to internal organs.

18 The defendants accepted that there were risks of migration, expulsion, perforation and metal leaching that may be associated with adverse health outcomes. They argued that these risks were associated with many biomedical devices and surgical procedures, that the degree of risk was low, that the magnitude of an adverse health outcome if a risk eventuated was likely to be small, and that the risks were the subject of adequate warnings. The defendants argued that the only evidence of the devices breaking or fragmenting was in the process of surgical implantation or removal, and that Turner had not proven a risk that Essure devices could corrode or fatigue resulting in them breaking or fragmenting in vivo.

19 The third feature of Turner's case was her allegation that the defendants distributed patient information brochures ('PIBs') and published webpages about Essure which did not adequately disclose the risks of adverse events and outcomes Essure could cause. The defendants accepted they did not provide a warning that Essure could cause ongoing chronic inflammation resulting in CPP, dysmenorrhea or AUB because they said that risk did not exist. They argued that the warnings and information they provided about Essure included the content of training programs for gynaecologists who performed the Essure procedure, physician training manuals ('PTMs') provided to gynaecologists, and Instructions For Use ('IFUs') supplied with Essure devices. They argued that this material adequately disclosed risks that were associated with Essure, and that Turner had not demonstrated any relevant deficiency in the information provided about the device.

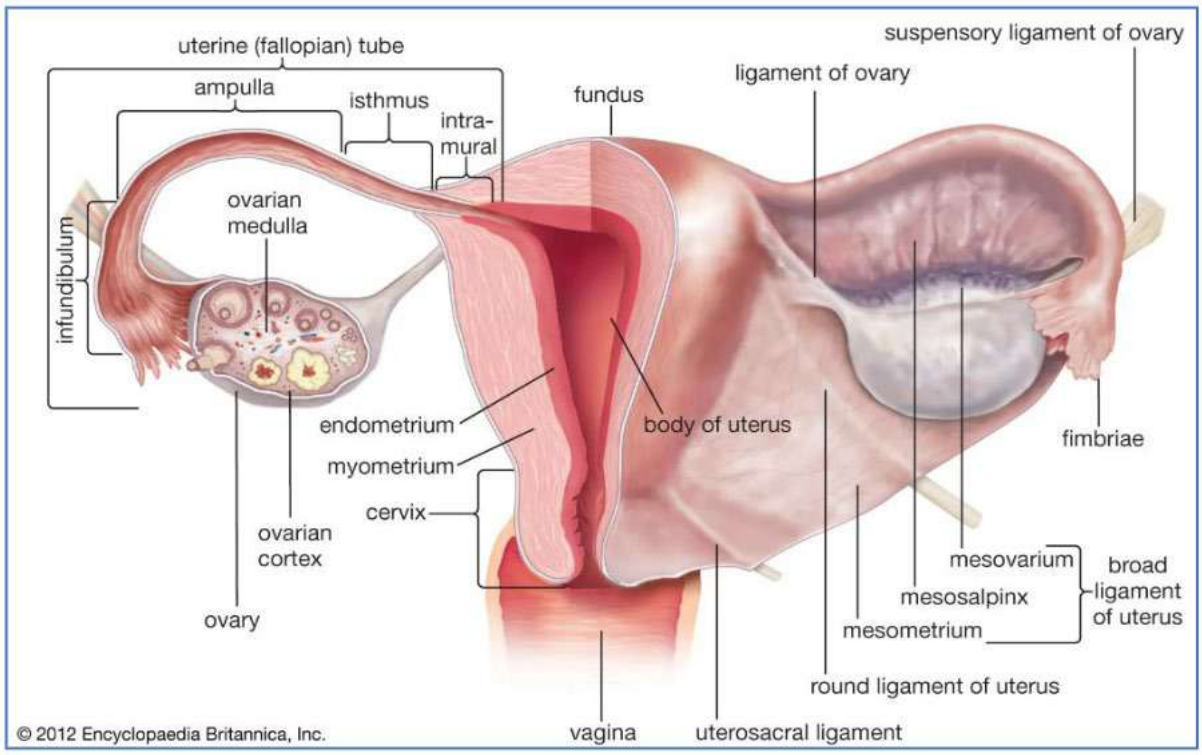
20 There was a risk that an Essure device could migrate, be expulsed from the fallopian tube, perforate organs, corrode, and leach nickel or other metals into the body. I conclude that in most cases, the degree and magnitude of these risks were small and that they were often associated with placement or removal of the device. I do not accept that there was a risk that Essure could break, fragment or fatigue once implanted in the body.

21 I have again largely accepted the defendants arguments. I have concluded that the defendants provided adequate warnings of the established Essure risks in the PTMs and IFUs. It was reasonable to expect that treating gynaecologists would provide information and warnings about the established risks to their patients based upon their own specialist skill, expertise and experience and the information provided by the defendants. The PIBs and webpages relied on by Turner did not represent the entirety of the information and warnings about the Essure risks provided by the defendants and available to women considering undergoing the Essure procedure.

22 For the reasons that follow, I have concluded that the three claims made by Turner have failed.

II. ANATOMY OF THE UTERUS AND FALLOPIAN TUBES

23 The uterus is an inverted pear-shaped muscular organ of the female reproductive system, located in the middle of the pelvis in the space between the bladder and the rectum.[1] A circular narrowing in the inferior portion of the uterus divides it in two. The upper part is called the *uterine corpus* (body of the uterus). The lower part is called the *uterine cervix* (cervix), and is a tubular structure that connects the endometrial cavity and the vagina. The cervix, uterine corpus, fallopian tubes and ovaries together form the female upper genital tract (shown in the following diagram).[2]



24 The uterus has three main layers. The outer layer that forms the surface of the organ facing the peritoneal cavity is the *serosa* or *perimetrium*. The thick muscular wall of the uterus is the *myometrium*. The inner layer of the uterus is the *endometrium*, where embryos normally implant and develop when a pregnancy occurs.[3] The endometrium itself is divided into three layers: the thin surface layer called the *epithelium*; the

1 Lam at 19 [2.4] (EXP.001.002.0006).
2 As-Sanie at 11 [33] (EXP.001.002.0005).
3 Robertson at 64 [238] (EXP.001.001.0127).

functionalis or 'functional' layer, which contains glands that are most responsive to the hormones estrogen and progesterone during the menstrual cycle and is completely shed during menstruation; and the less responsive *basalis* or 'basal' layer located between the functionalis and myometrium.[4]

25 The epithelium consists of a single layer of epithelial cells. It provides a degree of protection from infectious organisms but is soft, easily damaged and does not protect against chemical agents or trauma.[5]

26 The hormonal response of the functionalis results in transient changes to its physical structure, cellular composition and function over the course of the menstrual cycle. Each month, estrogen stimulates the dynamic growth and proliferation of the functionalis, followed by degeneration and shedding in response to progesterone. The cycle of menstruation then regeneration, represented in the following diagram, is unique to the uterus.[6]

4 Murdock at 10 [14] (EXP.001.002.0008).
5 Robertson at 64-5 [238] (EXP.001.001.0127).
6 Ibid at 65 [242].

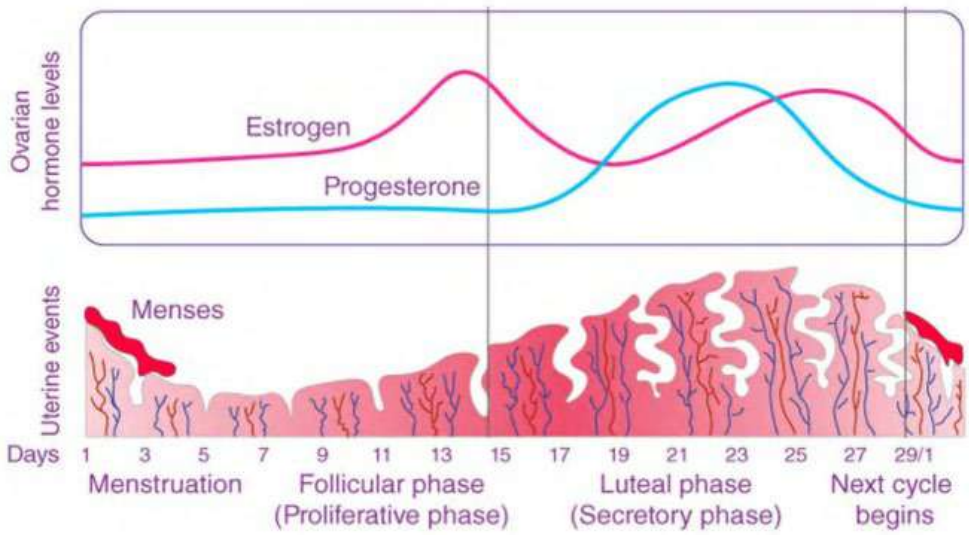


Figure 6. Diagrammatic representation of changes in the uterine endometrium over the course of a normal menstrual cycle, showing the three stages (menstruation, follicular phase, and luteal phase, and the changing thickness of the endometrial functionalis and its vascular supply (red and blue), and corresponding fluctuations in sex steroid hormones.

Glands in the functionalis become progressively more secretory in the second half of the menstrual cycle, delivering fluids into the endometrial cavity to support an embryo that may have formed in the event of conception. If conception has not occurred the endometrial layer will undergo a phase of senescence, with cells beginning to die and be progressively lost as menstrual fluid.[7]

27 The myometrium has robust contractile action that is most important for labour and birth, but also promotes shedding and expulsion of endometrial tissue during menstruation. This can cause menstrual cramping and pain that should not occur to the level that interferes with normal daily functions.[8]

28 The two fallopian tubes arise from the body of the uterus and provide the connection between the uterus and each ovary.

29 The fallopian tube has four segments. The funnel-shaped *infundibulum* is the distal end of the tube that opens into the peritoneal cavity adjacent to the ovary. Attached

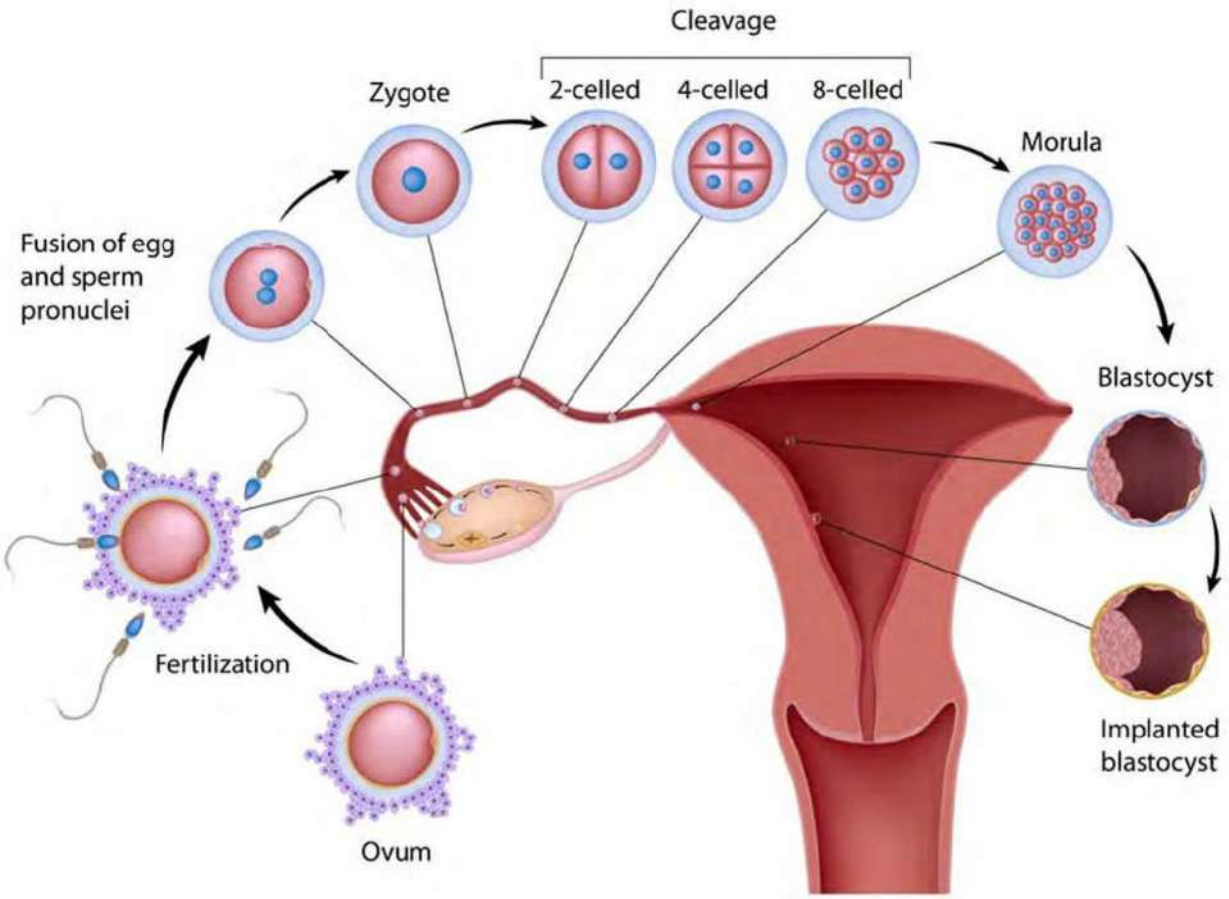
7 T2674-5 (TRA.500.029.0001 at 0020_28-0021_3).
8 Robertson at 66 [243] (EXP.001.001.0127).

to the distal end of the infundibulum are *fimbria*, which are finger-like mucosal projections which project over the medial surface of the ovary. The *ampulla* is the longest segment of the fallopian tube. Fertilisation usually takes place within the lumen of the ampulla.[9] The final two segments of the fallopian tube are the *isthmus* which is about 2–3 cm long, followed by the intramural region (also known as interstitial region or *SUTJ*) which is approximately 1 cm long and connects the fallopian tube and the uterus.[10]

30 The fallopian tube has three layers: an outer serosa layer, a middle smooth muscle layer and an inner mucosal layer comprised of *lamina propria* (a thin layer of connective tissue) covered by a single columnar epithelial lining.

31 The features and dimensions of different segments of the tube vary relative to the role played in transporting ova, sperm and early embryos; conception; and early embryo development.[11] A diagrammatic illustration of conception in the fallopian tube and implantation of the embryo in the uterus follows:[12]

9 As-Sanie at 12 [38] (EXP.001.002.0005)
10 Robertson at 78 (EXP.001.001.0127); As-Sanie at 12 (EXP.001.002.0005).
11 Robertson at 74 [276] (EXP.001.001.0127)
12 Ibid at 232.



32 The external diameter of the fallopian tube and the internal diameter of the lumen progressively reduce along its length as it approaches the uterus. The ampulla has large numbers of branching folds that appear in cross-section as a labyrinth of finger-like projections with little space between them. The folds are less highly branched and numerous in the isthmus, and less again in the intramural region.[13] These features are demonstrated in the following figure:[14]

13 Ibid at 74 [278].
14 Murdock at 8 (EXP.001.002.0008).

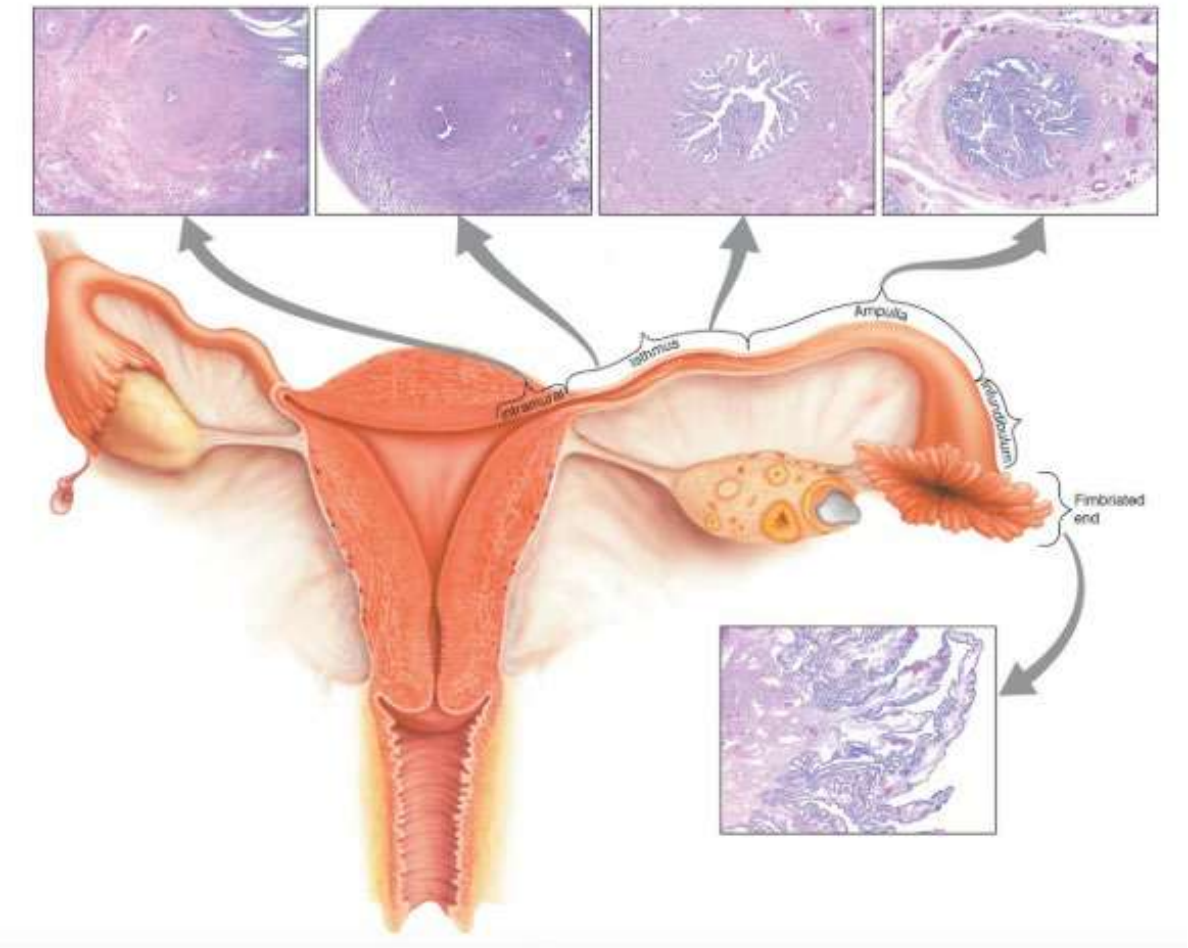


Figure 2. Normal fallopian tube anatomy and the microscopic findings at each segment. All histologic images are at 10x, low magnification except the second isthmus image, which is at 20x, medium magnification. The intramural cross section demonstrates a fallopian tube lumen with surrounding uterine smooth muscle (myometrium). The first cross section of isthmus is surrounded by the fallopian tube muscular wall (myosalpinx), which is composed of 3 layers 1) an inner longitudinal layer, 2) a circular layer 3) an outer longitudinal layer. The second cross section of isthmus shows a thick-walled muscle layer. Note the expanded lumen with more plica (longitudinal branching folds) compared to the first cross section of isthmus. The ampulla has a thin-walled muscular area and an expanded lumen with normal plicae. The fimbriated end has numerous finger-like projections, each covered with a single layer of epithelium.

The narrowing of the lumen of the fallopian tube is necessary to allow the inner walls to form contact with the embryo and propel it towards the uterus.[15]

33 The transport of ova and embryos in the direction of the uterus is mediated by delicate *cilia* (fine hair-like structures) on the surface of the fimbriae in specialised cells of the

[15] Robertson at 74 (EXP.001.001.0127).

tubal epithelium. These cilia cells beat in the direction of the uterus, creating a current that transports the ovum towards the site of fertilisation.[16] Peristaltic activity in the tubal muscular layer propels sperm against the current of the cilia from the uterine end of the fallopian tube into the ampulla, where fertilisation of the ovum takes place.[17]

34 Any surgical procedure that prevents transport of the ovum, sperm and/or early embryo along the fallopian tube by occluding, interrupting or removing a segment or the entirety of both tubes is a method of permanent sterilisation.[18]

III. ESSURE

35 Essure was developed as an alternative to tubal ligation. Each Essure device is comprised of:

(a) a 316L stainless steel inner coil;

(b) a chromium doped nitinol (nickel/titanium) dynamically expanding outer coil;

(c) PET fibres attached to the inner coil;

(d) a ball tip at the distal end of the inner coil, composed of either silver-tin solder or remelted 316L stainless steel;[19]

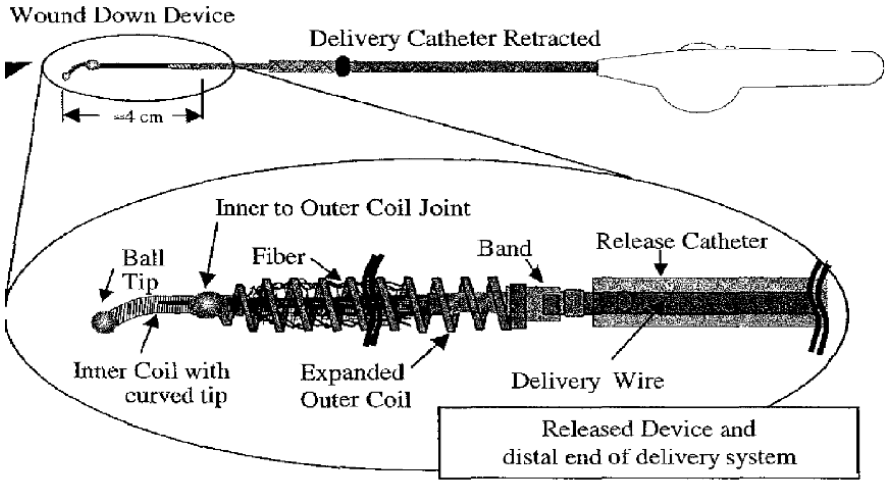
(e) a platinum/iridium half band at the proximal end of the outer coil; and

(f) a platinum/iridium positioning marker attached to the inner coil.[20]

36 Each device was delivered hysteroscopically into the fallopian tube in a wound down configuration, attached to a delivery wire, constrained by a release catheter and sheathed by a flexible, hydrophilically coated delivery catheter. In the wound down

16 Ibid at 75 [281].
17 Ibid at 75.
18 As-Sanie at 13 [39] (EXP.001.002.0005).
19 SBM.001.001.0004 at 11 [19].
20 BAY-ESSURE-0004422; BAY-ESSURE-0004934.

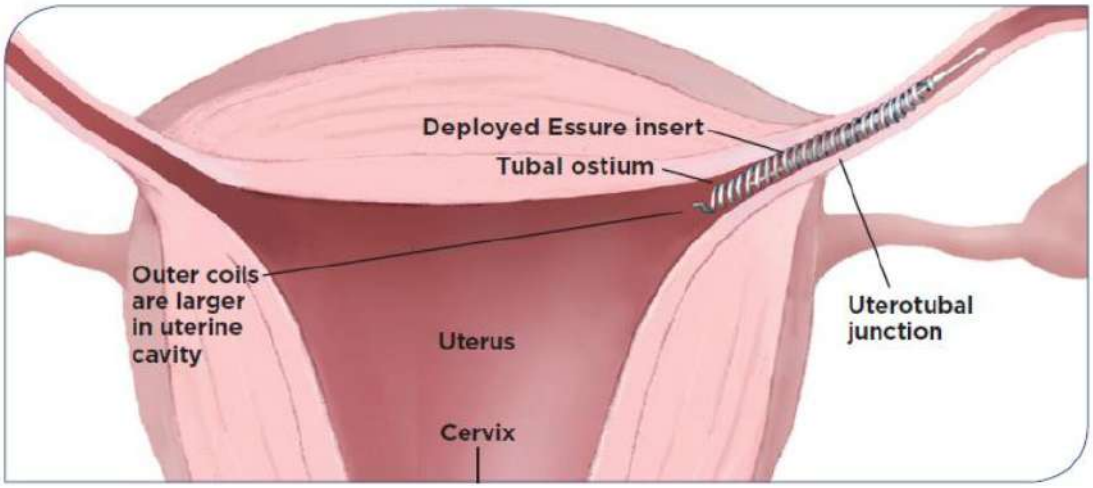
configuration, an Essure device was approximately 4 cm in length and 0.8 mm in diameter. The delivery catheter extended only to the joint between the inner and outer coil. The unsheathed ball tip acted as a guidewire to cannulate the fallopian tube. The platinum/iridium half band and positioning marker acted as a visual guide for the physician to determine the correct depth of insertion into the fallopian tube. Once released, the device expanded to an approximate diameter of 2.0 mm to acutely anchor itself into the fallopian tube, with a number of outer coils trailing into the uterus. A drawing of the Essure device and the internal delivery components is shown below:



37 The Essure insertion procedure was designed to be performed without the need for incisions. In Australia, the Essure procedure was performed under anaesthetic in an operating theatre setting by a gynaecologist.[21]

38 The intended placement of the Essure insert in the fallopian tube and uterine cavity is shown in the following diagram:[22]

21 Rosen (EXP.001.002.0002); T2636 (TRA.500.028.0001_2 at 0099_10).
22 PLE.001.002.0001 at 9.



39 The PET fibres were intended to promote an inflammatory response resulting in fibrotic tissue ingrowth that secured the device in place and occluded the fallopian tube lumen, resulting in permanent sterilisation.

IV. PARTIES

Plaintiff

40 Turner was born in 1986. She has three children. In September 2013 after the birth of her youngest child, Turner underwent hysteroscopic implantation of Essure into each of her fallopian tubes. Turner had hysterectomy surgery resulting in explantation of the devices on 25 June 2018.

Group members

41 Turner brings this proceeding on behalf of all women who had Essure devices implanted at any time on or before 31 December 2018, and who have suffered harm as a result.

42 Essure was at all times manufactured overseas and imported into Australia. From the late 1990s, some Essure devices were supplied for clinical trials conducted in Australia that involved implantation into participating women. The defendants admitted that Essure devices were commercially supplied in Australia from about 2001 to 28 August 2017 ('commercial supply period').

Defendants

First defendant – Bayer Australia Ltd ('Bayer Australia')

43 Bayer Australia is an Australian corporation in the Bayer group of companies which was the registered sponsor of Essure on the ARTG under the *TG Act* from 29 January 2018 to 9 February 2018. Bayer Australia admitted that its name was included on some material published in Australia regarding Essure between 1 July 2013 and August 2017.[23] What further role, if any, Bayer Australia played in relation to Essure was in issue. Turner alleged that Bayer Australia was a 'manufacturer' of Essure within the meaning of s 7 of the ACL. Bayer Australia submitted that it did not supply Essure in Australia and was not a manufacturer of Essure for the purposes of the ACL.

Second defendant – Bayer AG

44 Bayer AG is a corporation registered in Germany. It has no place of business or registered office in Australia.

45 Bayer AG is the owner of the following trademarks numbered 1950359, 242139, 242143 and 1188965:

From around 1 July 2013 to August 2017, one or more of these trademarks appeared on some material published in Australia regarding Essure. Turner submitted the evidence established that Bayer AG was a manufacturer of Essure under the ACL from 5 June 2013. Bayer AG submitted that because of the extra-territorial provisions of the ACL, the legislation did not apply to it; and that in any event, it was not a manufacturer of Essure within the meaning of the ACL and did not supply the device in Australia.

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23 PLE.500.001.0008 at [7](c).

Third defendant – Bayer HealthCare

46 Bayer HealthCare is an indirect subsidiary of Bayer AG and is a limited liability company registered in Delaware in the US.

47 Bayer HealthCare admitted that:

(a) it was responsible for the design and development of Essure from around 5 June 2013 to 1 January 2016;

(b) it was responsible for limited manufacturing and assembly of Essure from around 1 July 2013 to 1 January 2016;

(c) it supplied Essure for importation into, and distribution in, Australia from around 1 July 2013 to 31 May 2017;

(d) from around 1 July 2013 to August 2017, some material published in Australia regarding Essure included the name of Bayer HealthCare; and

(e) it was the registered manufacturer of Essure on the ARTG from around May 2014 to 9 February 2018.[24]

Bayer HealthCare admitted that it was a manufacturer of Essure in accordance with the *TPA* and ACL from 5 June 2013 until about 9 February 2018.[25] However, it denied that it came within the extra-territorial jurisdiction of the *TPA* and ACL and argued that the statutory provisions Turner relied on did not apply to it.

Fourth defendant – Bayer Essure

48 Bayer Essure is a company registered in Delaware in the US.

49 From 1992 to 25 October 2013, Bayer Essure was named Conceptus Inc ('Conceptus'). On 5 June 2013, Conceptus was acquired by a wholly owned subsidiary of Bayer HealthCare. On 25 October 2013, Conceptus changed its name to Bayer Essure Inc.

24 Ibid at [9].
25 Ibid at [9](e)(ii).

50 During the period from December 1999 to around 1 July 2013, Bayer Essure (as Conceptus) designed, developed and manufactured Essure and supplied the device for importation to Australia.[26] Bayer Essure admitted that from about 1999 to about 2014 it:

(a) owned the trademark 'Conceptus' and the Conceptus logo; and

(b) was listed on the ARTG as the manufacturer of Essure.[27]

51 Bayer Essure admitted that it was a manufacturer of Essure from about 1999 to about 1 May 2014 within the meaning of s 74A of the *TPA* and s 7 of the ACL.[28] Bayer Essure denied that it was a manufacturer of Essure under the ACL at any time from 1 May 2014. Further, Bayer Essure denied that it came within the extra-territorial jurisdiction of the *TPA* or ACL.

Fifth defendant – Gytech Pty Ltd ('Gytech')

52 Gytech was the importer and the exclusive distributor of Essure in Australia, and the registered sponsor of the device on the ARTG, from 19 August 2010 to 31 December 2014. Gytech admitted it was a manufacturer of Essure for the purposes of the *TPA* and ACL during this period.[29]

Sixth defendant – Australian Medical & Scientific Ltd ('AMSL')

53 AMSL is incorporated in New Zealand and registered in Australia as a foreign company. From around 23 January 2015 to 28 January 2018, AMSL was the registered sponsor of Essure on the ARTG. From 1 January 2015 to around 31 May 2017, AMSL was the importer and sole distributor of Essure in Australia. From 2015 to 2017, AMSL promoted and marketed Essure in Australia and the AMSL name appeared on material relating to Essure during this time. AMSL admitted it was a manufacturer of Essure within the meaning of s 7 of the ACL from 1 January 2015 to 1 August 2017.[30]

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26 Ibid at [10](c).
27 Ibid at [10](d).
28 Ibid at [10](e).
29 SBM.500.001.0003_2 at 105 [8.4].
30 PLE.500.001.0008 at [12](d).

V. PLEADED CLAIMS

54 Turner alleged that Essure was defective, and that this resulted in the risk of women who had the devices implanted suffering from adverse events and injuries. She alleged that the defendants failed to disclose the existence of the defects and the risk of adverse events in the marketing material they published. These allegations were the foundation of each of the claims advanced by Turner.

Inherent defects

55 In paragraph [18] of her amended statement of claim ('ASOC'), Turner alleged that by reason of its design and method of operation, Essure:

a. disrupted the inner layers of the uterine horn and/or the fallopian tubes;

b. caused initial acute inflammation in the fallopian tubes and/or endometrium;

c. caused ongoing chronic inflammation in the fallopian tubes and/or endometrium; and/or

d. incited a foreign body response to the Essure Insert in the fallopian tubes and/or endometrium and/or uterine cavity.[31]

In her final submissions, Turner clarified that the matters alleged in sub-paragraphs (a), (b) and (d) above were not relied on as separate defects, but were part of the explanation for why Essure caused chronic inflammation in some women. A central issue at trial was whether Turner had established the allegation in (c) above.

56 Turner alleged that an ongoing chronic inflammatory response to Essure occurred in some women implanted with the device by reason of:

(i) the acute inflammatory response not resolving;

(ii) limited biocompatibility in the constituent materials of the Essure Insert hindering the physiological healing process following acute inflammation;

[31] PLE.001.002.0001 at [18].

(iii) lack of surface functionalisation of the Essure Insert;

(iv) the metal and synthetic components of the Essure Insert including the mixing of metals of different electrochemical potential;

(v) corrosion and metal ion release;

(vi) micromovements causing ongoing mechanical injury in the tissue of the fallopian tube;

(vii) the Essure Insert not resorbing in the body;

(viii) the Essure Insert not promoting a functional integration with host tissues;

(ix) the propensity of female reproductive tissue and organs towards a pro-inflammatory response; and/or

(x) the interaction of the female reproductive tissue with the Essure Insert as a foreign body and the elicitation of the foreign body response.[32]

57 The defendants agreed that Essure was designed to disrupt the inner layers of the fallopian tube upon insertion, cause acute inflammation and incite a foreign body response. They said that this was a necessary part of the process leading to development of fibrotic scar tissue to occlude the fallopian tube. However, the defendants denied that Essure caused an ongoing chronic inflammatory response as alleged.

Failure defects

58 In paragraph [19] of the ASOC, Turner pleaded that there was a risk that following implantation, an Essure device:

a. would:

i. migrate, including into the abdominal cavity;

ii. be expulsed from the fallopian tube and/or uterus;

iii. break or fragment;

iv. corrode;

v. fatigue; and/or

b. would perforate the fallopian tube, uterus or other organs such as the

[32] AID.001.001.0002 at 18–19.

bowel; and/or

c. would:

i. leach nickel or other metals into the body of the recipient; …[33]

59 The defendants agreed that unsatisfactory location of the device during implantation could be associated with migration, expulsion or perforation of the fallopian tube, uterus or bowel in some patients. They said that nickel alloys were commonly used in medical devices, and that nickel may be released at low levels from an Essure device following implantation. They said that during the commercial supply period, publications were made available to doctors and patients in Australia regarding Essure that contained information and risk warnings about matters including the following:

(i) the fact that all medical procedures and implantable devices carry risks and that there were risks associated with implantation and use of the Essure Device; and

(ii) risks that may be associated with implantation, use and/or removal of the Essure Device included:

A. movement of the Essure Insert such as migration or expulsion from the fallopian tube;

B. breakage or fragmentation of the Essure Insert during removal;

C. perforation of or damage to internal organs such as the uterus during implantation or as a result of unsatisfactory location of the Essure Insert during the implantation process;

D. an allergic reaction to nickel-titanium;

E. pain; and

F. bleeding.[34]

60 The defendants accepted that an Essure device may corrode in vivo. However, they denied that there was a risk that a device might break or fragment because of corrosion or fatigue, or that this could result in migration, expulsion, perforation or injury.

61 The defendants argued that the degree and magnitude of the admitted risks were

[33] PLE.001.002.0001 at [19].
[34] PLE.500.001.0008 at [19](c)(i)-(ii).

small.

Adverse events

62 Turner alleged in paragraph [20] of the ASOC that, by reason of any one or more of the inherent defects and/or the failure defects, there was a risk that an Essure insert would cause:

a. pain or increased pain, including serious, chronic and/or recurring pain;

b. new, increased or worsened menorrhagia (heavy menstrual bleeding);

c. new, increased or worsened dysmenorrhoea (intense uterine cramping and pain); and/or

d. damage to internal organs.[35]

('adverse events').

63 Turner principally relied on ongoing chronic inflammation as the cause of the adverse events in (a), (b) and (c) above. At trial, those adverse events were described broadly as CPP, dysmenorrhea and AUB. The risk of the adverse event in (d) was alleged to arise from perforation, migration, breakage or fragmentation of the device and to result in pain and bleeding.

64 The defendants denied there was a risk that Essure could cause ongoing pathologic chronic inflammation resulting in CPP or AUB.

65 The defendants relied on the information and warnings they had made available to doctors and patients in Australia regarding the risk of adverse events associated with Essure.

Removal limitation

66 It was not in dispute that Essure was designed to anchor in a woman's fallopian tube after insertion and quickly become embedded in fibrotic tissue.

67 Turner alleged that a woman who experienced an adverse event associated with

[35] PLE.001.002.0001 at [20].

Essure would be unable to resolve the adverse event without abdominal surgery to remove the insert. This removal surgery would likely involve a salpingectomy or hysterectomy. Turner relied on the removal limitation as being relevant to the magnitude of the risk of an adverse event.

68 The defendants admitted that Essure was designed to promote tissue ingrowth and long-term anchoring, and might require salpingectomy or hysterectomy to effect its removal if a patient experienced an adverse event. They alleged that information and risk warnings made available to doctors and patients regarding Essure included:

> A. the fact that all medical procedures and implantable devices carry risks and that there were risks associated with implantation and use of the Essure Device;
>
> B. the Essure Device procedure was permanent and not reversible;
>
> C. removal of the Essure Insert may require surgery; and
>
> D. if surgical removal of the Essure Insert was required, a salpingectomy or hysterectomy might be required[.][36]

Injuries

69 Turner pleaded that:

> …[b]y reason of one or more of the Inherent Defects, the Failure Defects and/or the Removal Limitation and/or the occurrence of one or more of the Adverse Events, the Plaintiff and group members suffered injuries as a result of implantation of the Essure Insert.[37]

70 The particulars of injuries allegedly resulting from the inherent defects include:

> (iv) By reason of the Inherent Defects and/or the Removal Limitation, some Group Members suffered the following injuries (GM Implantation Injuries):
>
> …
>
> B. the development of acute and then chronic or persistent chronic inflammation in the fallopian tubes and/or endometrium; and
>
> C. associated symptoms or conditions of pain (including pelvic or abdominal pain o[r] cramping) and/or abnormal uterine bleeding, and/or menstrual abnormalities, (including exacerbation of any of the above), some with resulting sexual

36 PLE.500.001.0008 at [21](d)(ii).
37 PLE.001.002.0001 at [23].

dysfunction, and/or psychological conditions or symptoms;

D. in some cases requiring:

1. hysterectomy (with or without bilateral or unilateral salpingectomy and with or without oophorectomy);

2. salpingectomy (bilateral or unilateral, with or without oophorectomy and/or corneal resection)[.] [38]

71 Turner particularised injuries resulting from the failure defects as follows:

> (vii) By reason of the Failure Defects, in some Group Members the Essure Device migrated, was expulsed from the fallopian tube or uterus, broke or fragmented, corroded, fatigued and/or leached nickel or other metals into the body of the recipient.
>
> (viii) By reason of the matters in the previous subparagraph, some Group Members suffered:
>
> A. disruption of tissue;
>
> B. acute inflammation;
>
> C. chronic or persistent chronic inflammation; and/or
>
> D. damage to internal organs; and/or
>
> E. associated symptoms or conditions of pain (including abdominal, pelvic pain and cramping) and/or bleeding (including menstrual abnormalities) (including exacerbation of any of the above), some with resulting sexual dysfunction, and/or psychological conditions or symptoms;
>
> F. in some cases requiring:
>
> 1. hysterectomy (with or without bilateral or unilateral salpingectomy and with or without oophorectomy)
>
> 2. salpingectomy (bilateral or unilateral, with or without oophorectomy and/or corneal resection);
>
> 3. surgery to investigate the cause of symptoms or conditions;
>
> 4. other surgery to excise the device from the body; and/or
>
> 5. removal of other organs or part of an organ.[39]

72 The defendants' case was that there were known or expected risks associated with

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38 AID.001.001.0002 at 36–38.

39 Ibid at 39–40.

implantation of a biomedical device such as Essure; that they communicated information and warnings about those risks in published material made available to doctors and potential recipients of Essure; and that the degree and magnitude of the risks were small.

Marketing conduct

73 Turner alleged that between 1999 and 2018, the defendants published PIBs and webpages about Essure which were directed to potential recipients of the device ('marketing material'). Turner alleged:

> The Marketing Material did not or did not adequately disclose the existence of the Inherent Defects, the Failure Defects, the risk of Adverse Events, and/or the Removal Limitation (the Marketing Conduct).
>
> **Particulars**
>
> (i) The Marketing Material did not contain express references to the Inherent Defects, the Failure Defects, the risk Adverse Events and/or the Removal Limitation.
>
> (ii) To the extent that the Marketing Material made any references to any one or more of the Inherent Defects, the Failure Defects, the Adverse Events and/or the Removal Limitation, any risks were downplayed and/or were represented as rare and/or temporary.
>
> (iii) The general impression given by the Marketing Material was that the Essure Device was safe, gentle and had a low impact on the body.
>
> (iv) There was no or no adequate reference to the Essure Insert operating as an intrauterine device nor to any increased risks associated with the Essure Device and any pain or bleeding conditions. [40]
>
> …

74 The defendants responded that Essure was supplied to women via their treating gynaecologist, and that publications they made available to gynaecologists and women regarding Essure disclosed the risks associated with implantation of the device. The publications relied on by the defendants were the PIBs, IFUs contained in the boxes in which Essure was supplied, and PTMs provided to doctors as part of

[40] PLE.001.002.0001 at [25].

training for the Essure procedure. The defendants alleged that prior to performing the Essure procedure the gynaecologist would, as a matter of course, have consulted with the patient, synthesised information relevant to the patient's needs, provided information and advice about Essure, and made recommendations as to the most appropriate contraceptive option for the patient. The defendants alleged that in those circumstances, it was reasonable for them to expect that a patient undergoing the Essure procedure would be informed by their doctor of the risks and benefits associated with alternative contraceptive options, including Essure.

75 The defendants' response to the risks associated with Essure alleged by Turner dictated the central matters in issue at trial. As stated above, the defendants accepted that some of the alleged risks existed. The defendants argued that context relevant to consideration of the accepted risks included the following: every contraceptive option carries risks; all medical procedures and implantable devices carry risks; information and warnings were made available to doctors and patients in Australia regarding the risks; it was reasonable to expect that doctors would inform their patients about the comparative risks and benefits of Essure; and the magnitude and degree of the accepted risks was small.

76 The defendants understandably took a different approach to the pleaded risks which they argued did not exist. The defendants accepted that they did not provide information or warnings to doctors or patients about the risk that Essure could cause ongoing pathologic chronic inflammation resulting in CPP or AUB, because they denied that risk existed. The most significant issue at trial was whether Turner had established the existence, degree and magnitude of this alleged risk.

Statutory claims

77 Turner alleged that by reason of the inherent defects, failure defects, adverse events and removal limitation, the Essure devices acquired by her and group members were not sufficiently fit for purpose, free from defects or as safe as would be expected by a reasonable consumer. Turner alleged on this basis that Essure was not of

merchantable quality within the meaning of ss 74D(1) and 74D(3) of the *TPA* and/or was not of acceptable quality within the meaning of s 54 of the ACL.

78 Turner alleged that by reason of the inherent defects, failure defects, adverse events and the removal limitation, along with the marketing conduct, the safety of Essure was not such as persons generally were entitled to expect. Turner alleged on this basis that Essure had a defect within the meaning of s 75AC of the *TPA* and/or a safety defect within the meaning of s 9 of the ACL.

79 Turner alleged that she and group members had suffered loss and damage by reason of Essure not being of merchantable/acceptable quality and/or having a defect/safety defect. She claimed that group members were entitled to damages under the *TPA* against Bayer Essure in respect of the period to 31 December 2010, and under the ACL against all defendants for the period from 1 January 2011.

Negligence

80 Turner made a claim in negligence against Bayer Essure as manufacturer for the whole period that Essure was supplied in Australia. Turner alleged that the inherent defects, failure defects, adverse events and removal limitation gave rise to risks of harm that were foreseeable and not insignificant. She alleged that a reasonable person in the position of Bayer Essure would have:

(a) not designed, developed or manufactured Essure; and/or

(b) not distributed or supplied the device for sale in Australia.

81 Turner alleged in the alternative that a reasonable person in the position of Bayer Essure would have taken reasonable care to ensure that:

(a) Essure was promoted or marketed to potential recipients with adequate warnings about the inherent defects, the failure defects, the risk of adverse events and the removal limitation; and

(b) information disclosing the inherent defects, failure defects and risk of adverse events was made available to persons who had already received Essure.

82 Turner alleged that Bayer Essure breached its duty of care to her and group members by:

(a) designing, developing and manufacturing Essure;

(b) distributing or supplying Essure for sale in Australia;

(c) promoting or marketing Essure without adequate warnings about the inherent defects, failure defects, risk of adverse events and removal limitation;

(d) failing to make available to the plaintiff and group members who had already received Essure, information disclosing the inherent defects, failure defects, and/or risk of adverse events.

83 Turner made a claim in the same terms against Bayer HealthCare from 1 July 2013.

84 Turner made claims against Gytech and AMSL for the period that each was the importer and exclusive distributor of Essure in Australia. She alleged that each of those companies knew or ought to have known that Essure had the inherent defects, failure defects, risk of adverse events and removal limitation. She alleged that Gytech and AMSL breached the duties they owed by failing to warn group members about those matters.

85 Turner also made a 'failure to warn' claim against Bayer Australia for the period from 2014.

VI. PLEADED DEFENCES

86 The defendants raised a number of defences in relation to Turner's pleaded claims. Some of the defences are relevant to the consideration of the individual claims of group members and are unnecessary to discuss further in these reasons.

Limitation periods

87 The defendants pleaded reliance on State-based limitations statutes in relation to the negligence claim: ss 74J, 75AO, 82 and div 2 of Part VIB of the *TPA*; div 2 of Part VIB of the *CCA*; and ss 143 and 236 of the ACL.

88 The defendants do not allege that Turner's case is statute-barred.

89 I will return to the issue of limitations in Chapter XXII of these reasons.

State of scientific knowledge

90 The defendants alleged that should the Court find some of the defects alleged by Turner were caused by Essure, that the state of scientific and technical knowledge during the relevant period was not such as to enable those defects to be discovered.[41] The defendants relied on s 75AK(1)(c) of the *TPA* and s 142(c) of the ACL.

91 The defence is invoked in respect of the following alleged defects:

(a) 'ongoing chronic inflammation', insofar as that term refers to persistent, pathologic chronic inflammation;

(b) the inherent defects insofar as they are alleged to have operated outside of the fallopian tubes (namely, in the endometrium and/or uterine cavity and/or uterine horn);

(c) a number of the alleged failure defects, being the risks of:

(i) corrosion (other than in relation to the silver-tin solder component of the device, and beyond the ordinary low-level rate at which all implanted medical devices release metal ions in situ);

(ii) fatigue;

(iii) leaching of nickel or other metals (other than in respect of hypersensitivity reactions, and beyond the ordinary low-level rate at

41 SBM.500.001.0003_2 at 181 [1.17](d).

which all implanted medical devices release metal ions in situ); and

(iv) the alleged 'adverse events' other than the pain, bleeding and damage to internal organs specifically warned of during the relevant period.[42]

92 The defence is not invoked in respect of those risks associated with Essure which the defendants accept exist.[43]

93 I will return to this defence in Chapter XXIII.

Safety defects did not exist at the time of supply

94 The defendants also relied on s 75AK(1)(a) of the *TPA* and s 142(a) of the ACL in relation to the Defect claim. Section 142(a) of the ACL relevantly provides:

> In a defective goods action, it is a defence if it is established that:
>
> (a) the safety defect in the goods that is alleged to have caused the loss or damage did not exist:
>
> …
>
> (ii) in any other case—at the time when the goods were supplied by their actual manufacturer[.]

95 This defence requires the manufacturer to prove that the defect did not exist at the time that the goods 'passed from the manufacturer's control'.[44]

96 The defendants relied on this defence to the extent any safety defects that are found came into existence by reason of the acts or omissions of gynaecologists who consulted with women and performed Essure procedures, where those gynaecologists:

(a) did not provide advice and warnings to women about matters contained in information made available to them regarding Essure;

(b) did not carry out the Essure procedure properly.

97 Consideration of this defence does not arise in Turner's own case or on the common

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42 Ibid at 180 [1.17](b).
43 Ibid at 180.
44 *Carey-Hazell v Getz Bros & Co (Aust) Pty Ltd* [2004] FCA 853 at [207] (Kiefel J) ('*Carey-Hazell*').

questions. The defence may arise for consideration on the circumstances of an individual group member's claim. It does not need to be further addressed in these reasons.

Significant injury

98 To the extent that Turner's pleaded claims are subject to the *Wrongs Act,* the defendants submitted that in the event the Court accepts that the personal injuries alleged to have been suffered by Turner are the result of Essure and but for Essure would not have been suffered, they accept that Turner satisfies the 'significant injury' threshold, and is therefore entitled to recover damages for non-economic loss.

99 I return to the application of the *Wrongs Act* to the assessment of Turner's claim in Chapter XIX.

100 The defendants further rely on the applicable State and federal civil liability legislation in respect of the determination of individual group members' claims. This does not need to be further addressed in these reasons.

VII. WITNESSES

Lay witnesses

Turner

Lorraine Shields

101 Lorraine Shields is Turner's mother. She lives in Mount Gambier and is a registered nurse. Turner lived with Shields for brief periods of time in late 2015 and late 2016.

Jason Smith

102 Jason Smith is Turner's partner. They began dating in November 2015 and he lived with her in Ballarat between around March 2018 and June 2019.

Defendants

Ulrike Bodesheim

103 Ulrike Bodesheim is the current head of regulatory affairs, strategy, cardiology and nephrology for the second defendant, Bayer AG. Bodesheim worked within the Global Regulatory Affairs team at Bayer AG from about June 2006, and was head of the Regulatory Affairs Strategy Women's Health Care team from about July 2015 until about March 2021. The latter team is part of the Global Regulatory Affairs team, which is broadly responsible for developing and implementing integrated global regulatory strategies.

Christian Schalk

104 Christian Schalk is a lawyer and the senior trademark counsel at Bayer Intellectual Property GmbH, a fully owned affiliate of Bayer AG. He has been in this role since 2007. He oversees all trademark matters related to the pharmaceutical division of Bayer AG.

Patricia Carney

105 Patricia Carney is a trained doctor who was employed by Bayer HealthCare from 2009 to 2012 and 2013 to 2020. She was the Essure medical lead from 2013 to 2017 and the Essure global safety lead from 2018 to 2020. Carney ceased full-time employment with Bayer in 2020 but continued to provide consulting services in relation to clinical trials, regulatory affairs, benefit/risk management, pharmacovigilance and litigation until about April 2022. This included giving two depositions about Essure in related legal proceedings in the US.

Janet Padgham

106 Janet Padgham is the managing director and co-founder of the fifth defendant, Gytech. Padgham is a trained nurse.

Christine Merrell

107 Christine Merrell is a trained nurse and midwife, and the current corporate development manager of the sixth defendant, AMSL. She was also the national Essure

product expert at AMSL during the period of its distributorship of Essure in Australia. She commenced employment with AMSL in about September 2005 and has held a number of roles within the company since then.

Samy Saad

108 Samy Saad is a trained doctor and the general manager of AMSL. He began working for AMSL in about June 2011. Saad was the corporate development manager from February 2012 and the medical division manager from July 2013 until March 2016. He then worked as the division manager (diabetes and medical) from March 2016 to August 2021, before taking up his current role.

Suhayl Khan

109 Suhayl Khan is a trained pharmacist who began working for AMSL as a corporate development associate in January 2014. In early 2015, Khan transitioned into a quality assurance and regulatory affairs role.

Expert witnesses

110 The expert witnesses gave evidence under the following topic headings:

(a) Gynaecology specific to Turner: Dr Bernadette White and Associate Professor Alan Lam;

(b) Gynaecology: Professor Andrew Korda and Dr Sawsan As-Sanie;

(c) Pathology: Professor Sarah Robertson and Dr Tricia Murdock;

(d) Immunology: Professor Sarah Robertson and Associate Professor Caroline Sokol;

(e) Biomaterials: Professor Sarah Robertson, Professor Wojciech Chrzanowski, Dr Stephen Badylak and Dr Lawrence Eiselstein;

(f) Epidemiology: Professor Ian Gordon, Professor Val Gebski and Dr Arthur Brandwood; and

(g) Regulatory: Kea Dent and Dr Arthur Brandwood.

111 Each of the experts prepared primary reports, and in some cases reply and supplementary reports. Conclaves were held, joint expert reports ('JERs') were prepared, and the experts gave concurrent evidence under each of the above topic headings.

112 Two further experts gave evidence. Dr David Weissman prepared a medico-legal psychiatric report in relation to Turner that was tendered. Weissman did not give oral evidence.

113 Dr David Rosen is a gynaecologist who gave evidence about Essure training, performing the Essure procedure and contraception generally.

Turner gynaecology

Bernadette White

114 Bernadette White has worked in Melbourne as an obstetrician and gynaecologist since 1988. She was appointed as the clinical director of obstetrics at the Mercy Hospital for Women in 2003. She is included on the Royal Australian and New Zealand College of Obstetricians and Gynaecologists ('RANZCOG') register of expert witnesses qualified to give an opinion in the area of general obstetrics and gynaecology.

Alan Lam

115 Alan Lam is a gynaecologist and clinical associate professor at Northern Sydney Medical School where he teaches about pelvic pain and endometriosis. He is the director of the Centre for Advanced Reproductive Endosurgery. Lam was previously the chair of the RANZCOG Endometriosis Online e-Learning Resources Steering Committee and the president of the Australian Gynecological Endoscopy and Surgical Society. He was also on the editorial board of the *Journal of Minimally Invasive Gynecology* from 2005 to 2007.

116 I do not accept Turner's criticism that Lam acted as an advocate rather than an

independent expert. In his comprehensive primary report, Lam set out in a detailed and even-handed fashion the relevant clinical history, reported scans and surgical outcomes. Lam gave a fulsome explanation of gynaecological conditions to be considered as part of a differential diagnosis. His report contains a great deal of information about current standards and diagnostic processes. Lam did seem relatively determined to settle on a diagnosis for Turner's symptoms. However, I conclude that this was a matter of enthusiastic scientific enquiry and not advocacy for the defendants' case.

Gynaecology

Andrew Korda

117 Andrew Korda has practised in Sydney as a gynaecologist and urogynaecologist since 1969. He has held university and teaching appointments in obstetrics, gynaecology and urology in Australia and overseas since the mid-1970s. His experience includes the management of reversible and permanent contraception, and hysteroscopic and laparoscopic procedures. He has performed six hysterectomies to remove Essure devices over a period of 10 to 15 years. He has not personally implanted an Essure device.

Sawsan As-Sanie

118 Sawsan As-Sanie is an associate professor, co-chief of gynaecology, and director of minimally invasive gynaecological surgery in the department of obstetrics and gynaecology at the University of Michigan. She is director of the University of Michigan Chronic Pelvic Pain and Endometriosis Consultative Clinic. In addition to her specialist training in obstetrics and gynaecology, As-Sanie completed a further two years to obtain additional sub-speciality training in complex gynaecologic surgery with a large focus on CPP and endometriosis, together with an additional year in order to obtain a masters in public health and epidemiology. As-Sanie devotes half her work time to clinical practice that involves receiving referrals from other physicians of patients who have complex gynaecological conditions including CPP,

endometriosis, uterine fibroids, abnormal bleeding and/or ovarian masses. The balance of As-Sanie's work is taken up with teaching and training other physicians, supervising a team of clinicians and in her leadership positions, which included presidency of the International Pelvic Pain Society in 2018. She has given over 100 scientific lectures at national and international meetings on the topics of pelvic pain, dysmenorrhea, endometriosis, and AUB.

119 As-Sanie routinely treats women who have undergone Essure sterilisation, including evaluation of CPP and AUB.

120 As-Sanie has impressive research and clinical expertise and experience addressing complex gynaecologic disorders, particularly pelvic pain, dysmenorrhea and CPP. Her evidence about the presentation, causes and treatment of pelvic pain and AUB was comprehensive and clear.

121 As-Sanie's qualifications and expertise in epidemiology and biostatistics do not match those of Gordon (at [148]-[149] below). However, her analysis of relevant studies was informed by her unchallenged expertise in research and treatment of the gynaecological disorders of interest, and her unmatched clinical experience in the treatment of women with Essure devices implanted.

Pathology

Sarah Robertson

122 Sarah Robertson is a professor in the faculty of health science and biomedical researcher at the University of Adelaide with a PhD in reproductive immunology. She has specialised knowledge in reproductive biology, reproductive biomedicine, reproductive endocrinology, the immune causes and consequences of disease and injury, and the immunopathology of the female reproductive tract. She is the author or co-author of around 230 publications related to her areas of research and was editor of the *Journal of Reproductive Immunology* for four years from 2009. She is experienced in the development and commercialisation of interventions in reproductive medicine,

and has worked as an adviser and consultant to commercial organisations and government on this topic.

123 Turner submitted that:

(a) Robertson is a highly credentialled biomedical scientist with specialised knowledge in reproductive physiology and immunology whose career spans 30 years.

(b) Robertson has extensive experience and training in reviewing reproductive tissue histopathology and interpreting those results by reference to the body's immunological response.

(c) Robertson is involved in specialised research centres around reproductive immunology and the immune response of the fallopian tube, uterus, ovaries and female reproductive tract. She is a leading researcher and her knowledge and experience in this area is unmatched by any other expert in this proceeding. Her training and experience in immunological responses of the female reproductive system to stimuli put her in a unique position to opine and assist the Court with respect to the scientific issues in dispute.

(d) Robertson gave evidence in three separate concurrent evidence sessions in this proceeding, spanning twelve sitting days. Her opinions remained consistent and were clearly expressed. Robertson's independence as an expert witness was never challenged.[45]

124 The defendants submitted that Robertson's evidence should be considered in light of the following:

(a) Robertson gave evidence that she approached her task of giving expert evidence in this proceeding as a 'brainstorm'. Rather than confining her evidence to hypotheses for which she could identify direct (or even indirect)

[45] SBM.001.001.0004 at 83 [240].

evidence in support, her written evidence extends to hypotheses that are apparently without any evidentiary support, and are more accurately characterised (by Robertson herself) as possibilities or mere 'biological plausibilities'. The chief consequence of this is that her evidence is voluminous, ranges far beyond the scope of Turner's pleaded case, and makes it difficult for the Court to distinguish between:

(i) opinions without scientific support;

(ii) extrapolations from different circumstances to Essure; and

(iii) opinions for which there is actual, direct evidence of their application to Essure.

This is a significant problem because the probative weight of each category of evidence is not equal.

(b) She was prepared to venture opinions that she was unqualified to give.

(c) During the course of her oral evidence, there were occasions where it was revealed that certain studies Robertson cited in her written evidence did not, in fact, stand for the propositions for which they were cited.

(d) During oral evidence, she not infrequently sought to defend unreasonable or extreme contentions and/or failed to make reasonable concessions during cross-examination.[46]

125 Robertson's primary report is 203 pages.[47] Her reference list of scientific studies and articles runs to a further 18 pages. Robertson also prepared a 177-page reply report,[48] a 16-page supplementary report,[49] and made significant contributions to the pathology, immunology and biomaterials JERs. Robertson's written evidence is

46 SBM.500.001.0003_2 at 654 [5.35].
47 EXP.001.001.0127_2.
48 EXP.001.002.0015_2.
49 EXP.001.002.0020_2.

replete with interrelated theories and hypotheses. She was asked in cross-examination the following question about her approach to preparing her evidence in chief:

> … Your report on one level represents a little bit of a brainstorm, doesn't it, an educated one but one where you are sitting down and identifying all of the ways in which you possibly can, that you think this device might contribute to either a failed wound healing response or other adverse effects on patients?---Yes, I have tried to give a full response and I think that I've used appropriate language to discriminate and to … indicate very clearly … how strong I consider the evidence to be and what is the sort of biological rationale … [T]here's a big distinction between a hypothesis, a theory, and a fact… and then there is a huge space in the middle. A lot of what scientists do is find the right words and terms to discuss that space in the middle and to provide the right weighting to and use language appropriately to ensure that a qualified person reading that information will understand the weight of evidence. In this case I've used the word 'could' … to indicate that this is a possibility in my mind … I have used appropriate language to distinguish things that are based in strong evidence from things that are more at the theoretical end.[50]

Robertson's approach to giving evidence made it necessary to carefully examine the language she used when espousing a hypothesis or theory, or giving an opinion about its relevance, and whether there was evidence in scientific studies or articles, or from other sources, to support it.

126 The broad and complex evidence given by Robertson in the proceeding, and her participation in the pathology, immunology and biomaterials conclaves and concurrent evidence sessions, meant that it was important to keep the boundaries and limits of her expertise in mind. Relevant concessions made by Robertson in oral evidence included:

(a) acknowledging that while she has some understanding of 'epidemiological studies', an epidemiologist was better placed than her to comment on the epidemiological studies;[51]

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50 T4142-3 (TRA.500.041.0001_2 at 0060_10–0061_8).

51 T4372 (TRA.500.043.0001_2 at 0090_18).

(b) accepting that while she works closely with gynaecologists and obstetricians, she is not a qualified or practising gynaecologist or clinician;[52]

(c) agreeing that she did not have the benefit of a gynaecologist's clinical experience and consultation with real patients;[53]

(d) accepting that she is 'not an expert in how metal devices break down in the body'[54] or 'corrosion of devices in salt baths in laboratories and the physics of that';[55]

(e) saying, when asked about the histology studies:

> … I'm not a biostatistician and I'm not a clinician and, as I've indicated in my reports, I'm aware of these studies and I'm aware that they align with and are consistent with my biological interpretations and synthesis of facts, but I'm going to be cautious about being drawn on inferring information from them given the boundaries of my expertise.[56]

127 Robertson said that while she was not a qualified pathologist, she had trained in immunology, a key component of which involved histological evaluation of tissues. She said she uses histological and pathological approaches to understand the component parts of the female reproductive tract.[57] Robertson said she had evaluated fallopian tube and uterine tissue on many occasions over the course of her career.

128 I give further consideration to Robertson's evidence throughout these reasons.

Tricia Murdock

129 Tricia Murdock is a clinical faculty member of the gynaecologic pathology division at John Hopkins Hospital in the US. She has a bachelor of science in biochemistry and a degree in medicine. She completed an obstetrics and gynaecology residency in 2012 and in that time became familiar with Essure and implanted devices in several

52 T4372 (TRA.500.043.0001_2 at 0090_26).
53 T4372 (TRA.500.043.0001_2 at 0090_30).
54 T4433 (TRA.500.045.0001_2 at 0003_30-1).
55 T4439 (TRA.500.045.0001_2 at 0009_29-31).
56 T4253 (TRA.500.042.0001_2 at 0031_2).
57 T2692 (TRA.500.029.0001_2 at 0038_14-6).

patients. She has also completed pathology residencies at the University of Vermont and John Hopkins Hospital. Murdock's daily clinical work involves reviewing specimens from the fallopian tube, broad ligaments, ovaries, uterus, endometrium, vulva and vagina. Murdock is also involved in research projects focused on discovering the different genes that cause gynaecologic cancer, and is the author or editor of pathology textbooks.

130 Turner submitted that unlike Robertson, Murdock is in the early stages of her career; is not a leader in her field; has only authored a small number of publications; and has not held any editorial positions. I reject this criticism. Murdock trained as a gynaecologist and obstetrician, and is a qualified clinical pathologist who specialises in gynaecologic pathology. In her work as a clinical pathologist Murdock examines an average of between 30 and 40 fallopian tube tissue samples per day, as well as other tissue samples from the female reproductive tract.[58] While Robertson has undertaken some training in pathology, she is not formally qualified as a clinical pathologist. I conclude that in the specialist field of clinical pathology Murdock's expertise and experience is superior to that of Robertson. For reasons I will come to, I reject Turner's criticism that Murdock took extreme positions in her evidence that were unsupported by authorities she cited or other evidence.

Immunology

Caroline Sokol

131 Caroline Sokol is an Assistant Professor in Medicine at Harvard Medical School and an Assistant Physician in Medicine at Massachusetts General Hospital, with a speciality in allergy and immunology. She has a bachelor in biochemistry and masters of chemistry from the University of Pennsylvania, and a medical degree and PhD in immunology from Yale University School of Medicine. Sokol is a diplomate of the American Board of Internal Medicine and the American Board of Allergy and Immunology. She is also a fellow of the American Academy of Allergy, Asthma and

[58] T2668, 2670 (TRA.500.029.0001_2 at 0014, 0016).

Immunology. Sokol's research focuses on the mechanisms which drive immune cell recognition of and activation to allergens; by which peripheral neurons affect immune cell function; by which immune cells initiate allergic immune responses; and by which immune cells move in response to allergens. She has authored multiple peer-reviewed research articles and reviews and presented internationally on these topics.

132 Turner made a number of criticisms of Sokol's evidence. First, she submitted that Sokol was fairly junior in her speciality compared to Robertson. Turner noted Sokol's evidence where she accepted she had no immunology specialty in the reproductive biologic context, and had not published any papers on that topic. These matters do not devalue Sokol's evidence. She is obviously a very well-qualified immunologist with the advantage of a clinical practice. I generally found her opinions to be logical, clearly explained and well supported by her cited articles and studies.

133 Second, Turner criticised Sokol for acting as a paid consultant for Bayer since 2020. Sokol properly disclosed this matter in her primary report. Sokol was not retained by Bayer. She has consulted on and off since 2020, giving opinions on hypersensitivity reactions to metals and systemic hypersensitivity reactions to biomedical implants. Neither Sokol's consultancy work nor the manner in which she gave her evidence demonstrated any lack of independence as an expert.

134 Third, Turner criticised Sokol for resiling from positions of agreement taken in the immunology conclave. I deal with this issue at [783] of these reasons. I accept Sokol's evidence that there is no inconsistency between the agreed positions in the immunology conclave and her evidence in the concurrent session.

Biomaterials

Wojciech Chrzanowski

135 Wojciech Chrzanowski is a professor of nanomedicine at the University of Sydney with a PhD in biomedical engineering. His specialty is biomaterials and biomedical engineering. A focus of his work has been the characterisation and assessment of

interactions between biomaterials and biological systems. He has lead the Nanomedicine and Nano-Bio-Characterisation laboratory in the faculty of medicine and health at the University of Sydney since 2010, and in 2017 became the health and medicine team leader at the University of Sydney 'Nano Institute'. He has published over 200 peer-reviewed articles, edited three books and has five patents. He has advised the World Health Organisation on methods to assess risks of nanomaterials.

136 Turner submitted that Chrzanowski's experience as a biomedical engineer was unmatched by any other expert called in the proceeding. The defendants submitted that the weight attributed to Chrzanowski's evidence should be reduced because he not infrequently sought to defend unreasonable or extreme contentions, and was prepared to venture opinions that he was not qualified to give.

137 I accept that Chrzanowski's evidence about what he and Robertson described as the 'fundamental tenets' of biocompatibility can be criticised.[59]

138 The occasions when Chrzanowski strayed into giving evidence outside his field of expertise did not substantially undermine his biomaterials evidence.

Lawrence Eiselstein

139 Lawrence Eiselstein is a metallurgist, corrosion engineer and the principal engineer at Exponent, the largest engineering firm in the US. He has consulted on design analysis and testing for FDA approval of numerous types of implantable devices manufactured from plastics, ceramics, stainless steel, superelastic Nitinol, cobalt-chromium alloys and other materials. Eiselstein is also a licensed professional engineer in the fields of metallurgical engineering and corrosion engineering in California.

140 The defendants emphasised Eiselstein's 40 plus years' experience as a metallurgist and corrosion engineer, specialising in material science as applied to product design and material testing and evaluation. They submitted that Eiselstein has extensive medical

[59] See Chapter XI.

device consulting experience for FDA approval design analysis and testing, including but not limited to devices manufactured from stainless steel and super elastic nitinol, and has conducted numerous corrosion resistance, metal leaching and fretting quantification tests for FDA submissions. They submitted that Eiselstein has published extensively on corrosion, durability and metal testing, and has been part of American Society for Testing and Materials ('ASTM') committees for implantable medical devices which focus on developing appropriate test standards.

141 Turner criticised Eiselstein for adopting a selective approach when commenting on the published studies on device corrosion and metal leaching. I reject this criticism.

142 While both Chrzanowski and Eiselstein are very well qualified, I considered Eiselstein's lengthy experience more pertinent to the biomaterials issues in this case. Eiselstein's experience related more directly to design analysis and testing of biomedical devices relevant to the process of FDA approval. Eiselstein comprehensively analysed the biomaterials issues and the relevant evidence. His reasoning from that foundation was clear and considered, and based on his considerable expertise. He comprehensively analysed the corrosion testing undertaken on Essure, relevant testing standards, and the outcomes of corrosion studies relating to the device.

Stephen Badylak

143 Stephen Badylak is the deputy director of the McGowan Institute for Regenerative Medicine and the director of the Centre for Preclinical Studies at the University of Pittsburgh. Badylak has trained as a veterinarian, a clinical pathologist, an anatomic pathologist (PhD), a medical doctor, and a biomaterials scientist. He practiced clinical medicine from 1985 to 2001 and has conducted research since 1985 in the field of biomaterials related to tissue engineering and regenerative medicine, and the design of implantable surgical mesh devices including polypropylene. Badylak has authored more than 400 peer-reviewed articles in this area of study. Badylak has served on advisory committees for the FDA and has participated in the preparation of

applications to the FDA for approvals, clearances, and labelling of new medical devices. He is a member of the immunology devices panel of the medical devices advisory committee at the FDA.

144 The defendants emphasised Badylak's qualifications as a medical doctor, clinical pathologist, anatomic pathologist and biomaterials scientist with 38 years' research experience.

145 Turner submitted that despite Badylak's experience and credentials, he presented as an advocate who was unwilling to accept any evidence of active inflammation. Turner submitted that Badylak actively sought to explain every case report of chronic inflammation associated with Essure as 'normal' and 'expected', despite a contradictory position in his own expert report concerning the hallmarks of inflammation. She submitted that Badylak's evidence about chronic inflammation strained logic and could not be accepted. I accept that Badylak sometimes delivered his evidence in a lecture-like manner. While the strength with which Badylak expressed his opinions may not have always been justified, I do not accept that he presented as an advocate.

146 Turner also criticised Badylak as being untruthful when he said repeatedly in cross-examination that he had not seen the acute and chronic inflammation graphs and some histologic section assessments from the pre-hysterectomy study,[60] which had in fact been previously shown to him in a conference with counsel. Badylak explained that he did not recall having previously seen the documents, that he had been shown many documents, and that he had recently arrived from the US before the conference and was tired. I do not conclude that Badylak was being untruthful when giving his evidence about these documents in cross-examination. As Badylak said, there was no reason for him to deny having seen the documents.

147 When he was challenged on these matters, Badylak said that his credibility had never

[60] See Chapter X.

been questioned before. A decision of the United States District Court for the Eastern District of Virginia which contained comments on him as an expert witness was put to Badylak. He said that he had not seen the document before. In the circumstances, that aspect of cross-examination went nowhere.

Clinical data

Ian Gordon

148 Ian Gordon is a professor of statistics and director of the Statistical Consulting Centre at the University of Melbourne. He has worked as an applied statistician for approximately 40 years and is accredited by the Statistical Society of Australia. He has a PhD in statistics from the University of Melbourne and has worked on research projects for government, business, industry and academia, including published work on randomised trials in the field of medical statistics.

149 Gordon has unquestioned expertise in biostatistics and epidemiology. His evidence was clear and precise. The reasoning to his expressed conclusions was transparent and logical. My only reservation is that in his evidence in chief, Gordon focused on the weaknesses and limitations of the available biostatistical evidence. It was only in cross-examination that Gordon agreed that some of the studies comparing adverse outcomes from Essure and laparoscopic sterilisation were of some value in assessing the safety of Essure. Further, I have rejected Gordon's criticism of the approach taken by As-Sanie to analysis of the comparative studies.

Val Gebski

150 Val Gebski is a professor of biostatistics and research methodology at the University of Sydney. He is involved in curriculum development and teaching in public health, clinical epidemiology and medicine at the university. He is a senior biostatistician at the Crown Princess Mary Cancer Care Centre based at Westmead Hospital, Sydney and an honorary fellow of the Royal Australian and New Zealand College of Radiologists. He is the group statistician for several national collaborative clinical trials groups in oncology including Breast Cancer Australia, the Australian Gastro-

Intestinal Trial Group and ANZ Gynaecological Oncology. He is also a member of a number of editorial committees including the statistical editor at the *ANZ Journal of Surgery*, associate editor of *Pharmaceutical Statistics*, and the *American Journal of Clinical Oncology*.

151 Turner submitted that on contentious matters, Gebski's written and oral evidence was unreliable and should be rejected. She submitted that Gebski's evidence was contaminated by undisclosed interactions with the defendants' lawyers, that he was unwilling to bring an independent mind to the questions on which he was briefed, and was unwilling to give responsive answers or make obvious concessions in oral evidence.[61]

152 I reject Turner's criticisms. Little turns on the fact that Gebski did not disclose in his reports that the outcomes he attempted to measure using his pooled analysis were suggested by the defendants' lawyers. There was nothing inappropriate about the outcomes that Gebski analysed. While Gebski's evidence at times lacked the clarity achieved by Gordon, I do not agree that he was an unresponsive witness.

Regulatory

Kea Dent

153 Kea Dent is the managing director of KD&A Pty Ltd, an Australian based company established in 2005 which provides regulatory and quality management system advice to medical device companies selling on Australian and international markets. Dent founded and was the managing director of Dentsleeve Pty Ltd, a medical device (gastrointestinal catheter) manufacturing business from 1993 to 2003. During that time, Dent said she obtained the regulatory approvals required for supply of the device in 44 countries.

Arthur Brandwood

154 Arthur Brandwood is a medical device and biomaterials development and regulation

[61] SBM.001.001.0004 at 145 [452].

expert. He has experience in applied research teaching, the manufacturing industry, as a senior officer for the TGA, and as an advisor to government regulatory agencies and industry bodies. He holds a PhD in biomechanics and is a chartered engineer through the UK Institute of Materials, Minerals & Mining and the UK Council of Engineering. He founded medical devices regulatory consultancy firm Brandwood Biomedical in 2000 and clinical research organisation DevDx Clinical in 2012. He is the chair of Standards Australia He-30, the Australian committee responsible for preparation of technical standards on biological safety of medical devices.

Remaining experts

David Weissman

155 David Weissman is a consultant psychiatrist engaged by Turner for the purposes of providing a medico-legal psychiatric review and report. He obtained a bachelors of medicine and surgery and a masters in psychological medicine from Monash University, and is a fellow of the Royal Australian and New Zealand College of Psychiatrists. Weissman has completed Impairment Assessment Training, sat on medical panels and performed over 14,000 medico-legal assessments.

David Rosen

156 David Rosen is a gynaecologist with a special interest in minimally invasive (laparoscopic) gynaecological surgery. He is the director of the Sydney Women's Endosurgery Centre and the Centre of Excellence programme for that group. Rosen has performed over 150 Essure procedures and was engaged by Conceptus as a contractor from 2000 to 2005 to train fellow gynaecologists in the procedure. He has also lectured widely and published in Australian and international journals on the Essure procedure.

VIII. GYNAECOLOGICAL CONDITIONS

157 Turner alleges that Essure caused adverse events that are broadly described as CPP, dysmenorrhea and AUB. It is relevant to describe those conditions and to say

something about their prevalence and aetiology.

Pelvic pain and dysmenorrhea

158 Pelvic pain is any pain that occurs in the lowest part of the abdomen and pelvis,[62] which can sometimes radiate to the lower back, buttocks or thighs. Pelvic pain can be acute, lasting less than three to six months, or chronic, lasting three to six months or longer.

159 As-Sanie said the patterns of persistent pelvic pain that can occur over time:

> … include chronic non-menstrual pain (often referred to as "chronic pelvic pain"), dysmenorrhea, dyspareunia, dysuria, and dyschezia. While some women experience only one type or pattern of pain, most women with persistent pelvic pain experience a combination of two or more of these patterns of pain. Each pattern of pain symptoms can occur as a consequence of many different underlying conditions and any given condition can have a variety of pain patterns. This means that while the pattern of symptoms can help narrow the differential diagnosis, diagnosing the cause (or causes) of pelvic pain cannot be done solely based on the pattern of pain.[63]

160 CPP occurs on most days of the month and is severe enough to cause functional disability or lead to medical care. As-Sanie said that:

> CPP affects approximately 15% of women in the United States and contributes substantially to direct and indirect healthcare spending as it is the primary indication for up to 20% of gynecologic office visits, 40% of hysterectomies performed by laparotomy or laparoscopy for benign indications, and 40% of gynecologic diagnostic laparoscopies.[64]

161 Dysmenorrhea, which is painful menstruation or pelvic pain during menstrual periods, is further sub-classified as 'primary' or 'secondary':

> Primary dysmenorrhea is painful menstruation in the absence of anatomic pathology, whereas secondary dysmenorrhea is painful menstruation in the presence of anatomic pathology, such as endometriosis or adenomyosis.[65]

As-Sanie said:

> Dysmenorrhea is the most common pain disorder among women, estimated to affect approximately 40-90% of women in their reproductive years. Up to 20%

62 As-Sanie at 15 [48] (EXP.001.002.0005).
63 Ibid.
64 Ibid at 15-16 [50].
65 Ibid at 16 [51].

> of women report pain severe enough to interfere with usual activities. … While the mechanism of pain is not fully understood, an overproduction of uterine prostaglandins has been shown to contribute to myometrial hypercontractility, arteriolar vasoconstriction, and endometrial ischemia.[66]

162 Dyspareunia is defined as pain with sexual intercourse.

163 Dysuria is defined as pain with urination.

164 Dyschezia is defined as pain with bowel movements.[67]

165 As-Sanie explained that because there are so many conditions within the pelvis that can contribute to symptoms, the evaluation and management of CPP is usually complex. She said that most often '[CPP] is associated with several diagnoses arising from multiple conditions and treatment is multimodal but not curative'.[68]

166 As-Sanie explained that there are no standard clinical tests or radiological studies for women with CPP. Rather, the tests and studies that are applied are guided by clinical history and physical examination. There are a large range of conditions that can cause or contribute to CPP. The following table, taken from As-Sanie's expert report, summarises the conditions in each organ system which can be associated with dysmenorrhea and CPP.[69]

System	**Conditions**
Gynecologic	Endometriosis*, leiomyomata (uterine fibroids)*, adenomyosis*, ovarian remnant syndrome*, pelvic inflammatory disease*, pelvic adhesions, adnexal/ovarian cysts, chronic post-ablation tubal sterilization syndrome
Gastrointestinal	Irritable bowel syndrome (IBS)*, inflammatory bowel disease*, celiac disease, abdominal/pelvic hernias
Urologic	Interstitial cystitis/painful bladder syndrome*, radiation cystitis*, recurrent urinary tract infections, urethral syndrome, recurrent/chronic urolithiasis
Musculoskeletal	Abdominal wall myofascial pain (including trigger points)*, coccygodynia*, degenerative disk/joint disease, fibromyalgia*, pelvic floor tension myalgia*, stress fractures
Neurologic	Central sensitization of pain*, pudendal neuralgia, abdominal wall nerve entrapment (ilioinguinal and iliohypogastric)*

66 Ibid at 16 [52].
67 Ibid at 16 [53].
68 Ibid at 17 [56].
69 Ibid at 20.

Vascular	Pelvic congestion syndrome*, vulvar varicosities

* Conditions excluding cancer associated with to chronic pelvic pain. The condition marked with an asterisk (*) are those that there is high-level evidence for a causal relationship with CPP.

As-Sanie emphasised that:

> … the presence of any of these conditions does not always cause pain and even when one or more of these conditions is present, they [are] not necessarily the cause of pain or the only cause of pain in an individual patient.[70]

Similarly, White said that pelvic pain is a very complex condition which is not well understood, and that in some women there will be no detectable pathology to explain their pain.[71] White said that the fact that hysterectomy surgery does not relieve CPP for some women indicates that in those cases, the underlying mechanism of pain is not understood.[72]

167 As-Sanie said that the most common gynaecological causes of pelvic pain and dysmenorrhea are endometriosis, adenomyosis, leiomyomas, intra-abdominal adhesions, pelvic inflammatory disease ('PID'), pelvic congestion syndrome, ovarian remnant and residual ovarian syndrome and gynaecologic malignancy.

168 As-Sanie described endometriosis as 'a systemic, chronic inflammatory disease characterised by the growth of endometrial-like tissue outside of the uterus'. She said that endometriosis was the most common gynaecological cause of CPP and dysmenorrhea.[73] She said that 10% of reproductive-age women suffer endometriosis, but that the condition may not cause dysmenorrhea or CPP and 'the presence and severity of endometriosis does not correlate with symptom severity'.[74]

169 Adenomyosis is characterised by the presence of endometrial glands and stroma within the myometrium. It is a common disorder in reproductive-age women but its relationship to CPP is not fully understood. Symptoms are variable and a significant

70 Ibid at 20 [70] (emphasis in original).
71 T1888-9 (TRA.500.019.0001_2 at 0043_5 – 0044_1).
72 T1889 (TRA.500.019.0001_2 at 0044__11).
73 As-Sanie at 21 [72] (EXP.001.002.0005).
74 Ibid.

proportion of cases are asymptomatic.[75]

170 Most women are affected by leiomyomas (uterine fibroids) during their lifetime. As-Sanie said that peritoneal adhesions develop following most abdominal surgeries, though in varying severity. However, As-Sanie said that the relationships between these disorders and CPP is poorly defined.[76]

171 As-Sanie said that PID 'refers to acute (fevers, pain, elevated white blood cell count, and tenderness on exam) or subclinical infection (no symptoms of fever or tenderness, but infection is still present and causes sequela) of the upper genital tract in women'.[77] She said that the self-reported lifetime prevalence rates of PID range from approximately 3% to 10%, and that up to 30% of women with PID subsequently develop CPP.

172 As-Sanie said that the non-gynaecological causes of pelvic pain included irritable bowel syndrome ('IBS'), interstitial cystitis/bladder pain syndrome ('IC/BPS'), myofascial pelvic pain syndrome ('MPPS') and fibromyalgia.

173 Approximately 10% of the population has symptoms compatible with IBS. Women are diagnosed more often than men. As-Sanie said that CPP has been reported as occurring in up to 35% of women diagnosed with IBS, but that 'in many women with CPP and IBS, the IBS has not been diagnosed or treated'.[78]

174 A diagnosis of IC/BPS is applied to patients with chronic bladder pain and urinary urgency and frequency in the absence of other etiologies. It is a common cause of CPP.[79]

175 As-Sanie described myofascial pelvic pain as 'pain that arises from dysfunction, spasticity, and/or hypersensitivity of the muscle, fascia, or joints in the abdominal

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75 Ibid at 21 [73]; Gynaecology JER at 5 (EXP.500.001.0005).
76 As-Sanie at 22 [74]-[75] (EXP.001.002.0005).
77 Ibid at 22 [76].
78 Ibid at 24 [81].
79 Ibid at 24 [82].

wall, pelvic floor, and/or low back'.[80] She said that MPPS 'is an extremely common but under-recognized source of pain in women with CPP'.[81]

176 Fibromyalgia is a chronic pain syndrome characterised by sensitisation of the central nervous system. CPP is sometimes identified as the primary symptom in women with fibromyalgia.

177 As-Sanie said that the evaluation of women with CPP must also take into account the correlation with psychosocial disorders, opioid dependency, any history of physical or sexual abuse, depression and other mood disorders.[82]

Abnormal uterine bleeding and menorrhagia

178 AUB is any uterine bleeding that is abnormal in quantity, duration or schedule in reproductive-age, non-pregnant women.[83] Menorrhagia or 'heavy menstrual bleeding' is defined as 'excessive menstrual blood loss that interferes with a woman's physical, social, emotional or material quality of life'.[84]

179 In the gynaecology JER, Korda and As-Sanie agreed:

> [A]bnormal bleeding is a less challenging issue when associated with a sterilization because it can be treated by medical therapy (such as hormonal contraceptive medications), can be cured by a hysterectomy and is a very common condition in any event.[85]The acronym 'PALM-COEIN' refers to the causes of AUB and is widely used to guide the evaluation and management of the condition. 'PALM' refers to the structural causes of AUB, being polyps, adenomyosis, leiomyoma and malignancy. 'COEIN' refers to non-structural causes — coagulopathy, ovulatory, endometrial, iatrogenic and 'not-yet-classified'.

180 Endometrial polyps are common, but women with this condition are often asymptomatic. Among patients with symptoms of endometrial polyps, intermenstrual bleeding is the most frequent symptom.[86]

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80 Ibid at 24 [83].
81 Ibid.
82 Ibid at 27 [93].
83 Ibid.
84 Ibid at 28 [94].
85 Gynaecology JER at 9 [24] (EXP.500.001.0001).
86 As-Sanie at 29 [98] (EXP.001.002.0005).

181 As-Sanie said that 'many patients with adenomyosis do not have symptoms of AUB, and others describe heavy, prolonged or painful menstrual periods'.[87]

182 Approximately 25% of patients with leiomyomas experience bothersome symptoms, most commonly AUB and pelvic pain.[88]

183 As-Sanie said that 15% to 29% of women presenting with heavy menstrual bleeding have some type of predisposition to a bleeding disorder.[89]

184 Ovulatory dysfunction is one of the most common causes of AUB. The '[p]ossible causes of ovulatory dysfunction include postmenarche and menopausal transition, polycystic ovarian syndrome ('PCOS'), thyroid disease, liver and kidney disease, and stress or poor nutrition'.[90]

185 Endometrial dysfunction refers to the disturbance of molecular and cellular mechanisms responsible for regulation of the volume of blood lost at menstruation. Relevant conditions 'include local endometrial hemostasis disorders, endometritis and pelvic inflammatory disease'.[91]

186 Iatrogenic causes of AUB include hormonal contraceptives and anticoagulants.

187 White said that in many women who have hysterectomy surgery because of heavy and painful periods, pathological examination does not reveal a specific pathological cause such as uterine fibroids, infection or adenomyosis. In those cases, it is assumed that the symptoms relate to some unidentified dysfunction or pathology in the endometrium.[92]

IX. CONTRACEPTION

87 Ibid at 29 [99].
88 Ibid at 29 [100].
89 Ibid at 29 [102].
90 Ibid at 30 [103].
91 Ibid at 30 [104].
92 T1887 (TRA.500.019.0001_2 at 0042_10).

188 Pregnancy and childbirth carry risks of morbidity and mortality.[93] All forms of female contraception carry risks and benefits.[94] Access to contraception and the opportunity to choose a form of contraception that is appropriate to individual needs are important health issues.

189 Female tubal sterilisation is the most commonly used form of contraception worldwide.[95] Other common methods include oral contraception, condoms, intrauterine devices ('IUD') and injectables.

190 Female tubal sterilisation 'prevents conception by blocking transporter sperm from the lower genital tract to an ovulated oocyte'.[96] Laparoscopic sterilisation is the main method for permanent contraception. A common method involves placement of Filshie clips, which are made of silastic with a titanium coating, across the lumen of the fallopian tubes. The surgery is performed under general anaesthetic and involves inserting a laparoscope into the abdomen through the umbilicus via a trocar. Risks of the procedure include damage to pelvic organs and blood vessels with insertion of the trocar, incorrect placement of the Filshie clip and subsequent pregnancy, and post-operative pain associated with the abdominal incisions, the procedure itself and placement of the Filshie clip. Patients often require one to three days' rest to recover from surgery.[97]

191 The risks and benefits of other contraceptive options were discussed by Rosen. In summary he said:

(a) While condoms are universally available and have spontaneous application, they have a high failure rate and are generally rejected by long-term couples who do not wish to conceive again.[98]

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93 As-Sanie at 9 [24] (EXP.001.002.0005); Korda at 6 [5.7] (EXP.001.001.0025).
94 As-Sanie at 9 [24] (EXP.001.002.0005); Korda at 14 [33.1] (EXP.001.002.0011); Rosen at 18 [7.1] (EXP.001.002.0002_2).
95 As-Sanie at 13 [41] (EXP.001.002.0005); Korda at 7 [5.8] (EXP.001.001.0025).
96 As-Sanie at 13 [42] (EXP.001.002.0005).
97 Rosen at 6 [2.1.5]-[2.1.6] (EXP.001.002.0002_2).
98 Ibid at 9 [3.1.1.].

(b) Diaphragms are not commonly used in Australia and lack the benefit of spontaneity, requiring insertion with appropriate spermicide applied 1–2 hours before and 6 hours after sexual intercourse.[99]

(c) Copper IUDs are an effective, long-acting, immediately reversible contraceptive device with no hormonal effect on the user. However, a copper IUD requires removal and replacement every five years; insertion may cause significant discomfort and may not be feasible in the outpatient setting; and may cause an increase in menstrual loss, dysmenorrhea and an increased risk of PID in the user.[100]

(d) The hormonal oral contraceptive pill ('OCP') is the most commonly prescribed and used form of contraception in Australia. Advantages include reduction in menstrual loss and discomfort, accessibility, and that no medical procedure is required. Disadvantages include that the user must remember to take the pill daily, it may compete with other medication, and it carries an increased risk of cardiovascular complications.[101]

(e) Long-acting reversible contraceptives such as the Depo-Provera injection, the Implanon implant and the Mirena IUD are highly effective, reversible on removal and user independent. The disadvantages of these contraceptives include issues or discomfort with insertion, mood changes, acne, spot bleeding and weight gain.[102]

192 Permanent sterilisation can be achieved by hysterectomy or salpingectomy. The risks of salpingectomy include infection, bleeding, trauma to vessels or viscera (pelvic organs) and the risks of laparoscopic entry.[103] I will deal with risks associated with hysterectomy later in these reasons.

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99 Ibid.
100 Ibid at 10 [3.1.2].
101 Ibid at 10 [3.1.3b].
102 Ibid at 10 [3.1.4].
103 Ibid at 6 [2.1.5]; see also 18 [7.1].

X. HISTORY OF ESSURE

193 Conceptus began to develop Essure in 1995. The device was developed to provide women seeking permanent contraception a non-incisional alternative to surgical tubal ligation, which at that time was the most common form of permanent birth control worldwide.

194 Essure was developed in five design concept phases between 1995 to 2001: the 'Alpha' design; 'Beta' design; 'Pre-Gamma' design; 'Gamma' design; and copper/faux cooper[104] versions of the Beta and Gamma designs. Each design concept was clinically evaluated. The Gamma design, with its dynamic outer coil, was ultimately adopted and branded as the Selective Tubal Occlusion Procedural ('STOP') device. The device name changed to 'Essure' in around 2001.[105] The other four designs were not pursued due to issues with either device placement or device retention.

Pre-market testing and clinical studies

Non-clinical laboratory testing

195 Between approximately 1995 and 2002, the early device designs underwent non-clinical laboratory testing[106] which consisted of:

(a) evaluation of navigation and deployment in pig fallopian tubes; tensile testing of raw materials; initial tip fatigue evaluation; release mechanism testing; delivery wire release testing; handle process evaluation; initial corrosion analysis and fibering evaluation (concept testing);

(b) positioning marker evaluation; catheter tip integrity testing; new fibre configuration testing; tracking and retraction evaluation; initial handle

104 BAY-ESSURE-0004422 at 85.
105 Ibid at 8.
106 BAY-ESSURE-0005174; BAY-ESSURE-0006158.

functional testing and initial corrosion/leaching evaluation (feasibility testing); and

(c) tensile testing to show design and process repeatability; functional testing; environmental cycle testing of the final Essure device to show material and component stability; chemical analysis of the etched nitinol material and corrosion analysis (verification testing).

196 The performance categories tested in the non-clinical laboratory testing were flexibility; navigation (tracking); retraction, deployment; disengagement, anchoring/expansive forces; chemistry (including corrosion and other chemical analysis); and magnetic resonance, safety and compatibility.

Animal studies

197 Between 1995 and 1997 Conceptus conducted three studies on rabbits to provide early proof of concept and effectiveness data, and one study on rats to assess the effect of varying amounts of PET fibre and different fibre configurations on the tissue reaction to the device.[107] The conclusion of two of the rabbit studies was that 'the rabbit animal model was a potential viable model in which to conduct effectiveness studies'.[108] The other rabbit study of device effectiveness concluded that an early Essure design iteration prevented conception in 100% of cases in which the inserts were correctly placed. The rat study concluded that a greater amount of PET fibre in the device could possibly result in a more robust tissue reaction, with potential improvement of device retention and effectiveness.[109]

Biocompatibility studies

198 Conceptus also planned biocompatibility testing of Essure components with feedback from the FDA. This included studies on cytotoxicity, sensitisation, genotoxicity, muscle implantation, vaginal irritation, mutagenicity, sub-chronic toxicity and acute

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107 BAY-ESSURE-0004422.
108 Ibid at 76.
109 Ibid.

systemic toxicity.

199 Specific tests included a 12-week muscle implantation study of Essure inserts in rabbits, conducted in 2000 ('12-week rabbit study'). The findings of the pathologist who initially undertook histopathological tissue analysis and reported on the inflammatory tissue response to PET fibres were subsequently reviewed by a second pathologist at Conceptus' request, who reached different conclusions. The outcome and relevance of the 12-week rabbit study was the subject of expert evidence at trial. I will return to this study and that evidence later in these reasons.

200 The biocompatibility tests were reported as showing that Essure did not exhibit toxicity or elicit any evidence of acute or sub-chronic toxicity, and that the results were consistent with the long history of the safe use of the constituent materials in the insert and the well-characterised in vivo response to PET fibre. The biocompatibility studies conducted by Conceptus are summarised in the tables in Schedule 1 to these reasons.[110]

Pre-market clinical studies

201 Following the completion of non-clinical testing, Essure entered the clinical testing phase of development. Four clinical studies were conducted in this phase to measure:

(a) placement feasibility in patients immediately prior to hysterectomy ('peri-hysterectomy study');

(b) placement, safety and the mechanism of action in patients scheduled for hysterectomy ('pre-hysterectomy study');

(c) preliminary long-term safety and effectiveness ('Phase II study'); and

(d) long-term safety and effectiveness to inform the PMA application to the FDA ('Pivotal trial').

110 BAY-ESSURE-0006158 at 30–33.

Peri-hysterectomy study

202 The peri-hysterectomy study was conducted from September 1995 to late 2000. The study was designed to evaluate the feasibility of the five Essure design iterations in terms of device placement and initial safety.[111] Participants enrolled in the study were already scheduled to undergo a hysterectomy, and had Essure inserted after anaesthesia and immediately prior to the start of the hysterectomy procedure. While the study allowed for device placement by either hysteroscopy, ultrasonography or fluoroscopy, the vast majority of evaluations were performed using the hysteroscopic placement method. All data collected on the Gamma design (which eventually became Essure) was gathered from cases performed using hysteroscopic placement.[112]

203 Success in the study was measured by the ability to cannulate and place Essure in the proximal portion of the fallopian tube, either bilaterally or unilaterally.[113] The study was performed using the Gamma device on 99 participants. The procedures were performed by 23 investigators, all of whom were physicians experienced in hysteroscopy. Four of the 99 participants implanted with the Gamma model were excluded from the final data analysis due to the untimely death of one of the investigators.

204 Three percent (3/99) of participants experienced a perforation during the procedure. No other adverse events were reported during the study. Bilateral cannulation was achieved in 80% (76/95) of participants, and unilateral cannulation was achieved in 6.3% (6/95) of participants. Cannulation was not possible in 13.7% (13/95) of participants. Bilateral placement was achieved in 72.6% (69/95) of participants, and unilateral placement was achieved in 12.6% (12/95) of participants. Devices could not be placed in 14.8% (14/95) of participants. Reasons for failure to place the device included thick endometrium, fibroids, prior tubal ligation, and device and cannulation related issues.[114]

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111 BAY-ESSURE-0004422 at 85.
112 Ibid at 86.
113 Ibid at 102.
114 Ibid.

205 Overall, the device could be placed in 96% of tubes accessed (either bilaterally or unilaterally), and 95% of inserts tested were acutely anchored. Immediate occlusion of the fallopian tube was seen in 82% of tubes tested. The study authors concluded that Essure could be reliably and safely placed at a reasonably high rate in the patient population, and was considered feasible and safe for evaluation in subsequent studies.[115] The peri-hysterectomy study was subsequently used as Essure placement training for clinical investigators who participated in the Pivotal trial.[116]

Pre-hysterectomy study

206 The pre-hysterectomy study commenced in October 1998 and was completed in December 2001.[117] The study was conducted by two investigators on 63 participants, all of whom were scheduled for hysterectomy.[118] The objectives of the study were to evaluate:

(a) placement of Essure in the proximal portion of the fallopian tube;

(b) detachment of Essure from the delivery wire;

(c) patient tolerance of and recovery from the placement procedure;

(d) device stability within the fallopian tube until hysterectomy;

(e) occlusion of the fallopian tube within the study period (24 hours to 12 weeks following placement);

(f) local tissue response to the device;

(g) the effect of PET fibre on the ability of Essure to create a local tissue response; and

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115 Ibid at 104.
116 Ibid at 86.
117 BAY-ESSURE-0006158 at 1290.
118 Ibid at 1293.

(h) the ability to retrieve Essure transcervically in a subset of the patient population pre-hysterectomy.[119]

207 The participants rated their tolerance of the placement procedure as 'good' to 'excellent' in all cases.[120] The device was successfully placed in 84.7% (100/118) of tubes visualised, with bilateral placement achieved in 73% (46/63) of participants and unilateral placement achieved in 12.7% (8/63) of participants. Devices could not be placed in 14.3% (9/63) of participants.[121] Reasons for failed placements included tube blockages, issues with the catheter release, tubal and uterine pathology, and difficult angles during placement.[122]

208 Participants completed a questionnaire one week post-Essure placement to assess post-procedural pain, bleeding and general satisfaction. Results were available from 52 participants. Fifty-four percent of participants reported pain post-procedure, which resolved in 8 hours or less in 63% of participants and within three days for 96% of participants. Eleven of the participants described the pain as moderately or significantly more than period pain, and 14 participants reported taking medication for the pain. Post-procedure bleeding or spotting was reported in 50% of participants; all bleeding was resolved within seven days.[123]

209 Participants in the study were followed until their hysterectomy. There were no reports of pain subsequent to the post-procedure pain described above. Participants wore the device for 24 hours up to 14+ weeks, as shown below:[124]

Table III. 7: Length of Micro-insert Wearing by Woman

Length of Micro-insert Wearing	Number of Women
< 4 weeks	5
4–6 weeks	16

119 Ibid at 1287.
120 Ibid at 1294.
121 Ibid at 1293.
122 Ibid at 1294.
123 Ibid at 1295.
124 Ibid at 1296.

10–14 weeks	24
> 14 weeks	6
Lost to follow-up	2
Total	**53**

210 Tubal occlusion was evaluated in 94.2% of participants by hysterosalpingography scans prior to hysterectomy. The study authors stated that 100% of the 92 tubes that contained a properly placed device were occluded, including in those participants who wore Essure for less than 12 weeks.[125]

211 Gross examination of the uteruses showed no evidence of inflammation, ulceration, or haemorrhage except in one participant with adenomyosis.[126] Following examination and x-ray the uterine specimens were bivalved and examined further to evaluate inflammation, haemorrhage and ulceration in the area of the *uterine cornua* (the points in the upper uterus where the fallopian tubes exit to meet the ovaries) which was in contact with the trailing length of the Essure insert. Mild gross inflammation was noted in two cornuas, as well as a slight haemorrhage in one cornua. There was no evidence of ulceration in any of the specimens.[127]

212 Following gross examination, the fallopian tube specimens were sent for microscopic evaluation. The pathologists were blinded to the wear times of each participant until the histological evaluation was completed.[128] The histological responses for each characteristic presented (acute and chronic inflammation, granulation tissue, loose and dense fibrosis, neovascularisation, disruption of epithelium and level of obliteration) were rated on a scale of '0-3', with '0' meaning 'absent' and '3' meaning 'severe.'

213 The histology findings from the pre-hysterectomy study were the subject of considerable expert evidence at trial, particularly in relation to the issue of chronic

125 Ibid at 1298.
126 Ibid at 1296.
127 Ibid at 1297.
128 Ibid at 1300.

inflammation. The study authors concluded that the Essure implantation procedure was 'safe with minimal post procedure discomfort and sequalae and minimal adverse events'. They found that the occlusive, benign tissue response demonstrated by the histological evaluation of the specimens supported the theorised mechanism of action, and that the acute inflammatory response and 'low level' chronic inflammatory response was consistent with other medical devices that used PET fibres. I will return to the histopathology from the pre-hysterectomy study and the related expert evidence later in these reasons.

Phase II study

214 The Phase II study of the Gamma model commenced in November 1998. Two hundred and sixty-nine women, all of whom were seeking permanent contraception, had been enrolled by June 2000 and 227 women ultimately underwent an Essure placement procedure. Bilateral device placement was achieved in 200 women and unilateral placement in six women.

215 The study followed the participants for up to 36 months and was conducted by five investigators across the US, Australia, Belgium and Spain.[129] The objectives of the study were to evaluate:

(a) tolerance of, and recovery from, the Essure placement procedure;

(b) safety of the Essure placement procedure;

(c) tolerance of the implanted device;

(d) long-term safety and stability of the implanted device; and

(e) effectiveness of Essure in preventing pregnancy.[130]

216 Participants completed a questionnaire at one week post-placement to document any symptoms they experienced following the procedure. They were also asked to keep

129 BAY-ESSURE-0008291 at 20-21.
130 Ibid at 17-18.

a diary for six months following the placement procedure detailing menstruation, sexual activity and any associated symptoms.[131] Participants underwent a hysterosalpingogram ('HSG') (and in some cases, ultrasound) at three months post-procedure to review the position and retention of Essure, and occlusion of the fallopian tubes.[132] The participants were then followed up at six, 12- and 18-months post-procedure, and at 24 months following discontinuation of alternative contraception.[133]

217 HSG scans performed on 200 participants at the three-month point showed satisfactory placement and bilateral occlusion in 187 women. Repeat scans of seven women after three months showed they also had satisfactory placement and occlusion.[134]

218 Participant tolerance to wearing Essure was ascertained at various points post-procedure:[135]

Table II.11. Tolerance to wearing Essure

Follow-up Time Point	Excellent	Very Good	Good	Fair	No response
3 Months N=203	178 (88%)	18 (9%)	4 (2%)	2 (1%)	1
6 Months N=199	179 (91%)	13 (7%)	4 (2%)	1 (1%)	2
12 Months N=197	173 (88%)	16 (8%)	6 (3%)	0	2
18 Months N—191	171 (90%)	16 (8%)	2 (1%)	0	2
24 Months N=112	105 (94%)	4 (4%)	2 (2%)	0	1
36-months N=2	1 (50%)	1 (50%)	0	0	0

131 Ibid at 18.
132 Ibid at 19.
133 Ibid.
134 Ibid at 40.
135 Ibid at 34.

219 Reports of pelvic pain were also recorded at follow-up visits:[136]

Table II.12: Pain reported at follow-up visits

	Pelvic pain			Other Pain
Follow-up visit	**Dysmenorrhea**	**Dyspareunia**	**Other Pelvic**	
3-month	29/203 (14%)	17/203 (8%)	5/203 (2%)	2/203 (< 1%)
6-month	11/199 (6%)	3/199 (1%)	3/199 (1%)	1/199 (< 1%)
12-month	5/197 (2%)	0	5/197 (2%)	0
18-month	2/191 (1%)	0	10/191 (5%)	2/191 (1%)
24-month	2/112 (2%)	0	4/112 (4%)	2/112 (2%)
36-month	0	0	0	0

Two participants reported recurrent (reported on two occasions) pain. No participant consistently reported pain at every visit.[137]

220 One participant asked to have the devices removed due to chronic menstrual pain that began following her two-year visit.

221 Unusual bleeding was not frequently reported by participants. Spotting was most commonly reported in the first six months post-procedure (in up to 3% of participants), and irregular menses was noted more frequently 12-24 months post-procedure (in up to 5% of participants).[138]

Table II.13: Unusual bleeding reported at follow-up visits

Follow-up visit	Irregular menses	Spotting	Changes in flow	Other
3-month[139]	N/a	N/a	N/a	N/a
6-month	3/199 (1%)	6/199 (3%)	3/199 (1%)	0
12-month	6/197 (3%)	5/197 (2%)	4/197 (2%)	0
18-month	9/191 (5%)	4/191 (2%)	5/191 (3%)	0
24-month	2/112 (2%)	1/112 (1%)	4/112 (4%)	1/112 (1%)
36-month	0	0	0	0

136 Ibid at 35.
137 Ibid at 36.
138 Ibid.
139 Women were not asked about unusual bleeding at the 3-month visit.

222 Adverse events that occurred after the day of the Essure implantation procedure were recorded in the following table:[140]

Table II.15: Adverse events

Adverse event	Number	Suspected Cause	Patient management
Unsatisfactory Device Location			
Perforation	6 (2.6%)	Preexisting tubal occlusion (2); perforation with use of the Support Catheter (4)	Laparoscopic sterilization (5) with device retrieval in 3; cornual resection and device removal (1)
Expulsion	1 (< 1%)	Due to initial proximal placement of Micro-insert	Second Micro-insert procedure unsuccessful due to stenotic tube, husband had vasectomy
Other Unsatisfactory Device location	1 (< 1%)	Due to initial distal placements of both Micro-inserts	Laparoscopic sterilization, bilateral salpingectomy
Other Events			
Retained Micro-insert fragment	1 (< 1%)	Excessive force used during removal attempt, resulting in broken distal ball tip	Repeat x-ray 3-months after procedure showed retained fragment, no further follow-up

223 The study authors concluded:

> The Essure Micro-insert placement procedure was found to be safe and acceptable to women. The procedure-related adverse events were within an expected and acceptable range for a hysteroscopic procedure, with less than 1% of women experiencing an adverse event on the day of the procedure. Adverse events experienced after the day of the procedure occurred in less than 4% of women.
>
> The primary adverse event experienced was perforation. Of the perforations, 4/6 (67%) utilized the Support Catheter, which was associated with a high rate of perforation. The Support Catheter was discontinued prior to commencement of the Pivotal Trial, and the perforation rate in the Pivotal Trial was less than 1%.
>
> The long-term acceptability of wearing the Essure Micro-inserts was found to be "good" to "excellent" in 99% of women who have been followed for l–3 years.
>
> The observed one-year effectiveness rate of 99.5% (98.1%–100%) and the two-year effectiveness rate of 99.4% are comparable to other methods of

140 BAY-ESSURE-0008291 at 43.

sterilization currently available.

> Thus, although the Phase II trial was initially designed to serve as a preliminary study of safety and effectiveness for purposes of supporting commencement of a Pivotal Trial, the data from this study support the safety, effectiveness, and patient satisfaction with the Essure placement procedure and the implanted Micro-insert.[141]

Pivotal trial

224 The Pivotal trial was conducted from May 2000 to December 2007.[142] The trial was designed as a multi-centre, non-randomized international study of women seeking permanent contraception. It was designed to capture five years of follow-up data, with the first year of data intended to inform a PMA application to the FDA. Participants were instructed to continue using alternative contraception during the first three months of Essure wear, with an HSG conducted at the three-month mark to evaluate insert location and tubal occlusion. Assuming both were satisfactory, participants were then instructed to discontinue alternative contraception (thus relying solely on Essure for contraception) and followed up at the six and 12-month points.[143]

225 The study endpoints were summarised as follows:

> The primary endpoints for this study were:
>
> - Prevention of pregnancy;
> - Safety of the Micro-insert placement procedure; and
> - Safety of the Micro-insert wearing.
>
> The secondary endpoints for this study were as follows:
>
> - Participant satisfaction with the Micro-insert placement procedure;
> - Participant satisfaction with Micro-insert wearing;
> - Bilateral Micro-insert placement rate; and
> - Development of a profile for an appropriate candidate for the

141 Ibid at 50-51.
142 BAY-ESSURE-0016353 at 501.
143 Ibid at 523.

Essure procedure.[144]

226 Of the 507 women enrolled in the study, bilateral placement was achieved in 464 women and single insert placement was achieved in two women with unicornuate uteruses.

227 Of the 456 women with bilateral placement who completed the three-month visit, 446 were ultimately found to have Essure inserts in satisfactory locations with bilateral occlusion.

228 In relation to pain, the study authors recorded:

> During the 3-month PDP and 3, 6, and 12-month PAC follow-up visits, women were asked about unusual pain they experienced since the last contact… Of the women who reported pain, only one woman reported "persistent" pelvic pain. Ten women (2.1 %) had "recurrent" dysmenorrhea, 8 women (1.7%) reported "recurrent" dyspareunia, 2 women (0.4%) reported "recurrent" ovulatory pain, and 15 (3.2%) recorded "recurrent" other pelvic pain that could not clearly be classified into a different category.[145]

229 In relation to changes in menstrual pattern, the authors recorded for the one year follow-up data:

> … women reported episodes of both heavier than normal and lighter than normal menstrual flow. "Recurrent" changes in menstrual pattern were noted infrequently and "persistent" changes were reported rarely, with almost equal percentages of women reporting persistent increase or decrease in menstrual flow, for no significant net change overall.[146]

230 Adverse events reported during the first year of reliance and rated by investigators as at least 'possibly' related to Essure are recorded in the following table:[147]

Table 46. Adverse Events by Body System

Rated by Investigator as at least possibly related: For the First Year of Reliance*
N=6885 women months of follow-up for 476 patients with at least 1 Micro-insert

Adverse Event	Number	Probability
Abdominal		
Abdominal pain / abdominal cramps	18	2.6
Gas / bloating	6	0.9

144 Ibid at 522.
145 Ibid at 608.
146 Ibid at 604.
147 BAY-EDPA-0097235 at 293.

Musculo-skeletal		
Back pain / low back pain	43	6.2
Arm/leg pain	4	0.6
Nervous/psychiatric		
Headache	12	1.7
PMS	4	0.6
Genitourinary		
Dysmenorrhea / menstrual cramps (severe)	14	2.0
Pelvic / lower abdominal pain (severe)	12	1.7
Persistent increase in menstrual flow	9**	1.3
Vaginal discharge / vaginal infection	7	1.0
Abnormal bleeding – timing not specified (severe)	9	1.3
Menorrhagia / prolonged menses (severe)	5	0.7
Dyspareunia	17	2.5
Pain/discomfort – uncharacterized	14	2.0
TOTAL	174	--

Probability of an AE is expressed as number of reports/number of woman months of follow-up (6885)

* Only events occurring in ≥ 2.5/1000 women-months are reported

** Eight women reported persistent *decrease* in menstrual flow.

231 After one year of follow-up, the study authors made the following finding in relation to patient satisfaction and comfort:

> Women in the study consistently rated their overall satisfaction and comfort in wearing the Micro-inserts as very high. One-week post-device placement, >95% of women rated their comfort as 'good' to 'excellent' and their satisfaction as 'somewhat satisfied' to 'very satisfied'. At all subsequent study visits, 99% of women rated their comfort with wearing Essure as 'good' to 'excellent'. At all study visits, at least 98% of women rated their overall satisfaction as somewhat to very satisfied (this included women who were not able to rely on Essure).[148]

232 In relation to the first year of data, the study authors summarised their conclusions as follows:

> In summary, we believe that the data contained in this Pivotal Trial Report, together with the data provided elsewhere in the PMA, provide a reasonable assurance of the safety and effectiveness of the Essure System based on valid scientific evidence.[149]

Corrosion testing

233 Bayer also conducted a bench test in a simulated corrosive environment to assess the risk of corrosion of the metallic components of the Essure insert (resulting in loss of

148 BAY-ESSURE-0016353 at 516.

149 Ibid at 517.

mechanical integrity of the insert) and the release of ions during the corrosion process ('corrosion bench test').

234 The corrosion bench test was performed over 180 days on two sample groups of inserts. 'Group A' samples were placed in saline in a heated water bath for periods of time ranging from seven to 180 days. 'Group B' samples were placed in similar solution, with the saline removed for analysis at specified points and replaced with fresh saline.

235 The corrosion bench test acceptance criteria were:

> **8.1 Leaching Rate of Nickel**
>
> The leaching rate of nickel ions from the samples must be lower than the average levels of human intake of nickel from diet and the environment.
>
> **8.2 Mechanical Integrity**
>
> The Micro-inserts must maintain mechanical integrity for at least three months. That is, each Micro-insert must still be in one piece after exposure to a corrosive saline environment for three months. In particular, the fibered inner coil must remain attached to the outer coil.[150]

236 The study authors concluded that the test passed both acceptance criteria.

237 Corrosion of the solder on the inserts was described as follows:

> As expected, the solder showed signs of corrosion resulting in pitting and increasing porosity with the worst corrosion damage on the ball tip. At the three-month time point, approximately 25-50% of the solder had corroded. At the six-month time point, the ball tips of some of the samples were almost completely corroded, but all of the solder bonds continued to hold together. In all cases, the outer coil remained attached to the fibered inner coil. This is an acceptable level of solder corrosion, because it did not result in the loss of mechanical integrity. No other components showed signs of corrosion.[151]

238 The study authors noted the following conclusions:

- The Essure Micro-insert passes the corrosion susceptibility bench test.

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150 BAY-JCCP-0361121 at 1733.
151 Ibid at 1737.

- The daily leaching rate of nickel and tin ions released are at least 2000 times less than everyday intake of food and water and exposure to environment.
- The daily leaching rate of chromium is below the detection limit.
- The Essure Micro-insert maintained mechanical integrity during the six months of exposure to a bench top corrosive saline environment.
- The corrosion rate of the solder is acceptably low.
- Besides the solder, no other signs of corrosion were visible in the SEM images.[152]

239 The outcomes and adequacy of the corrosion bench test were the subject of expert evidence. I will return to this test and that evidence later in these reasons.

Regulatory approval

Pre-market approval application to the FDA

240 Conceptus submitted its PMA application to the FDA for approval of Essure as a Class III device (the highest risk classification for a medical device) in the following stages:

(a) Module I was submitted on 21 November 2001. It provided general information about Essure, a description of the device, and a summary of the animal studies and peri-hysterectomy study.[153]

(b) A further submission was provided on 24 January 2002 which responded to FDA questions and included a revised version of Module I with changes to the device description.[154]

(c) Module II was submitted on 14 February 2002. It provided a hazard analysis and non-clinical laboratory studies for physical and chemical performance which addressed bench testing of the inserts and delivery system, corrosion and MRI compatibility.[155]

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152 Ibid at 1739.
153 BAY-ESSURE-0004422.
154 BAY-ESSURE-0004934.
155 BAY-ESSURE-0005174.

(d) A further submission was provided on 5 April 2002 which responded to FDA questions and provided updated summary tables and test data.[156]

(e) Module III was submitted on 8 April 2002, and contained the results of non-clinical biocompatibility studies and the pre-hysterectomy study.[157]

(f) Volume 5 of Module III, which was missing from the original submission, was submitted on 17 June 2002.[158]

(g) Module IV was submitted on 15 April 2002. It included information on the methods used in, and the facilities and controls used for, the manufacture, processing, packing and storage of Essure.[159]

(h) An amendment to Module IV was submitted on 15 May 2002 regarding the expiration date of Essure, along with supporting documents.[160]

(i) Module V was submitted on 9 April 2002. It included the results of the Phase II study, marketing studies and information about marketing in countries outside of the US.[161]

241 On 22 May 2002, the FDA notified Conceptus that the PMA application was sufficiently complete to begin the substantive review process. The FDA Obstetric and Gynecology Devices Advisory Panel ('OGDAP') was convened on 22-23 July 2002 to review the PMA application.[162] Conceptus submitted a package of documents with key information from the PMA application for distribution to the OGDAP prior to the meeting.[163]

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156 BAY-ESSURE-0006003.
157 BAY-ESSURE-0006158.
158 BAY-ESSURE-0018723.
159 BAY.ESSURE.0009017.
160 BAY-ESSURE-0013607.
161 BAY- ESSURE-0008291.
162 BAY-ESSURE-0014062.
163 BAY-ESSURE- 0017580.

242 At a public hearing on 22 July 2002, the OGDAP considered questions about device effectiveness, safety, labelling, training, and post-approval studies based on the key information package provided by Conceptus.[164]

243 Dr Thomas Wright, who was engaged as a consultant by Conceptus to perform the histopathological analysis of specimens from the pre-hysterectomy study, gave evidence at the hearing.[165] Wright summarised his findings as follows:

> … Key histological features observed in the sections were graded in a blinded fashion. Over time, we observed an increase in the amount of dense fibrosis which is shown in the yellow line and a reduction in the amount of acute inflammation which is shown in the white line. Both chronic inflammation and loose fibrosis appeared relatively stable up to a 15-week period of looking at these devices.
>
> In conclusion, the prehysterectomy study has shown total tubal occlusion by hysterosalpingograms in all of the participants at all of the time points, including even those women who wore the device for less than four weeks. The histological studies have shown that the tissue response to the device is predictable and is progressive. It is occlusive in nature and it produces a dense fibrosis.
>
> Finally, the tissue response is quite localized. Sections from the tubes taken approximately five millimeters distal to where the device was showed a normal tubal architecture and there was no evidence that the reaction to the device extended out to the serosal surfaces of the tube. So the reaction was confined to the area around the device.[166]

During the hearing, the OGDAP discussed the long-term efficacy of Essure in occluding the fallopian tubes and achieving sterilisation. The following exchange took place between Wright and OGDAP member Dr Gerald Shirk in relation to the mechanism of action of the PET fibres:

> [WRIGHT:] … If you have a loose weave, such as what we are seeing here, in the space between the inner and the outer coil, you've got a lot of inflammatory infiltrate, then you will get a dense fibrosis.
>
> In systems that this event looked at over time, this response appears to be very durable in that it does not diminish, it remains as it is, and you maintain a chronic inflammatory infiltrate at the site of the fibers which is the way it remains as a durable fibrotic response.

164 BAY-ESSURE-0019660 at 3-5.
165 Ibid at 65.
166 Ibid at 68-69.

Does that answer your question?

SHIRK: Yes. I just wanted some information what the fibers were made out of and obviously it creates a chronic kind of inflammatory response?

WRIGHT: An acute initially and then a chronic.

SHIRK: During the patient's entire lifespan?

WRIGHT: That's right, and with vascular grafts, we have long histories of patients who wear these for very long periods of time, showing that it does not cause adverse effects.[167]

244 OGDAP member Dr Subir Roy then raised a related concern that long-term placement of PET fibres may be associated with abnormal growth of cells in that part of the body:

ROY: The last concern would be, is there any reason for us to be wondering whether these giant cells that infiltrate this area or are produced are in any way precursors for a neoplastic process?

WRIGHT: Right, and I didn't answer to that. It's the same sort. The pictures I showed you with giant cells could be from any vascular graft in the body, and we have a very long history of use of devices using PET fibers for long-term implants and they have been shown to be neoplastic.

ROY: But those vascular grafts are typically in much older individuals and for reasonably shorter periods of time than what we're envisioning here. If we're anticipating the use of this as a sterilization process in women in their twenties who presumably and hopefully would live to their eighties, so is that differential time span a concern to someone such as yourself who's been involved in these investigations and processes?

WRIGHT: That is not a concern to me, because I know of no data to suggest or to implicate PET for producing neoplasms long term, and in fact many of the implantable devices, such as cardiac valves which have PET as a dense mass around the valve rings which it's there in order to suture into, are put into quite young, you know, children get cardiac valves which contain PET.[168]

Turner relied on this exchange as putting the defendants on notice of the need to consider possible adverse consequences from long-term placement of Essure related to an inflammatory process stimulated by the PET fibres.

245 Wright told the OGDAP that he knew of no analogous situation where an implantable medical device containing PET fibres had been used to occlude an epithelial line

167 Ibid at 87-90.
168 Ibid at 90-91.

structure such as the fallopian tube.[169] He added that histopathology from the pre-hysterectomy study showed ingrowth of dense fibrosis together with some smooth muscle tissue, which was typical of the histopathological response to PET at a variety of different body sites.

246 Dr Charles Carignan, Vice-President of Clinical Research and Medical Affairs at Conceptus, gave evidence about the Pivotal trial to the OGDAP. In relation to adverse events, he said:

> This table shows the number of events reported and the number that you can see here, the most frequent were low back pain, abdominal pain or cramps, and dyspareunia. Only eight events were rated as definitely related to the Essure device. The reports of pain, bleeding and adverse events are kept in perspective when looking at satisfaction with Essure. From the three-month post-device placement visit onward, more than 90 percent of women rated their satisfaction with Essure as very satisfied.[170]

247 Conceptus advised that it had conducted all biocompatibility testing required by FDA guidelines, and that the results demonstrated that Essure was not chronically toxic or mutagenic. The FDA lead reviewer advised the OGDAP that 'the appropriate testing [had been] conducted for this implant device' and that Conceptus had '[chosen] a material that has a long history as an implant material.'[171]

248 Ultimately, the OGDAP voted in favour of approving the PMA application with the following conditions:

(a) that an HSG be performed three months' after implantation;[172]

(b) that physician training occur and that it be a training requisite that the physician be knowledgeable in hysteroscopy;[173]

169 Ibid at 174.
170 Ibid at 75.
171 Ibid at 117.
172 Ibid at 306.
173 Ibid.

(c) that Essure labelling address success/failure rate, age of patient, young age, potential sequelae, metal sensitivity, electrocautery, and pregnancy subsequent to the procedure;[174]

(d) that physicians be given recommendations regarding procedure time length and a 1,500 millilitre saline limit for use in the patient;[175]

(e) that the procedure be performed at the proliferative phase of the menstrual cycle;

(f) that written informed consent be obtained from patients (with Conceptus to provide the FDA an example of the consent form);[176]

(g) that recommendations be included in the patient pamphlet about what to do if the patient misses a period and a fallback plan if Essure insertion is unsuccessful;[177] and

(h) that Conceptus continue observation of current Essure patients for five years to better assess insertion rate failure for the purpose of patient counselling and labelling.[178]

249 On 4 November 2002, the FDA approved the PMA application subject to the following conditions:[179]

(a) Conceptus was to follow Phase II study and Pivotal trial participants to assess safety and effectiveness at two, three, four and five years after implantation or discontinuation of alternative contraception. The data collected was to be reported to the FDA each year.[180]

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174 Ibid.
175 Ibid.
176 Ibid.
177 Ibid at 306-7.
178 Ibid.
179 BAY-ESSURE-0039034 at 9037-9041.
180 Ibid.

(b) Conceptus was to conduct a post-approval study in the US intended to document the bilateral placement rate for newly trained physicians.[181]

(c) Before making any change affecting the safety or effectiveness of Essure, Conceptus was to submit a PMA supplement for review and approval by the FDA (subject to certain exceptions). A PMA supplement was to be submitted if and when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitated a labelling, manufacturing or device modification.[182]

(d) Conceptus was to submit annual post-approval reports ('annual PMA reports') which included, along with follow up data from existing studies:[183]

(i) identification of, among other things, new indications for use of the device; labelling changes; changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device; and

(ii) a summary of any information not previously submitted which is known or should reasonably be known to Conceptus, including unpublished reports of data from any clinical investigations or non-clinical laboratory studies involving the device or reports in the scientific literature concerning the device or related devices.[184]

(e) Conceptus was to provide a report to the FDA after receiving or becoming aware of any information:

(iii) concerning a mix-up of the device or its labelling with another article; or

(iv) about any adverse reaction, side effect, injury, toxicity, or sensitivity

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181 Ibid.
182 Ibid.
183 Ibid.
184 BAY-ESSURE-0039034 at 9037-9041.

reaction attributable to the device which had not been addressed on the device labelling, or that had occurred with unexpected severity or frequency.[185]

Essure was commercially available in the US from the date of FDA approval.

Regulatory approval outside the United States

250 Neither Australia nor Europe recognise the regulatory status of medical devices under FDA regulations. The FDA PMA processes for Essure therefore had no bearing on the determination of regulatory approval in those jurisdictions. However, at the time of the Essure PMA application, the FDA PMA process was recognised globally as the most rigorous regulatory process for high risk devices.[186]

251 In 1997, the TGA acknowledged Conceptus' notification of importation of the STOP device (as Essure was then known) for the purpose of conducting clinical trials.[187]

252 Conceptus was first registered with the TGA as manufacturer of Essure in 1999. Essure was listed on the ARTG that same year, which was a necessary precondition for sale of the device in Australia.[188] At that time, approval for the sale of medical devices like Essure in Australia did not involve a formal evaluation process. Instead, TGA approval required:

(a) information which reasonably demonstrated the safety and quality of the device for its intended use;

(b) contact and address details of the device sponsor and manufacturer;

(c) a copy of the manufacturing quality management systems certificate; and

(d) copies of product manuals and labelling.

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185 Ibid.
186 Brandwood at 59 [252] (EXP.001.002.0009).
187 BAY-EDPA-4197110 at 5.
188 BAU.001.001.0180.

The TGA did not require that risk management files, safety testing, design data or clinical evidence be supplied for devices such as Essure.

253 Bayer Essure and/or Bayer HealthCare supplied Essure to the following companies, for importation into and distribution in Australia:

(a) Bepen Pty Ltd between about 1 December 1999 and about 6 November 2000;

(b) Conceptus (Australia) Pty Ltd between about 6 November 2000 and about January 2005;

(c) N Stenning & Co Pty Ltd between about January 2005 and August 2010;

(d) Gytech between about August 2010 and January 2015; and

(e) AMSL between about January 2015 and August 2017.[189]

254 Module V of the PMA application dated 9 April 2002 stated, in relation to commercial supply of Essure outside of the US:

> The Essure System is currently commercially available in the following countries: Australia, certain European countries, Singapore and Canada. Registration of the product for commercial sale in Australia and Singapore was made with the appropriate regulatory authorities. CE Mark approval was granted by TUV and a Medical Device License was granted by Health Canada.
>
> …
>
> The first commercial shipments of Essure began in the second quarter of 2001 to both Australia and Singapore, followed by the first commercial shipment to Europe in the third quarter of 2001, and the first commercial shipment to Canada in the first quarter of 2002. As of March, 2002, over 1,200 commercial units have been shipped, with an estimated number of Essure procedures conducted at over 750. In addition, over 175 physicians have undergone the Essure Physician Training Program.[190]

255 In the EU, devices which meet regulatory requirements for commercial supply are granted a CE Mark. Conceptus was granted a CE Mark of certification for Essure in

189 PLE.500.001.0008 at [44].
190 BAY-ESSURE-0008291 at 53.

2001.

Essure supply in Australia

256 As outlined at [194] above, Conceptus evaluated several Essure designs before adopting the Gamma model. The first commercial shipments of Essure model number 'ESS004' to Australia began in the second quarter of 2001. The ESS004 model was approved by the FDA on 4 November 2002. It underwent several design changes during the period in which it was commercially available, but those changes related primarily to the disposal delivery system.

257 A subsequent device model, 'ESS205', was approved by the FDA in March 2003. Around this time, Conceptus sought a revision to the anchoring of the longitudinal PET fibres in the ESS205 model. The changes were to mitigate the risk of the proximal anchoring loops of the fibres becoming wrapped around the delivery wire, which made it difficult to remove the wire from the insert. The change was approved by the FDA on 1 July 2003 and made commercially available in Australia.

258 A subsequent iteration of Essure, the 'ESS305' model, was approved by the FDA in June 2007. The only difference between this model and the ESS205 related to the delivery catheter.

259 I will return to the post-market clinical evaluations undertaken by Conceptus of the ESS205 and ESS305 models later in these reasons.

Post-Market clinical studies

Phase II study 5-year follow-up

260 Conceptus submitted the final Phase II study in its annual PMA report to the FDA on 19 June 2006. The final reporting period was between 8 October 2002 and 6 January 2006.[191] As required by the FDA, the reporting period captured data in relation to the contraceptive efficacy and safety of Essure at two, three, four, and five years post-insertion (for participants using the device for safety only), or from discontinuation of

[191] BAY-ESSURE-0039034 at 36.

alternative contraception (for participants using the device for contraception).[192] Of the 206 subjects in whom bilateral or unilateral placement of the device was initially achieved, 171 completed the five year study.[193]

261 The tolerance to wearing Essure reported by participants is recorded in the following table:[194]

Table II.11: Tolerance to wearing Essure

Follow-up Time Point	Excellent	Very Good	Good	Fair	No response
3 Months N=203	178 (88%)	18 (9%)	4 (2%)	2 (1%)	1
6 Months N=199	170 (90%)	13 (7%)	4 (2%)	1 (1%)	2
12 Months N=196	172 (88%)	16 (8%)	6 (3%)	0	2
18 Months N=193	172 (89%)	17 (9%)	2 (1%)	0	2
24 Months N=194	178 (92%)	10 (5%)	5 (3%)	0	1
36 Months N=182	155 (85%)	23 (13%)	4 (2%)	0	0
48 Months N=176	157 (89%)	14 (8%)	4 (2%)	1 (1%)	0
60 Months N=171	155 (91%)	11 (7%)	4 (2%)	0	1

262 Pain reported by participants at follow-up visits is recorded in the following table:[195]

Table II.12: Pain reported at follow-up visits

Follow-up visit	Pelvic pain			Other Pain
	Dysmenorrhea	Dyspareunia	Other Pelvic	

192 Ibid at 4-5; 42-43.
193 Ibid at 42 [3].
194 Ibid at 26.
195 Ibid at 27.

3-month	29/203 (14%)	17/203 (8%	5/203 (2%)	2/203 (<1%)
6-month	11/199 (6%)	3/199 (2%)	3/199 (2%)	1/199 (<1%)
12-month	5/196 (3%)	0	5/196 (3%)	0
18-month	2/193 (1%)	0	10/193 (5%)	2/193 (1%)
24-month*	8/194 (4%)	0	6/194 (3%)	6/194 (3%)
36-month*	7/182 (4%)	1/182 (<1%)	2/182 (1%)	1/182 (<1%)
48-month*	9/176 (5%)	2/176 (1%)	2/176 (1%)	2/176 (1%)
60-month*	4/171 (2%)	1/171 (<1%)	3/171 (2%)	2/171 (1%)

* No data reported for some women that indicated unusual pain (N=2 at 24 months; N=1 at 36, 48 and 60 months)

There were a further six instances of pain being reported by participants at unscheduled visits. Thirteen participants (6.5%) reported recurrent[196] pain. The most common types of pain reported were dysmenorrhea, dyspareunia, and other pelvic pain (mostly ovulation pain).[197]

263 Unusual bleeding reported by participants at follow-up visits is recorded in the following table:[198]

Table II.14: Unusual bleeding reported at follow-up visits

Follow-up visit	Irregular menses	Spotting	Changes in flow	Other
3-month	not asked	not asked	not asked	not asked
6-month	3/199 (2%)	6/199 (3%)	3/199 (2%)	0
12-month	6/196 (3%)	5/196 (3%)	4/196 (2%)	0
18-month	9/193 (5%)	4/193 (2%)	5/193 (3%)	0
24-month*	4/194 (2%)	4/194 (2%)	10/194 (5%)	1/194 (<1%)
36-month*	4/182 (2%)	3/182 (2%)	4/182 (2%)	2/182 (1%)
48-month*	4/176 (2%)	3/176 (2%)	9/176 (5%)	2/176 (1%)
60-month*	16/171 (9%)	3/171 (2%)	11/171 (6%)	2/171 (1%)

*No data reported for some women that indicated unusual bleeding (N=2 at 24 months; N=1 at 36, 48 and 60 months)

There were a further 13 reports by participants of unusual bleeding made at unscheduled meetings. Fifteen participants (7.5%) reported recurrent menstrual changes. One participant (0.5%) reported recurrent post-coital bleeding.[199]

196 'Recurrent' meaning reported on two or more visits that may or may not be consecutive.
197 BAY-ESSURE-0039034 at 26.
198 Ibid at 28.
199 Ibid at 43 [3].

264 Investigators assessed and rated adverse events[200] according to their likely relationship to Essure as 'highly probable', 'probable', 'possible', or 'unlikely'.[201] No adverse events were rated as 'highly probable' or 'probable', and only three were rated as 'possible' during the reporting period. Fifty-five adverse events were assessed as having an 'unlikely' relationship to the device.[202] It is not clear what criteria investigators applied to determine the relationship, if any, between adverse events and Essure. The table extracted below lists all 'possibly related' adverse events during the period 8 October 2002 to 6 January 2006. [203]

Table II.19: AE's that began or ended from 10/08/2002 to 01/06/2006 that are at least "Possibly Related" to Essure

This table is sorted by 'Start Date'

Pt. No.	Adverse Event	Start Date Stop Date	Severity	Treatment Required	Other Treatment/Outcome
Relationship to study Device = HIGHLY PROBABLE					
S7-345	Proximal band detached from device	03/04/00 03/04/03	Mild	None	Pt is continuing in study with no adverse effects as of 3-yr visit. X-rays are OK.
Relationship to study Device = POSSIBLE					
S7-244	Possible ovulation pain reported 5/31/02	01/01/00 03/01/03	Moderate	Medication commenced 3/2003	Controlled with medication
S10-201	Ovarian discomfort with menses	11/28/00 Termed	Mild	None	*Completed 5-year study on 12/09/2004*
S7-335	Periods heavier and closer together	02/01/01 Termed	Mild	None	*Completed 5-year study on 05/27/2005*
S7-332	Pain on R or L side of pelvis during period	02/15/01 05/17/04	Mild	None	
S7-299	Cycle varies between 4-8 weeks	04/27/01 02/11/03	Mild	None	No problems with periods at 3-year visit February 2003
S7-301	Premenstrual spotting	07/01/01 02/11/03	Mild	Observe and follow-up in 6 months	No spotting as of 3-year visit on 2/11/03
S7-268	Cycle irregular	09/01/01 Termed	Mild	None	*Completed 5-year study on 11/26/2004*
S7-235	Heavy periods	12/02/01 08/04/03	Moderate	Medication	Resolved with medication as of 4-year visit August 2003
S7-229	Period irregular and heavy, lower abdominal pain	02/01/02 08/03/03	Moderate	Laparoscopy and D&C 6/8/02	No pain present as of 4-year visit – August 2003
S7-251	Hysterectomy for heavy periods	12/13/02 12/13/02	Moderate	Hospitalization	Patient had a hysterectomy and was termed from study 12/13/02 per

200 Defined as 'untoward deviations in subject health away from baseline' – see ibid at 104.
201 BAY-ESSURE-0039034 at 36 [2]-[3].
202 Ibid at 36 [3].
203 Ibid at 37.

					protocol
S10-119	Dysmenorrhea secondary to fibroids	01/02/03 01/02/03	Moderate	Medication	
S10-403	Hypermenorrhea	05/03/05 05/05/05	Moderate	Medication	

265 Five participants underwent a hysterectomy after Essure placement. Conceptus obtained the uteruses and/or fallopian tubes for histological analysis from two of these procedures, and the surgical pathology report from a third. The results of these histological analyses are recorded later in these reasons.[204]

266 The final report concluded that the data from the Phase II study supported the overall safety profile of Essure.[205] It stated (original emphasis):

> The Essure micro-insert placement procedure was found to be safe and acceptable to women. The procedure-related adverse events were within an expected and acceptable range for a hysteroscopic procedure, with less than 1% of women experiencing an adverse event on the day of the procedure. Adverse events experienced after the day of the procedure that prevented reliance on Essure occurred in less than 4% of women. There were no adverse events between October 8, 2002 and January 6, 2006 that were rated by the Investigator as having a high probability of relating to the Essure device. Furthermore, only three adverse events were reported during the same period that were rated as "possibly" related to Essure.
>
> …
>
> A woman's tolerance to wearing Essure was ascertained at the 3, 6, 12, 18, 24, 36 48, and 60-month follow-up, and has been rated as "good" to "excellent" in 99% of women at all visits.
>
> …
>
> **Persistent pain and bleeding were not reported. Recurrent pain and bleeding were rarely reported**. Thirteen women (13/199 = 6.5%) reported recurrent pain (reported on 2 or more visits that may or may not be consecutive) while persistent pain (reported at every visit) was not reported by any woman. Fifteen women (15/199 = 7.5%) reported recurrent menstrual changes, one woman (1/199 = 0.5%) reported recurrent post-coital bleeding and no women reported persistent menstrual changes.
>
> …
>
> In conclusion, the data from this study (in conjunction with the Pivotal Trial data) support the safety, effectiveness, and patient satisfaction with the Essure placement procedure and the implanted micro-insert. Five-year follow-up of

204 BAY-ESSURE-0039039 at 38; BAY-ESSURE-0028999_R at 573; see Chapter XII.
205 BAY-ESSURE-0039034 at 44.

patients in this study is complete.[206]

Pivotal trial five-year follow-up

267 Conceptus submitted the final Pivotal trial follow-up data to the FDA in its annual PMA report on 31 March 2008.[207] The data from both the Pivotal trial and Phase II study final annual PMA reports were not made publicly available until 2015.[208]

268 As outlined previously, participants in the Pivotal trial were instructed to rely on alternative contraception for the first three months following Essure placement. Those participants with satisfactory device placement and tubal occlusion at the three-month mark were then instructed to rely solely on Essure for contraception, thus entering the post-alternative contraception ('PAC') phase. The study followed up participants in the PAC phase after 18, 24, 36, 48 and 60 months.[209] The follow-ups included a pelvic exam; x-ray verification of insert retention at one, two and five years; and questions relating to adverse events, comfort, overall satisfaction, and plans for intrauterine procedures or extirpative surgery of reproductive organs.[210]

269 The study initially targeted a population of 400 women with the FDA later approving a population of 350 women during the follow-up period.[211] Of the 453 participants who relied on Essure for contraception, 364 completed the study with the remaining terminated or lost to follow-up.[212] The primary endpoints of the follow-up study were pregnancy prevention and safety.[213]

270 Bilateral placement was achieved in 92% of participants who had Essure devices implanted. Ninety-eight percent of the participants who completed the three month post-device placement visit successfully relied on Essure for contraception.[214]

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206 Ibid at 42–43.
207 BAY-EDPA-0097235 at 1.
208 T2237 (TRA.500.023.0001_2 at 0025_11-13).
209 BAY-EDPA-0097235 at 286, 234.
210 Ibid at 245.
211 Ibid at 238.
212 Ibid at 247.
213 Ibid at 238.
214 Ibid at 298.

271 Participants were asked to rate their comfort and overall satisfaction with Essure at each of their follow-up visits. At least 99% of women rated their comfort between 'good' and 'excellent' at all visits, while at least 95% rated their satisfaction between 'somewhat' and 'very satisfied' at all visits during the follow-up period.[215]

272 The following data were captured in relation to recurrent[216] changes in menstrual function:

(a) 14.8% of participants reported irregular menses;

(b) 18.8% of participants reported bleeding between menses;

(c) 37.5% of participants reported heavier than usual menstrual flow; and

(d) 23.3% of participants reported less than usual menstrual flow.[217]

The report noted that 46% of participants reported using oral contraceptives before entering the PAC phase, and said:

> Since discontinuation of oral contraceptives is known to cause menstrual changes in some women, and has been reported as a potential confounding variable in the literature on post-tubal ligation menstrual changes, the reported changes in menstrual function after the 3-month PDP visit could be influenced by the discontinuation of oral contraceptives.[218]

273 The proportion of participants reporting some pelvic pain at each visit is shown in the following table:[219]

Follow-up visit	Pelvic pain			
	Dysmenorrhea	Dyspareunia	Ovulatory pain	Other Pelvic***
Baseline (N=518)	183 (35%)	22 (4.2%)	N/a	N/a
3-month PDP (N=467)	29 (6.2%)	29 (6.2%)	5 (1.1%)	32 (6.9%)
3-month PAC	20 (4.5%)	10 (2.3%)	6 (1.4%)	26 (5.9%)

215 Ibid at 236.
216 'Recurrent' meaning reported at more than one visit during the follow-up period.
217 BAY-EDPA-0097235 at 286.
218 Ibid at 288 (citations omitted).
219 Ibid at 289.

(N=440)				
6-[month] PAC (N=436)	15 (3.4%)	8 (1.8%)	3 (0.7%)	16 (3.7%)
12-[month] PAC (N=460)	17 (3.7%)	15 (3.3%)	5 (1.1%)	27 (5.9%)
18-month PAC (N=410)	14 (3.4%)	9 (2.2%)	10 (2.4%)	11 (2.7%)
24-month PAC (N=435)	22 (5.1%)	9 (2.1%)	22 (5.1%)	13 (3.0%)
36-month PAC (N=422) (data missing on 1 pt)	14 (3.3%)	7 (1.7%)	12 (2.8%)	6 (1.4%)
48-month PAC (N=402)	3 (0.7%)	5 (1.2%)	6 (1.5%)	11 (2.7%)
60-month PAC (N=386)	14 (3.6%)	8 (2.1%)	10 (2.6%)	9 (2.3%)
Recurrent* (N=473)	29 (6.1%)	18 (3.8%)	14 (3.0%)	25 (5.3%)
Persistent** year 1 (N=460)	0	0	0	1 (0.2%)
Persistent** year 2 (N=435)	0	0	0	1 (0.2%)
Persistent** year 3 (N=422)	0	0	0	0
Persistent** year 4 (N=402)	0	0	0	0
Persistent** year 5 (N=386)	0	0	0	0

* *Recurrent:* symptom reported at more than one visit.
** *Persistent:* symptom reported at all prior visits.
*** *Other:* defined as pelvic pain that was not reported to be dysmenorrhea, dyspareunia or ovulatory pain.

274 Adverse events assessed as preventing reliance on Essure for contraception are recorded in the following table:[220]

Table 45. Adverse Events Preventing Reliance Among Bilateral Placements

Event	**Number *Initially* Diagnosed**	**Suspected Cause**	**Management**	**Ultimately Affected Reliance**
Expulsion	14 (3.0%)	Proximal placement (13); placement into endometrial tissue (1).	9 successfully underwent second Micro-insert placement procedure; 4 underwent laparoscopic sterilization; 1 required laparotomy due to preexisting Crohn's	5 (1.1%)

220 Ibid at 291.

			disease	
Perforation	4 (0.9%)	Pre-existing tubal occlusion (2); poorly identified ostium (2);	3 underwent laparoscopic sterilization; one requesting repeat Micro-insert placement procedure	4 (0.9%)
Proximal Micro-insert location and perforation	1 (0.2%)	Proximal placement on one side (0 mm trailing) and difficulty placing on the perforated side	Proximal Micro-insert removed hysteroscopically during lap sterilization, perforated side was suspicious on x-ray and confirmed during lap sterilization	1 (0.2%)
Proximal Micro-insert location	2 (0.4%)	Proximal placement (1); hydro-salpinx (1)	Awaiting women's decision to undergo lap sterilization (2)	2 (0.4%)
Total	**21 (4.5%)**			**12 (12.6%)**

Two participants whose expelled devices were initially retained in the uterus complained of mild spotting and intermittent cramping, which ceased upon device removal. There were no reports of symptoms by the remaining participants. All expulsions were found to have occurred in cases where the device was not placed in accordance with the placement criteria.[221]

275 Investigators assigned ratings to adverse events according to their severity and likely relationship to Essure. Investigators determined that 16 adverse events were at least 'possibly' related to Essure during the follow-up period.[222] This data is captured in the table below:[223]

Table 47. Adverse Events Reported from 10/15/02 to 12/05/07 (Rated at least "possibly" relating to Essure according to the Investigator)

Patient	Date of Report	Description	Date of Onset	Date Resolved	Severity	Treatment	Outcome

221 Ibid at 290.
222 Ibid at 294.
223 Ibid at 294-5.

44-103	10/28/02	heavy periods	08/23/02	Ongoing	Moderate	visit to professor Kerin – keep diaries for 3 months	Event continuing without treatment
09-002	03/14/03	heavy and irregular bleeding and pain.	09/01/02	8/8/03	Severe	NORADAY, Norethisterone, Surgery and hysterectomy	Recovered with treatment
44-108	11/12/02	Irregular period with abdominal pain	10/12/02	12/01/02	Moderate	Mersyndol, morphine~went to GP, admitted to hospital for 6 days	Recovered with treatment
03-019	06/09/03	pelvic pain	04/01/03	Ongoing	Moderate	None	Event continuing and not controlled with treatment
03-019	06/10/03	menorrhagia	04/01/03	Ongoing	Moderate	Meclomen	have not used meclomen yet
05-052	04/03/03	Right Pelvic Pain	09/01/02	09/08/03	Moderate	Abdominal Ultrasound~9/4/03	Recovered without treatment
16-052	06/08/04	Dysmenorrhea	06/08/04	06/09/04	Mild	None	Recovered without treatment
05-005	01/07/04	More frequent menses (every 2-3 weeks)	01/01/03	01/01/04	Mild	None	Recovered without treatment
44-079	02/02/04	Heavy painful periods with varying cycle	11/01/03	03/05/04	Moderate	Hysteroscopy, D&C 03/08/04	Recovered with treatment
16-036	06/08/04	Continuous bleeding	11/01/02	12/01/03	Moderate	Hysterectomy 12/01/03	Recovered with treatment
05-037	1/12/05	irregular menstrual bleeding	06/01/04	01/05/05	Severe	D&C performed 01/04/05	Recovered with treatment
19-007	04/04/05	Patient desired fertility	11/09/05	11/09/05	Mild	Bilateral salpingectomy	Recovered with treatment
44-063	1/18/05	heavy irregular periods and pelvic pain	02/01/04	08/11/04	Moderate	Hysterectomy 08/11/04	Recovered with treatment
24-002	2/3/05	increasingly heavy menstrual flow	09/01/04	01/26/05	Moderate	Birth control pill 01/02/05 and D&C 01/03/06	Recovered with treatment
20-013	05/29/06	Dyspareunia	01/15/01	Ongoing	Moderate	Change of position during intercourse	Event continuing and controlled with treatment
05-094	07/26/06	Spotting when ovulating	12/01/06	Ongoing	Mild	None	Event continuing

							without treatment

The only adverse event rated by investigators as 'definitely' related to Essure concerned a participant who desired fertility. Bilateral salpingectomy was performed to remove the devices in preparation for IVF implantation. No adverse events were rated as having a 'probable' relationship to Essure.

276 The report concluded in relation to safety, participant comfort and satisfaction with device wearing:

> There were 21 women (4.5%) who experienced an adverse event that initially prevented them from relying on the Micro-inserts for contraception. The vast majority of these events were Micro-insert expulsions, all of which occurred in cases where the Micro-insert was not placed in the tube or was placed too proximally, not in accordance with the placement criteria for trailing lengths. The majority of the women who experienced an expulsion (9/14, 64%) underwent a second Micro-insert placement procedure, and 9/9 (100%) achieved successful bilateral placement with subsequent finding of bilateral occlusion and satisfactorily located Micro-inserts on HSG. Therefore, overall, only 12/464 (2.6%) women who had bilateral placement were unable to rely on the Micro-insert for contraception due to an adverse event.
>
> None of the women who experienced these adverse events reported symptoms, other than two women whose expelled Micro-insert was retained in the uterus. They complained only of mild spotting and intermittent cramping, and these symptoms ceased when the Micro-inserts were removed from the uterus. It should also be noted that none of the adverse events initially preventing reliance occurred in women with properly placed Micro-inserts.
>
> …
>
> In conclusion, the data from this study (in conjunction with the Phase II study data) support the safety, effectiveness, and patient satisfaction with the Essure placement procedure and the implanted micro-insert. Five-year follow-up of patients in this study is complete.[224]

Newly trained physicians study final reports

277 The FDA PMA approval required Conceptus to conduct a study which documented bilateral placement rates for newly trained physicians for the purpose of evaluating training procedures and updating labelling.[225] Conceptus conducted two newly

224 Ibid at 298-9.
225 Carney at 34 (LAY.500.001.0008_2).

trained physician studies, the 'ESS205 Post- Approval Study' and the 'ESS305 Post-Approval Study'.[226]

ESS205 Post-Approval Study

278 Conceptus provided the results of the ESS205 Post-Approval Study to the FDA on 22 November 2005. The report contained data in relation to the 585 participants enrolled as of 3 October 2005.[227] Forty-one physicians at 39 sites in the US participated in the study to evaluate placement rates using the Gamma delivery device and coil catheter.[228]

279 The purpose of the study was stated as follows:

> … to document the bilateral placement rate for newly trained physicians. These data will be used to evaluate the training procedures and to update labeling. Data collected will include the following:
>
> > a. rates of successful bilateral placement of the Essure System at first attempt; and
> >
> > b. identification of factors predictive of failure to achieve bilateral placement [of] the Essure system at first attempt.[229]

280 In relation to the study design, the report stated:

> This study was designed to collect demographic and micro-insert placement data on a total of 800 women from 40 physicians in the commercial setting in whom an Essure System is placed through an operating channel of the hysteroscope. Data were also collected on women in whom the procedure was begun, but in whom an Essure System was not placed through the operating channel of the hysteroscope ("non-attempts").[230]

281 In relation to adverse events, it reported:

> Adverse events that occurred during and after the Essure placement procedure have been reported in 15/585 women (2.6%). All reported events were minor with the exception of Patient 32-013. One micro-insert perforated the left uterine fundus and embedded in omentum causing pain. The peritoneal portion of the micro-insert was laparoscopically removed and each tube was banded with Falope rings. The patient reported increased pain of unknown etiology and was to be scheduled for diagnostic studies and became lost to

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226 Ibid at 34; 37 [116], [123].
227 Ibid at 34.
228 Ibid at 35.
229 BAY-ESSURE-0034368_R at 13.
230 Ibid.

follow-up. None of these events represent unanticipated adverse effects…[231]

ESS305 Post-Approval Study

282 Conceptus submitted the results of the ESS305 Post-Approval Study to the FDA on 11 June 2009.[232]

283 The purpose of the study was stated as follows:

> … this study is intended to document the bilateral placement rate for the ESS305. These data will be used to evaluate the training procedures and to update labelling. Data collected include the following:
>
> a. bilateral placement of the ESS305 micro-insert at first attempt;
>
> b. identification of factors predictive of failure to achieve bilateral placement of the ESS305 at first attempt;
>
> c. comparison of bilateral placement success between newly trained physicians and experienced physicians;
>
> d. evaluation of aspects of the ESS305 design that may impact bilateral placement rate;
>
> e. hysteroscopy time to perform the procedure;
>
> f. adverse device effects; and
>
> g. adverse procedure events.[233]

284 The study was initially designed to collect data on a minimum of 800 women from 80 physicians implanting the ESS305 model. The FDA later approved a request to terminate the study early with 584 subjects enrolled, with no requirement for a hypothesis test comparing placement rates between experienced and newly trained physicians.[234] Seventy-six physicians performed placement procedures at 76 sites in the US.[235]

285 Bilateral placement was achieved in 562 participants. Unilateral insert placement

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231 Ibid at 40.
232 Carney at 37 (LAY.500.001.0008_2).
233 BAY-EDPA-0990375 at 5-6.
234 Carney at 37 (LAY.500.001.0008_2).
235 Ibid.

failed in 10 participants, and bilateral insert placement failed in six participants.[236]

286 Device issues were reported in 14 procedures, and six adverse events were reported during and after the procedure.[237] The final report concluded in relation to adverse events:

> All reported events were minor with the exception of Patient 80-04. The patient was hospitalized after hysteroscopy resulted in a uterine perforation by the hysteroscope. The Essure device did not cause the injury to the patient. None of these events represent unanticipated adverse device effects.[238]

Subsequent clinical trials

SUCCES II clinical trial

287 The SUCCES II clinical trial was initiated by Conceptus France in 2008, with the final report delivered on 27 January 2017.[239] SUCCES II was a prospective, multi-centre, non-interventional observational study. The study collected data using questionnaires and assessed satisfaction, effectiveness and complications of the Essure procedure in the short (three months), middle (12 and 24 months) and long-term (five years).[240]

288 The study had the following objectives:

> Primary
>
> To assess patient satisfaction with the Essure® procedure at 5 years. Patients with complications (Essure® migration, Essure® expulsion, upper genital tract infection) or pregnancy during the follow-up are considered as not satisfied by convention.
>
> Secondary
>
> To assess:
>
> - dissatisfaction and its causes at all time points;
>
> - pain experienced during and after Essure® placement and the potential risk factors for pain;
>
> - methods used and the interpretation of the 3-month control test; - effectiveness, complications and satisfaction of the Essure® procedure

236 BAY-EDPA-0990375 at 25.
237 Ibid at 28-29.
238 Ibid at 29.
239 BAY-JCCP-0127692 at 4.
240 Ibid at 31.

in the short and middle tern;

- long term regret of patients to have undergone an Essure® procedure;

Safety

To collect adverse events (AEs), with a specific focus on removal and perforation.[241]

289 The primary objective was evaluated by the number of patients who reported being 'very satisfied' or 'satisfied' at five years. Patients were considered 'not satisfied' by default when any of the following outcomes occurred:

(a) a complication or unintended pregnancy;

(b) placement or procedure failure;

(c) hysterectomy related to Essure;

(d) Essure removal related to the device; or

(e) dissatisfaction at the last observation (in the case of premature discontinuation not related to the procedure).

290 The study results captured data from 2,593 patients from 13 centres.[242] These patients comprised the 'intention to treat set' ('ITTS'). Of those, 2,218 patients (85.5%) had a successful Essure placement, meaning they could rely on Essure for contraception.[243] These patients comprised the 'per protocol set' ('PPS'). Nine hundred and seventy patients, or 37.4% of the ITTS, were lost to follow-up.

291 In summary, the study found:

(a) Of 1,392 assessable patients in the PPS, the satisfaction rate at five years was 94%. Sixty out of 1,385 patients (4.3%) reported they were 'not satisfied' after five years, independent of whether or not they experienced complication/s or pregnancy. The rate of patients who experienced at least one complication

241 Ibid at 31.
242 Ibid at 34.
243 Ibid.

(upper genital tract infection, expulsion or migration) or pregnancy during the follow-up period was between 1.4% to 2.2%.[244]

(b) At each interim time point (three, 12 and 24 months), between 1.9% and 2.9% of patients reported that they were 'not satisfied'. At the same time points, the rate of patients who experienced at least one complication ranged from 0.5% to 1.9%. One unintended pregnancy was reported at the three month follow-up visit; five were reported at the 12 month follow-up; four at the 24 month follow-up; and one at the five year follow-up.[245]

(c) Pain was a frequently reported symptom. Overall, pain was reported by 2,168 (83.6%) patients with 81.5% of the reports related to the placement procedure. Post-operative pain and cramping was reported by 590 patients (approximately 25%). In addition, post-operative bleeding was reported by 403 patients (17.3%). A total of 600 patients (23.1%) reported abdominal pain (which included post-operative pain/cramps and other pain events reported during the entire course of the study) and 49 patients (1.9%) reported pain related to their reproductive organs (e.g. pelvic pain).[246]

292 The results of the study were reported as follows:

> The patient satisfaction rate 5 years after a successful Essure® procedure (primary outcome) was 94.0%. This rate highlights a high level of satisfaction towards Essure®, but it should be noted that a final assessment of satisfaction could not be obtained in many patients due to their loss to follow up.
>
> Complications (migration, expulsion, infection) were in line with the rates observed in the clinical trials and reported in the literature. During the whole follow-up, abdominal migration of the device, expulsion and upper genital tract infection was observed in 1.6%, 0.9% and 0.6% of patients, respectively, while fallopian tube and uterine perforation were reported in 0.5% and 0.4% respectively. 165 patients (6.4%) underwent a subsequent surgical intervention on genital organs during the follow-up which entailed Essure® removal. This included 87 hysterectomies (3.4%), of which only one hysterectomy was considered related to Essure®, as well as for 78 removals other than hysterectomy (73 related to Essure®). Laparoscopic tubal sterilization was

244 Ibid at 35.
245 Ibid at 36.
246 Ibid.

> offered to 40 patients following placement failure while in a further 13 patients an incidental device removal was entailed after unilateral placement failure.
>
> Five patients became pregnant unintendedly after a satisfactory confirmation test indicating an efficacy rate of 99.8%. Six other unintended pregnancies were reported in patients told not to rely.
>
> The majority of adverse events were elicited through structured polar questions (Y / N) without further precision, at the 3-month visit, pertaining to the post-operative period. The reported rates are not unexpected in the context of post-operative complaints after hysteroscopy and Essure® insertion. The majority of patients who complained about pain or bleeding in the post-procedural period did not complain about such disturbances at any later time point. While the occurrence of some pain or vaginal bleeding is well known in the post-procedural period, the high satisfaction rate elicited at the 3-month follow-up and beyond provides evidence that these post-procedural bleeding and pain events had a low clinical impact. In conclusion, the final analysis of the SUCCES II study shows a high level of patient satisfaction, a high efficacy rate, and confirms the positive benefit/risk profile of Essure® without raising any new and unexpected safety concern.[247]

Transvaginal ultrasound clinical study

293 On 29 June 2015, the FDA approved a prospective clinical study to evaluate the effectiveness of use of transvaginal ultrasound ('TVU') to confirm Essure placement in patients ('TVU study').[248]

294 Prior to June 2015, an HSG was required to evaluate Essure location and tubal occlusion in the US.[249] Outside the US, TVU and/or pelvic x-ray were used to evaluate Essure location.[250] In those countries, an HSG was performed only for those patients whose pelvic x-ray or TVU findings showed suspicious or unsatisfactory Essure location.[251]

295 The primary purpose of the TVU study was to gain approval of a TVU/HSG 'confirmation test' algorithm in the US.[252] The study followed 620 patients for 10 years following discontinuation of alternative contraception.[253] Of these patients, 597

247 Ibid at 37-8.
248 BAY-EDPA-4360130 at 1.
249 Ibid at 12.
250 Ibid.
251 Ibid.
252 Ibid.
253 Ibid.

underwent the Essure procedure and 547 were told to rely on Essure for contraception.[254] At the time of trial, the study remained ongoing.[255]

296 A condition of approval was that the TVU study further evaluate pregnancies and adverse events, with reports including this information to be submitted to the FDA each year.[256]

297 The 2019 TVU study in the annual PMA report set out the following information about the study:

> **2.1 Study Co-Primary Endpoints**
>
> - Occurrence of confirmed pregnancy at 1 year among subjects relying on Essure inserts for birth control on the basis of the TVU/HSG confirmation test.
> - Intent-to-treat (ITT) reliance rate 3 months following TVU/HSG confirmation test protocol.
>
> **2.2 Study Secondary Endpoints**
>
> - Subject satisfaction with TVU
> - Occurrence of confirmed pregnancy at 10 years among subjects relying on Essure inserts for birth control on the basis of the TVU/HSG confirmation test.[257]

298 The report sets out the following results in relation to reliance on the device:

> **3.2.4 Reliance time to date**
>
> All calculations are based on the current data cut-off. The calculation summarizes the total number of women-months observed up to the data cut-off. As of the data cut-off date for this report, 291 subjects had a 6-year follow-up visit and 21 subjects had a 7-year follow-up visit. To date, 4 pregnancies occurred in a total of 33,189 women-months of follow-up.[258]

299 In relation to adverse events it states:

> As of the data cut-off date, 1560 AEs were reported in 383 (64.2%) subjects. Note that a subject may have reported more than one AE. AEs reported in >5%

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254 Ibid.
255 Ibid at 1.
256 Ibid at 14.
257 Ibid.
258 Ibid at 19.

> of subjects were menorrhagia (13.6%), pelvic pain (9.0%), dysmenorrhoea (7.9%), and abdominal pain (5.4%).[259]
>
> …
>
> Serious adverse events (SAEs) and pregnancies are presented in Table 3-1 l; there are 116 SAEs/pregnancies in 66 subjects listed.[260]

300 Finally, in relation to Essure removals it reports:

> Of the 548 subjects who were told to rely, 59 subjects (10.8%) had at least one device removed[.]
>
> …
>
> The mean number of days from the last insert procedure to the removal procedure was 1585 days. There were two instances of unintended removal (24-007 and 21-013) and 58 intended removal procedures. Among the primary reasons for intentional device removals (n=58), the most common was "Adverse events" 26 (43.3%), followed by "Removals in conjunction with other gynecologic surgery" 19 (31.7%), "Removal per subject request" 12 (20.0%), and "Other" 1 (1.7%). When possible, subjects who reported removal for reasons other than AE but reported concomitant Essure related AEs are being queried to clarify the primary reason for device removal.[261]

NovaSure endometrial ablation clinical trial

301 Endometrial ablation ('EA') is a treatment for pre-menopausal women with menorrhagia and dysfunctional uterine bleeding, and can be an alternative to hysterectomy in appropriate patients. The 'NovaSure' EA procedure delivers radio frequency into the uterine cavity via a bipolar electrode array in order to ablate the endometrium and decrease uterine bleeding.[262]

302 The NovaSure EA clinical trial was a prospective, multi-centre, single-arm observational study to monitor the effectiveness and safety of Essure when the NovaSure radiofrequency EA procedure is performed, following a successful Essure confirmation test.[263]

303 The purpose of the study was to:

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259 Ibid at 21.
260 Ibid at 31.
261 Ibid 38, 40.
262 BHC.001.001.0727 at 8.
263 BAY-JCCP-3929506 at 11.

> … evaluate the effectiveness and safety of the Essure system when a NovaSure EA procedure was performed following a successful Essure Confirmation Test.[264]

304 Bayer sent an interim report to the FDA on 22 February 2019.[265] The final report, dated 27 October 2021, was provided to the FDA on 7 January 2022.[266]

305 The objectives and endpoints of the study are listed in the interim report as follows:

> **Objectives**
>
> - Evaluate the contraceptive failure rate of Essure when NovaSure is performed following a successful Confirmation Test, and
> - Monitor the incidence of adverse events (AEs) and/or complications associated with the performance of NovaSure in the presence of Essure inserts.
>
> **Post-approval Study Endpoints**
>
> - Occurrence of confirmed pregnancy at 1 and 3 years after NovaSure EA among subjects relying on Essure inserts for permanent birth control when NovaSure is performed following a successful Confirmation Test.

306 The study population consisted of adult women between 21 and 50 years of age with menorrhagia who had completed a successful Essure confirmation test. The NovaSure EA procedure was performed on a total of 209 participants, of which 174 (83.3%) completed the study.[267]

307 The final report found, in relation to adverse events:

> The frequency of AEs was reported as an event count. A total of 398 events were reported in 116 subjects (55.0%) in the SAF population. The intensity of most of the AEs (240 events in 92 subjects [43.6%]) was considered mild. There were 123 moderate-intensity events reported in 55 subjects (26.1%) and 35 severe-intensity events reported in 19 subjects (9.0%).[268]

308 Four adverse events in three subjects were reportedly related to Essure.[269]

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264 BHC.001.001.0727 at 8.
265 BAY-JCCP-3929506 at 1.
266 BHC.001.001.0727 at 1.
267 Ibid at 8-9.
268 Ibid at 47.
269 Ibid.

309 The final report found, in relation to serious adverse events:

> A total of 28 SAEs were reported in 18 subjects (8.5%). The intensity of most (22 events) of the SAEs was considered severe (15 subjects, 7.1%). There were 4 moderate-intensity events reported in 3 subjects (1.4%) and 2 mild-intensity events in 2 subjects (0.9%). There were 2 SAEs in 2 subjects (0.9%) that were related to Essure device…[270]

522 study

310 In February 2016 the FDA directed Bayer to conduct a post-market surveillance ('PMS') study to gather more data about the benefits and risks, and the effectiveness, of Essure ('522 study').[271]

311 The 522 study is an open label, non-randomised, prospective observational cohort study of two cohorts of subjects who chose to undergo either the Essure procedure or laparoscopic tubal sterilisation.

312 The primary safety end points of the 522 study are:

(a) new onset or worsening chronic lower abdominal and/or pelvic pain;

(b) new onset or worsening AUB;

(c) new onset or worsening hypersensitivity and allergic reactions, and autoimmune disorders (new onset) or autoimmune-like reactions; and

(d) invasive gynaecologic surgery including Essure removal.

313 The 522 study is ongoing. From time to time the FDA has published interim data from the study.

314 Further consideration of the 522 study is undertaken in Chapter XV of these reasons.

<u>Post-market surveillance and risk management</u>

315 Carney gave evidence that Bayer had a number of processes and procedures in place

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270 Ibid.

271 Carney at 43 [148] (LAY.500.001.0008_2).

for PMS and risk management in relation to Essure.[272] These included:

> (a) the preparation of [the annual PMA reports];
>
> (b) the preparation of Clinical Evaluation Reports (or similar documents such as Clinical Evaluation Update Reports);
>
> (c) the preparation of various risk management file materials;
>
> (d) the preparation of periodic post-market surveillance reports;
>
> (e) the preparation of pharmacovigilance trend reports;
>
> (f) the preparation of risk analysis reports; and
>
> (g) discussion of issues and risks related to post-market surveillance activities relating to the Essure Device at Bayer Management Review Meetings.[273]

316 Carney said that because the US was considered the 'lead market' for Essure, many of the processes and procedures focused on matters concerning the US. However, she said that regulatory affairs matters related to Essure which arose in or relating to the US had implications for sales and distribution in other jurisdictions.[274] Some of Bayer's specific regulatory functions included:

> (a) performing a weekly review of all complaints arising from clinical trials;
>
> (b) conducting a weekly and monthly review of other complaints to identify new areas of concern;
>
> (c) conducting the verification process for potential safety signals and escalating verified safety signals to the Product Quality and Safety Committee (PQSC);
>
> (d) preparing and maintaining policies and procedures for complaint trending, data systems used for signal analysis and global complaint databases; and
>
> (e) preparing weekly literature reports related to Essure and permanent contraception more generally.[275]

Essure annual PMA reports

317 FDA regulations required Bayer to submit annual reports regarding the safety of Essure which addressed certain matters and reporting criteria. These included:

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272 Ibid at 44.
273 Ibid at 45.
274 Ibid at 45-46.
275 Ibid at 46.

(a) a summary of changes affecting the safety of Essure during the reporting period;

(b) a summary and analysis of pregnancies associated with Essure;

(c) a summary and analysis of unsatisfactory device location incidents; and

(d) a summary and analysis of device removal cases.[276]

Essure clinical evaluation reports

318 Bayer prepared a number of clinical evaluation reports in relation to Essure. The clinical evaluation reports typically included a description of Essure and its intended application; the context for the clinical evaluation and choice of clinical data types; and a summary of the clinical data.[277]

319 Carney gave evidence that she had direct responsibility for the preparation of two of these reports: the Clinical Evaluation Update Report dated 28 September 2018 and the Clinical Evaluation Update Report dated 19 September 2019.[278]

Periodic post-market surveillance reports

320 Bayer prepared quarterly risk management reports for Essure (from 2013 to 2015), which were subsequently called 'Post Market Surveillance Review Reports' (from 2015 to 2017). The reports were prepared by the Bayer pharmacovigilance team and covered, amongst other things, any new hazards associated with Essure.[279]

321 Bayer also prepared monthly 'Essure Post Market Surveillance Reports' from 2013 to 2015, which addressed the worldwide commercial distribution of Essure and noted key product technical complaints.[280]

Risk analysis reports

322 Bayer prepared a number of other risk analysis reports, later called 'Device Risk

276 Ibid.
277 Ibid at 47; BAY-JCCP-0661231 at 11.
278 Carney at 47 (LAY.500.001.0008_2).
279 Ibid.
280 Ibid at 48.

Management Reports'. These included the general characteristics and intended purpose of Essure, an evaluation and summary of possible hazards, the risk-to-benefit ratio, and details on specific device risk characteristics.[281]

323 Bayer also prepared, from time to time, a number of complaint trend reports for Essure.[282]

Bayer management review meetings

324 Between 2014 and January 2018, Bayer held quarterly PMS and risk management meetings relating to Essure.[283] Matters discussed at these meetings included updates about regulatory affairs; ongoing clinical studies and other medical affairs; pharmacovigilance; product supply and quality; sales and marketing; and risk assessment.[284]

Increased medical reporting and concerns about Essure

Social media

325 In November 2013, Carney commenced her role as director of the 'US Medical Affairs, Women's Healthcare' team at Bayer HealthCare. She said that from that time, her practice was to keep apprised of publications (including news articles) concerning Essure. This included reviewing alerts sent to her by the Bayer library team, some of which contained references to social media activism relating to Essure.[285] Carney said that around the time she commenced her role, it became apparent to her that the primary social media commentary about Essure was generated from a private Facebook group called 'Essure Problems'. Carney said that she was involved in formulating Bayer's response to the concerns raised by the 'Essure Problems' group and other social media activity.[286]

281 Ibid at 51; BAY-JCCP-5906659 at 7.
282 Carney at 51 (LAY.500.001.0008_2).
283 Ibid at 52.
284 BAY-JCCP-6901249.
285 Carney at 5 [177], [179] (LAY.500.001.0008_2).
286 Ibid at 54 [183].

326 It appears that from around this time, a social media monitoring report was circulated internally within Bayer Healthcare each week.[287] A report for the period 27 January 2015 to 2 February 2015 recorded the daily volume of Essure 'mentions' on Facebook, Twitter and other online forums.[288] These mentions were categorised by sentiment (positive, negative, neutral or mixed) and theme (side effects, removal, efficacy, news sharing, seeking information). The report also recorded the 'notable drivers' of Essure-related online conversation.

Medical device reporting in the US

327 Medical device reports ('MDRs') comprised one of the FDA PMS data sources. MDRs were submitted to the FDA Manufacturer and User Facility Device Experience ('MAUDE') database by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters (healthcare professionals, patients and consumers). The FDA used MDRs to monitor Essure performance, detect potential device-related safety issues and contribute to benefit-risk assessments of the product. MDRs were also used to establish a 'qualitative snapshot of adverse events' and detect actual or potential device problems in a 'real world' setting.[289]

Increase in Medical device reports

328 Carney said that Bayer reviewed and analysed MDRs related to Essure, including those from patients and implanting physicians. She said that in 2013, she learned there had been a sudden increase in the number of MDRs voluntarily submitted to the FDA compared to previous year-on-year figures, and that this trend continued into 2014 and beyond. Carney attributed the increased reporting rates in part to a shift in policies and procedures used to capture customer feedback, but said she was otherwise confused by the trend.[290]

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287 BAY-JCCP-2492871.
288 BAY-JCCP-2492873.
289 Carney at 54-5 [187]-[190] (LAY.500.001.0008_2); BAY-EDPA-0934554 at 4580-81.
290 Carney at 56 [191]-[193] (LAY.500.001.0008_2).

329 Bayer HealthCare conducted a global pharmacovigilance PMS review of Essure for the period 1 October 2013 to 30 June 2014.[291] The review reported the following trend analysis:

> Total numbers of medically confirmed and non-medically confirmed case reports independently of reported events are rendered in Table 5 and show that the number of medically confirmed case reports has only gone up slightly (26% increase over previous period) whereas the number of non-medically confirmed reports has increased disproportionally (310% increase over previous period). The increase in non-medically confirmed cases is mirrored in a disproportionate increase of case reporting for events which have a greater propensity to be described in consumer reports, such as hypersensitivity type of events, pain, infections and device complications which constitutes of a broad range of unspecific terms.[292]

330 The review concluded that the observed increase in case and event reports after 1 October 2013 was not related to any safety or quality issue or any change in the known safety profile of Essure, but could be attributed to company procedure and external factors. Such factors included stimulated reporting due to media attention; active collection of adverse events from healthcare professionals within targeted markets; reimbursement programs; and changes to the processing and classification of adverse event case reports. Activities including 'online listening' were also said to have generated case reports which were not medically confirmed.[293]

331 In July 2014, Bayer HealthCare reported a major procedural and policy shift in customer feedback processes following Bayer's acquisition of Conceptus. It was reported that these procedural and policy changes also resulted in an increased capture rate of adverse events associated with Essure. Changes included an increase in sales force; the launch of the active 'online listening' program; responses to customer service inquiries as to the occurrence of an adverse event; and proactive literature searches.[294]

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291 BAY-JCCP-0086604.
292 Ibid at 12.
293 Ibid at 14.
294 BAY-JCCP-0086091 at 7.

ARGUS database

332 Bayer maintained the 'ARGUS' database as part of its internal pharmacovigilance system. The database recorded all reports of adverse events including, but not limited to, those concerning Essure.

333 The Bayer defendants produced spreadsheets of data from the ARGUS database relevant to Essure between 2000 and 2019. Turner prepared a summary of the data in a table which is reproduced below:[295]

[295] TUR.002.001.0067_2 at 1.

Cumulative cases recorded in ARGUS by 'Company causality (event assessment)', 'Medically confirmed' = 'MC' only	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
'pelvic pain : related'	0	0	0	2	4	9	17	26	43	76	101	128	169	260	446	811	1448	4088	4590	5120
'menorrhagia : related'	0	0	0	0	1	1	2	2	16	54	79	105	127	198	276	515	1062	3523	3845	4093
'dysmenorrhoea " related'	0	0	0	1	1	1	2	3	12	22	29	49	63	100	163	327	842	2998	3269	3502
'abdominal pain : related'	0	0	0	0	2	7	19	26	79	220	363	444	485	551	675	851	1246	2602	2869	3053
'dyspareunia : related'	0	0	0	0	0	1	2	3	7	11	15	21	34	77	135	289	752	2550	2766	2988
'back pain : related'	0	0	0	0	1	3	3	3	6	9	15	24	47	97	177	328	658	1718	1856	1952
'abdominal pain lower : related'	0	0	0	0	3	5	7	10	45	117	180	215	242	279	340	462	712	1905	2124	2218
'menstrual disorder : related'	0	0	0	0	0	0	0	0	0	5	8	12	19	30	46	86	150	624	690	706
'device dislocation : related' or 'device expulsion : related'	0	1	3	21	70	121	226	339	524	795	1006	1273	1556	1854	2267	2726	3274	4715	4993	5124
'allergy to metals : related'	0	0	2	2	4	8	10	11	15	24	40	55	69	107	186	306	521	1095	1204	1329
'perforation : related'	0	0	3	32	70	112	219	305	450	624	769	894	993	1136	1347	1636	2004	3073	3238	3385

334 Turner does not rely on this data as proof of causation of relevant adverse events, but as being relevant to the Bayer defendants' knowledge of the risk of adverse events, and therefore to foreseeability relevant to her negligence claim.

335 The defendants' spreadsheets contain a 'company causality (event assessment)' column and a 'case medically confirmed' column. With respect to data in the latter column, according to the user manual for ARGUS:

> A report is medically confirmed if it was initially received from a Health Care Professional (HCP) or reported on behalf of a HCP (e.g. if reported by the physician's office manager who is not a HCP), or at least one adverse event in a non-HCP report is subsequently suspected to be causally related to a BHC product by a HCP. It is important to distinguish between verification of the facts by the HCP (things did or did not happen as described by the patient) and the HCP's confirmation that a drug related adverse event occurred.[296]

336 Carney was asked in re-examination about what was meant by the descriptor 'medically confirmed':

> What does medically confirmed mean to you?---Medically confirmed means that either the initial reporter was a doctor, a nurse, someone with a medical background, or if it had been reported by, let's say, the patient, that we were able to get additional information about that patient's medical history.
>
> And what does not medically confirmed mean?---Not medically confirmed means whatever the complaint was we take it at face value but we have no other way of verifying any of the information.
>
> What, if any, relationship do those two terms bear in relation to whether something was caused by the relevant fact, in this case the device?---Causality is difficult and MDRs in and of themselves and, yes, I predominantly worked with the US and even the FDA says MDRs, it's extremely difficult to assess causality because you don't have the information. You don't have a medical history. You don't have what medication she's on. You don't have operative reports. Now, if you have a medically confirmed case you are more likely to be able to assess that information. But even then MDRs are not the easiest information to assess causality. Again, never ignored, they are - you can find out a whole lot of other things, but MDRs are really not designed to assess causality.
>
> Let me ask it this way. What is being confirmed in the phrase medically

[296] BAY-JCCP-5427453 at 69.

confirmed in your experience?---The complaint.[297]

337 With respect to the 'company causality' column, the database recorded data using the following descriptors:

> **Related:** There is a reasonable suspicion that the event was caused by the drug. Indicators for this may be but are not limited to: the timely sequence of the onset of the event to the administration of the drug and the unlikelihood that the event is attributed to concomitant, intercurrent or underlying diseases/conditions or other drugs or chemicals. In addition, the clinically reasonable response on withdrawal of the drug (de-challenge) can be used to suspect a causal relationship.
>
> **Unrelated:** There is [no] reasonable suspicion that the event was caused by the drug. Indicators for this may be but are not limited to: suspect medication has not been used before the onset of the event, a clear alternative explanation exists which excludes any causality by the drug (e.g. mechanical bleeding at a surgical site). Alliteratively, a causal relationship might not be plausible, examples: the patient is struck by an automobile and there is no indication that the drug caused disorientation that may have led to the event, or patient developed cancer a few days after drug administration.
>
> **Not assessable:** An adverse event cannot be assessed because information is insufficient or contradictory and which cannot be supplemented or verified. Any efforts to obtain more information and/or to clarify the contradiction must be performed (Follow-up requests).[298]

2015 FDA review

338 In 2015, the FDA conducted a review of Essure in advance of a meeting of the OGDAP held on 24 September of that year ('2015 OGDAP meeting').[299] The introduction to the FDA review report began:

> Sterilization for permanent birth control may be accomplished in a variety of ways. One method, hysteroscopic sterilization, began to be widely used in the United States after the 2002 FDA approval of the Essure System (P020014; original applicant, Conceptus, Inc.). Since initial approval, FDA has continued to monitor the safety and effectiveness of the Essure System and the, safety concerns that have been raised within the patient and healthcare provider community. FDA believes that, in keeping with its public health mission, it is appropriate to do the following:
>
> - have an open and transparent dialogue among FDA and its stakeholders, including the device manufacturer, health care providers, researchers, patients, and the public,

297 T2367-8 (TRA.500.024.0001_2 at 0045_22 – 0046_18).
298 Ibid.
299 BAY-EDPA-0934554.

- review and discuss available data regarding the benefits and risks associated with the use of the Essure System, and
- obtain FDA Advisory Committee and public input on the safety and effectiveness of the Essure System.

> As such, FDA's Obstetrics and Gynecology Devices Advisory Panel is being convened to review and discuss current information related to the effectiveness of the Essure System, adverse events associated with, or suggested to be associated with, the Essure device, and the overall benefitrisk profile of the device. The Committee will be asked to provide input regarding the need for product labeling changes, the collection of additional post-market safety data, or other mitigation steps, and the overall benefit-risk profile of the device based on current available information[.][300]

Under 'Regulatory History' the report stated:

> Beginning in late 2013, FDA has received a significant increase in the number of adverse event reports related to Essure; in particular, from patients who have received the device. The Agency has also been cognizant of complaints related to the device being conveyed in traditional and social media outlets. Accordingly, FDA has recently conducted an additional review of data related to the Essure system and determined that the information should be vetted and discussed in an open forum, i.e., this panel meeting.[301]

339 The FDA noted that limitations of MDRs included the potential submission of incomplete, inaccurate, untimely, unverified, or biased data, particularly in circumstances where the device in question had not been directly evaluated.[302] The review report stated that 'the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use.' The report also stated:

> Other limitations of MDRs include, but are not limited to:
>
> • MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
>
> • Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly

300 Ibid at 3.
301 Ibid at 11.
302 Ibid at 27.

evaluated.

> • MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
>
> • MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.[303]

340 The report also noted that the FDA sent copies of voluntary reports to the device manufacturer, who evaluated the data and submitted MDRs for those it considered met the mandatory reporting criteria. This meant there were 'many instances in which multiple MDR reports [were] submitted for the same event'.[304]

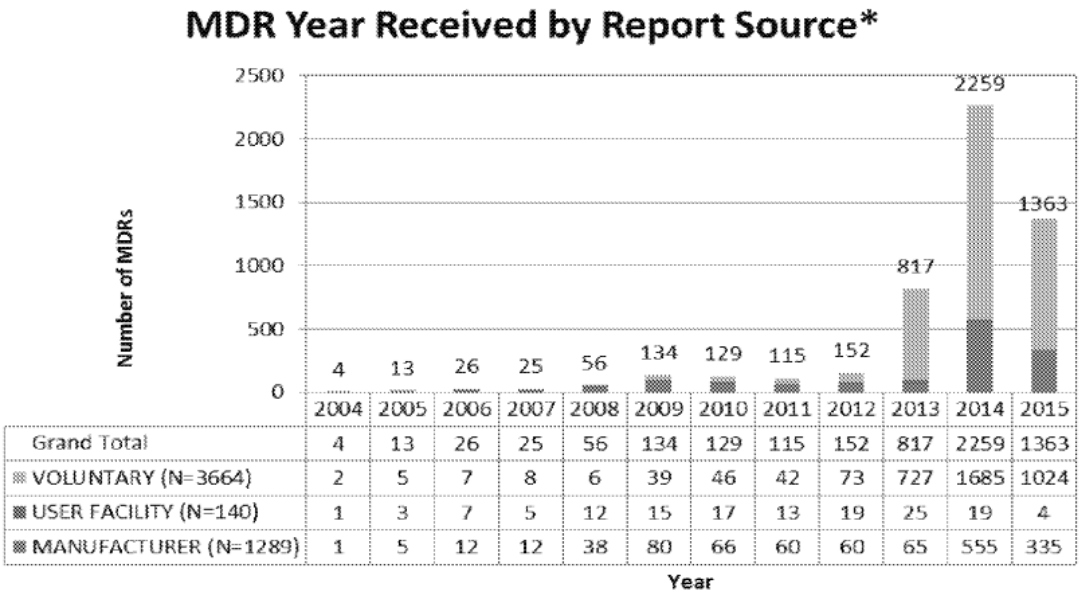
341 The review reported a 'sharp increase' in the number of MDRs received between 2013 and 2015, primarily due to a significant increase in voluntary reports.[305] It concluded that MDR data could not be used to establish rates of adverse events, or to confirm whether a device actually caused or worsened a specific event.[306] The report said:

> Because rates of events cannot be determined by MDR data, it is not possible to determine whether the numbers of reports represent a true increase in rates of particular known or expected events, or rather represents an increase in the reporting of adverse events or increase in the number of devices in clinical use.[307]

The figure below was included in the report and presented an overview of the number of MDRs received per year:[308]

303 Ibid at 27–28.
304 Ibid at 28.
305 Ibid.
306 Ibid at 73.
307 Ibid.
308 Ibid at 29.

Figure 5 – Number of MDRs Received per Year, Prior to June 1, 2015, by Report Source



342 The MDRs included a broad range of reported symptoms. The FDA focused on the more commonly discussed or reported adverse events which included:

- Pain and cramping (abdominal, pelvic) — with a focus on chronic/persistent pain
- Abnormal bleeding or menstrual irregularities
- Headache
- Metal allergy/sensitivity.[309]

343 The review report said that the majority of MDRs received by the FDA noted the presence of abdominal or pelvic pain and/or cramping.[310]

ANSM report

344 On 30 May 2017, an independent committee convened by the French National Agency for Medicines and Health Products Safety ('ANSM') prepared a report assessing concerns about Essure.[311] The committee was tasked with providing an opinion on the benefit-to-risk ratio of Essure and putting forward new recommendations if necessary, in the context of increasing regulatory concerns in the US, Canada, France

309 Ibid at 40.
310 Ibid at 43.
311 BAG.001.001.4728; SBM.500.001.0003_2 at 300.

and the Netherlands.

345 Following a meeting held on 19 April 2017, the committee unanimously concluded that:

(a) the data from the literature, medical device vigilance and the findings of the epidemiological study conducted by ANSM did not alter the favourable benefit-to-risk ratio of Essure;

(b) no new regulatory measures were required in view of ANSM's scientific knowledge at that time; and

(c) patients who were considering permanent contraception should be provided with independent information on all of the contraceptive methods available and, in particular, on the advantages and risks of the two methods of permanent female contraception to allow them to make an informed decision.[312]

Regulatory concerns from 2014 to 2017

346 The increase in adverse event reporting coincided with increased concerns about Essure from international regulators, including in the US, Canada, the EU and Australia.

United States

347 On 22 July 2015, the FDA announced it would convene the 2015 OGDAP meeting in order to:

> … seek expert scientific and clinical opinion on the risks and benefits of the Essure System. The committee will be asked to evaluate currently available scientific data pertaining to the safety and effectiveness of the Essure System, such as events related to implant perforation/migration, device removal, chronic pain, allergic reactions, and unintended pregnancy. The committee will be asked to provide recommendations regarding appropriate device use, product labeling, and potential need for additional postmarket clinical studies.[313]

312 SBM.500.001.0003_2 at 301.
313 PUB.500.002.0002.

348 The panel for the 2015 OGDAP meeting included medical professionals with speciality in gynaecology; reproductive epidemiology; biostatistics; pelvic medicine and reproductive surgery; allergy and immunology; biomedical engineering; reproductive endocrinology; dermatology and toxicology; an industry representative (external to Bayer); and consumer and patient representatives. Representatives of the FDA and Bayer and members of the public including patients, medical practitioners, non-profit organisations and medical professional societies, also attended.[314]

349 Carney said that the 2015 OGDAP meeting was broadly structured into four parts:

> (a) First, a presentation by the representatives of Bayer (including Dr Zampaglione, Dr Basinksi and [Carney]).
>
> (b) Secondly, a presentation by the representatives of the FDA.
>
> (c) Thirdly, submissions by members of the public in the "open public hearing".
>
> (d) Finally, after the 'open' portion of the meeting had concluded, the Panel considered six questions prepared by the FDA relating to the safety and effectiveness of the Essure Device.[315]

350 Bayer prepared two documents for the meeting: an Executive Summary dated 3 September 2015 which provided an overview of Essure including in relation to research, development and post-market monitoring; and a presentation based on the executive summary.[316] The presentation consisted of an introductory section, a 'clinical interest' section, and a risk-benefit section.[317]

351 The FDA presentation addressed the historical perspective and current landscape of female sterilisation, the FDA review of effectiveness and safety data concerning Essure, and an epidemiological review of this data.[318]

352 Carney said that 43 members of the public addressed the OGDAP during the open public hearings. Many identified themselves as members of the 'Essure Problems'

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314 Carney at 67 (LAY.500.001.0008_2).
315 Ibid at 68 [217].
316 BAY-JCCP-3707554.
317 Carney at 67 (LAY.500.001.0008_2).
318 Ibid at 69 [225]-[226].

Facebook group or as others advocating for the removal of Essure from the market.[319]

353 Finally, the OGDAP was directed to discuss and comment on the following six topics prepared by the FDA:

(a) the degree of association between adverse events and Essure;

(b) the clinical implications and possible risk mitigation strategies for each adverse event;

(c) general recommendations for modifications to the physician and/or patient labelling to address concerns;

(d) the need for any additional post-market bench and/or clinical data related to adverse events and risk mitigation;

(e) recommendations regarding the decision to pursue hysteroscopic or laparoscopic Essure removal; and

(f) the overall benefit-risk profile of Essure.[320]

The OGDAP discussion was not binding but provided guidance for the FDA and Bayer to consider.[321]

Events following the 2015 OGDAP meeting

354 On 26 September 2015, Bayer received the following summary of the OGDAP's discussion of the FDA topics:

> **Question 1**
> Regarding the topics of interest identified by FDA:
> - There is insufficient information in all instances to connect pelvic pain and bleeding to Essure
> - All events should be evaluated for relation to the device
>
> **Question 2**
> Regarding physician training, pre-operative evaluation / selection and post-

319 Ibid at 71 [228].
320 PUB.500.002.0007.
321 SBM.500.001.0003_2 at 290 [11.51].

operative monitoring, the panel discussed:

- Consent Form
- Patient Card
- Improved compliance with confirmation test
- Post procedural protocol to assist in providing guidance on potential complications
- Device removal advice and identification of qualified physicians
- Early imaging / TVU at the time of placement
- Hypersensitivity for nickel and other components; potential testing
- Consider pre-procedure checklist / screening to determine history of autoimmune or inflammatory disorder or any chronic pain, obtain data to assess, not clear on methods or targets

Question 3
Suggested modifications to the labeling included:

- Permanent surgical procedure that requires hysteroscopy
- More prominence of materials contained in the device
- Device removal

Question 4
Regarding additional data:

- Study patients who had device removed, obtaining medical history and pathology reports of tissue
- Analyze existing preclinical testing on biocompatibility
- Collect additional safety information from TVU long term study
- Consider registry, registry vs RCT — RCT low feasibility

Question 5
Regarding device removal:

- Persistent abdominal pain without evidence of incorrect placement, look at other causes
- Pain with incorrect positioning, consider near term removal
- Asymptomatic with suspected incorrect placement, consider removal and alternate contraception
- Hypersensitivity- more data needed on whether to remove device

Question 6
Regarding the Benefit / Risk:

- Favorable benefit / risk profile for patients; ideal Essure patient
- Patient specific considerations noted: hypersensitivity, autoimmune disorders, pelvic inflammatory disease, dysfunctional uterine bleeding, prior uterine surgery, chronic pelvic pain and those with complications at time of placement, however, Essure may still be the best option for some of these patients.[322]

355 In October 2015, Bayer and FDA representatives met to discuss Bayer's proposals for addressing the matters raised by the OGDAP. On 4 November 2015, Bayer provided

[322] BAY-EDPA-0963558, Carney at 71 [230] (LAY.500.001.0008_2).

a written submission to the FDA in relation to these matters. Actions included in the submission related to:

(a) physician training and patient counselling;

(b) data generation activities from ongoing clinical trials and database studies;

(c) Essure insert removal; and

(d) hypersensitivity / nickel allergy.[323]

356 Negotiations between Bayer and the FDA to prepare updated US product labelling and patient information followed throughout 2016. The proposed updates involved the addition of a 'boxed warning' which would appear at the top of an IFU or PIB and contain key information and warnings for the reader's immediate attention. Bayer provided a number of written submissions to the FDA outlining its proposed updates.

357 In March 2016, the FDA published a draft guidance document on labelling for hysteroscopically-placed tubal implants intended for sterilisation, which was followed by a 60-day feedback period ('draft guidance').[324] The draft guidance included the following:

> FDA believes that a boxed warning should be part of physician and patient labeling materials for a permanent, hysteroscopically-placed tubal implant for sterilization and should:
>
> - Note the types of significant and/or common adverse events that may be associated with the device and its insertion and/or removal procedures, including those noted in clinical trials, as well as those reported in device use experience.
>
> - Include a statement noting that these risks should be conveyed to the patient during the woman's decision-making process.[325]

The draft guidance also suggested introducing a patient decision checklist with key information about Essure, and proposed text for the boxed warning. Carney said that

323 BAY-JCCP-3645789; Carney at 73 [234] (LAY.500.001.0008_2).
324 Ibid at 80 [240]; BAY-ESSURE-0087693.
325 BAY.EDPA.0948415 at 7.

she and others within Bayer treated the draft guidance document as being, in effect, binding from this time.[326]

358 On 31 October 2016, the FDA issued the final version of the guidance document ('guidance document').[327] Although the guidance document related to all permanent, hysteroscopically-placed tubal implant devices intended to achieve sterilisation, Essure was the only such device supplied in the US at the time of publication.[328] The guidance document addressed new labelling components such as the boxed warning and patient decision checklist, and stated:

> This guidance identifies the content and format for certain labeling components for permanent, hysteroscopically-placed tubal implant devices intended for female sterilization. FDA believes this guidance will help to ensure that a woman receives and understands information regarding the benefits and risks of this type of device prior to undergoing implantation.
>
> FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.[329]

359 On 15 November 2016, the FDA approved the negotiated changes to the IFU and PIB labelling.[330] The final boxed warning in use from this time read:

> WARNING: Some patients implanted with the Essure System for Permanent Birth Control have experienced and/or reported adverse events, including perforation of the uterus and/or fallopian tubes, identification of inserts in the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions. If the device needs to be removed to address such an adverse event, a surgical procedure will be required. This information should be shared with patients considering sterilization with the Essure System for Permanent Birth Control during discussion of the benefits and risks of the device.[331]

360 On 9 April 2018, the FDA announced that the sale and distribution of Essure would

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326 Carney at 85 [252] (LAY.500.001.0008_2).
327 PUB.500.002.0009.
328 Carney at 85 [251] (LAY.500.001.0008_2).
329 PUB.500.002.0009 at 4.
330 BAY-ESSURE-0091652.
331 Carney at 87 [257] (LAY.500.001.0008_2).

be legally restricted to healthcare providers and facilities that adhered to the new labelling requirements. The FDA said it required this restriction:

> … after becoming aware that some women were not being adequately informed of Essure's risks before getting the device implanted, despite previous significant efforts to educate patients and doctors about the risks associated with this device.[332]

361 On 19 April 2018, Bayer submitted a plan for implementing new labelling language to alleviate the FDA's concerns, which included monitoring the use of the patient decision checklist. [333]

Canada

362 Around the same time that Bayer and the FDA were corresponding about the 2015 OGDAP meeting outcomes, Bayer was also corresponding with Health Canada about whether the Canadian IFU should include a boxed warning.

363 On 10 May 2016, Health Canada requested that, inter alia, Bayer:

(a) expand warnings (including by providing a boxed warning) and revise the 'Possible Adverse Effects' statement in the Canadian IFU;

(b) revise patient labelling to explain the expanded warnings and revisions;

(c) provide a 'safety information sheet' with similar content to the proposed US FDA Essure patient decision checklist;

(d) issue a risk communication which included a general discussion of Essure, types of adverse events, and reported patient outcomes; and

(e) provide an update on the 522 study and submit the results to Health Canada when available.[334]

364 On 31 May 2016, Health Canada posted a communication on its website informing

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332 TUR.002.001.0020.
333 BAY-JCCP-0135553.
334 BAY-EDPA-0948107; Carney at 110 [353] (LAY.500.001.0008_2).

healthcare professionals of the reported complications with Essure use.[335]

365 On 6 December 2016, Bayer submitted its proposed updated IFU, PIB and patient decision checklist (including amendments to the boxed warning) to Health Canada.[336] The changes were approved on 10 January 2017.[337] Health Canada announced the labelling changes the following month, summarising them as follows:

> 1. The addition of a Boxed Warning listing information on the Essure Confirmation test, adverse events that have been reported either in clinical studies or through post market surveillance and situations where device removal may be indicated.
>
> 2. The IFU has also been updated with additional information. This includes a new section on patient counseling in addition to revisions in the sections discussing safety, clinical studies, instructions for use and patient management.
>
> 3. The introduction of a PIB including a Checklist. The PIB, along with the Checklist, is intended to be reviewed by the physician and patient to facilitate the patient's understanding of birth control options, benefits and potential risks associated with the use of Essure, as well as what to expect during and after the Essure procedure.[338]

European Union

366 The NSAI, the relevant EU regulatory authority, also raised regulatory concerns about Essure between 2014 and 2017.

367 The NSAI suspended the Essure CE mark for a period of 90 days in July 2014 while investigations into device safety and performance were carried out following an audit.[339]

368 From around June 2016 until mid-2017, the NSAI carried out the Essure CE mark re-certification process.[340] In October 2016, the NSAI informed Bayer of several new re-certification requirements including that a statistically robust EU post-market clinical

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335 AMS.001.002.3278.
336 Carney at 116 [356] (LAY.500.001.0008_2).
337 BAY-EDPA-0466672.
338 AMS.001.001.0042.
339 BAU.001.002.0982; SBM.001.001.0004 at 219.
340 SBM.001.001.0004 at 210.

follow-up study of Essure be conducted.[341]

369 On 14 February 2017, ANSM informed Bayer that Essure promotion in France had been suspended while the regulator conducted a reassessment of Essure data.[342]

370 On 3 August 2017, Bayer received an NSAI 'query report' which identified a number of the NSAI and ANSM's concerns.[343] Among other matters, the query report stated:

> Bayer states the post market data is not consistent with other clinical data and that stimulated reporting is the reason for this in relation to allergy, pain and bleeding patterns. Bayer states that the PMCF study is being conducted because of the increased rate of pain, bleeding and allergy reported in PMS but this is due to stimulated reporting. Bayer will need to be open to the consideration that the need for this study is not just based on stimulated reporting and that there may be a problem in relation to pain, allergy and bleeding pattern[s].[344]

371 The query report also raised concerns about the Essure biocompatibility data and the limitations of the PMA testing that had been carried out. In particular, the report raised concern that there was no data addressing the inflammatory effect of Essure beyond three months, and that corrosion phenomena in vitro had not been assessed from a safety point of view.[345]

372 Accordingly, also on 3 August 2017, the NSAI notified Bayer of its decision to again suspend the Essure CE mark for 90 days. The notification letter stated (original emphasis):

> Pursuant to discussions held between NSAI and Bayer Pharma AG on June 7th 2017 and clarified by e mail on June 14th by NSAI to Bayer Pharma AG indicating that if the queries are not closed out prior to the expiration date, 3rd August 2017, NSAI ***will not*** be in a position to provide an extension to the certificates.
>
> The responses received by NSAI pursuant to the outstanding queries were available and reviewed by the NSAI team on Tues Aug 1st to Thursday August 3rd 2017, the responses were deemed inadequate to address the queries.

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341 BAY-EDPA-2673193 at 2.
342 AMS.001.001.0042 at 2.
343 BAY-EDPA-1566920; BAY-EDPA-1566921.
344 BAY-EDPA-1566921 at 71; SBM.001.001.0004 at 235.
345 BAY-EDPA-1566921 at 331.

> […]
>
> NSAI's Technical Review Committee have made the decision to suspend the product family certificates 252.618, **Fallopian Tube Occlusion Insert (Essure System),** Annex II.3 and II.4, for a period of 90 days **effective 3rd August 2017, until 2 Nov 2017**[.]
>
> The decision has been made based on inadequate clinical data coupled with outstanding biocompatibility data, as identified in report form 252.618.33.
>
> […]
>
> Bayer Pharma AG must immediately refrain from the use of any NSAI registration marks, advertising or labelling that makes use of or reference[s] the NSAI name, identification number, or trademark. Please confirm receipt of this communication and your cessation of placing these devices on the Market carrying CE Marking with NSAI's Notified Body Number until this issue is resolved[.][346]

373 Around this time, it appears that Bayer internally discussed its options in relation to the CE mark suspension, including not seeking CE mark renewal. On 6 September 2017, Bayer sought internal legal advice with respect to the CE mark withdrawal proposal.[347]

Australia

374 The TGA raised the issue of a boxed warning with Bayer and AMSL shortly after the FDA announced the proposed US warning.[348] On 2 March 2016, AMSL advised the TGA that it was aware of the draft guidance and that 'once the changes [had] been approved [AMSL expected] this to flow to any Essure devices sold in Australia'.[349]

375 The TGA followed up with AMSL on 15 April 2016 requesting confirmation of whether the Australian IFU would incorporate the boxed warning and whether the patient decision checklist would be provided as a risk mitigation.[350] AMSL replied on behalf of itself and Bayer on 29 April 2016:

> The discussions on the IFU which would include FDA's proposed boxed warning and the PIB with the proposed decision checklist are ongoing with FDA. We are in the process of revising the labelling based on FDA's feedback

346 AMS.001.001.0267.
347 BAG.001.002.7852 at 2; T2352 [TRA.500.024.0001_2 at 0030_2).
348 AMS.001.001.2860 at 1.
349 BAU.001.001.0028 at 1; see also attached letter at AMS.001.001.0213.
350 AMS.001.001.0182 at 1.

> and a planned submission is scheduled for mid-May. FDA will review Bayer's proposed revisions and in parallel review the public comments to the draft labelling guidance document. Once we have received FDA approval for the final labelling (IFU/PIB), we will work with TGA to implement the changes locally.[351]

376 On 5 May 2016, the TGA issued AMSL with a notice requiring provision of adverse event reports within a shorter timeframe, and annual reports for a further five years. The reasons included an 'increase in adverse event reports' and 'safety concerns' surrounding Essure.[352]

377 In June 2016, AMSL notified the TGA of Health Canada's risk communication. In July-August 2016, the TGA requested further updates from AMSL about the inclusion of a boxed warning, patient information sheet and patient decision checklist 'given the recent decisions made internationally including by the FDA and Health Canada'.[353] AMSL maintained that the changes were under review by the FDA, Health Canada and the NSAI, and that the proposed amendments would be submitted to the TGA for evaluation once approved.[354]

378 Following FDA approval of the US boxed warning in November 2016, the TGA again requested an update as to when the changes would be implemented in the Australian market.[355]

379 In February 2017, AMSL sent the TGA a draft IFU which included a boxed warning.[356] AMSL noted that the NSAI was yet to finalise the document and that a final version of the changes would be provided in due course.[357] Further TGA requests for timeline updates were met with the same response from AMSL.

380 In March 2017, AMSL notified the TGA that Health Canada had introduced the boxed

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351 AMS.001.001.0184 at 2.
352 AMS.001.001.9668 at 1.
353 AMS.001.002.1907.
354 Ibid.
355 AMS.001.001.9820 at 2.
356 BAU.001.001.0154.
357 BAU.001.001.0153.

warning in Canadian IFUs and PIBs, and that Essure had been suspended in France.[358]

381 On 9 May 2017, the TGA proposed suspending Essure ARTG registration. The TGA advised that it was undertaking a review 'in response to international regulatory action taken against this device as well as an increase in the number of adverse event reports being received by the TGA'.[359] The TGA correspondence set out a timeline of AMSL's failure to engage in relation to the boxed warning update, and stated:

> To demonstrate compliance with subsection 41GN(1)(b) [of the *TG Act*] you as the person in relation to whom the goods are included in the ARTG must be able to provide sufficient evidence to substantiate compliance with Essential Principles 2 and 13 as set out in the Act and/or the Regulations.
>
> Essential Principle 2 refers to "Design and construction of medical devices to conform with safety principles". Design and construction includes packaging, labelling and Instructions for Use. Essential Principle 2 requires the manufacturer to identify hazards and associated risks and foreseeable misuse of the device and if unable to mitigate these risks by design or other means, ensure that adequate protection measures are taken, including alarms if necessary, and inform the users of the residual risks that may arise due to any shortcomings of the protection measures adopted. You have identified a risk and developed a strategy to inform clinicians and patients of the risk; however you have not implemented this in Australia within a reason [sic] time frame. Therefore, I find that you are not compliant with Essential Principle 2.
>
> Essential Principle 13 refers to the information that must be provided with the device. This includes information about the intended performance of the device and any adverse events and contraindications. You have identified a risk and have not adequately informed the user of the device in the information that is provided with the device. Therefore, I find that your device does not comply with Essential Principle 13.[360]

382 In a meeting between Bayer, AMSL and TGA representatives on 19 May 2017, the TGA indicated that Bayer would need to submit a response package for TGA consideration within a matter of weeks to have the proposed suspension lifted.[361]

383 Bayer submitted a response package to the TGA on 24 May 2017. It proposed a black box warning to be included in IFUs and PIBs in the following terms:

- An Essure Confirmation Test should be performed three months after

358 SBM.001.001.0004 at 230 [753]; AMS.001.001.0042.
359 SBM.001.001.0004 at 232 [759]; AMS.001.002.0010.
360 AMS.001.002.0010 at 3-4.
361 AMS.001.002.2248 at 2; AMS.001.001.0134.

insert placement to evaluate insert retention and location. The patient must use alternative contraception until an Essure Confirmation Test demonstrates satisfactory results (see section XII 'Essure Confirmation Test').

- There have been reports of perforation of the uterus and/or fallopian tubes, inserts located in the intra-abdominal or pelvic cavity, persistent pain, and allergy or hypersensitivity reactions in some patients. Some of these reported events resulted in insert removal that required abdominal surgery. Device removal may lead to improvement or resolution of symptoms when: the onset is shortly after placement, imaging indicates an unsatisfactory insert location, and other etiologies for these symptoms have been considered. This information should be shared with patients consider[ing] sterilization with Essure during discussion of the benefits and risks of the device.[362]

384 I accept Turner's submission that there was an inordinate delay by AMSL and Bayer HealthCare in responding to the TGA in relation to the black box warning. However, for reasons set out in Chapter XX, the information and warnings in the IFUs that were in use about the risks addressed in the black box warning were not inadequate.

Global product discontinuance

385 On 31 May 2017, Bayer informed the TGA that it intended to discontinue the sale of Essure in Australia, Canada, Belgium, Czech Republic, Denmark, Finland, Italy, the Netherlands, Norway, Portugal, Slovenia, Sweden, United Kingdon, Chile, Columbia, Costa Rica, Mexico and New Zealand.[363]

386 On 30 August 2017, AMSL in consultation with the TGA issued a hazard alert referring to symptoms including chronic bleeding, perforation, migration and the requirement for abdominal surgery or hysterectomy for device removal.[364] Shortly after issuing the warning, AMSL recalled unused Essure stock in Australia and withdrew the device from the Australian market.[365] Around this time, Bayer noted in an internal communication that it had also agreed to recalls with Spanish and French health authorities.[366]

362 AMS.001.001.0139 at 2.
363 SBM.001.001.0004 at 235.
364 Ibid at 237; TUR.002.001.0019.
365 SBM.001.001.0004 at 237-8.
366 Ibid at 237 [774].

387 On 31 August 2017, Bayer discontinued the sale of Essure in Canada.[367]

388 On 18 September 2017, Bayer sent a letter to the NSAI confirming its decision to withdraw its application for re-certification of the CE mark, and undertaking not to place any Essure products bearing the NSAI number or mark on the market.[368]

389 On 18 July 2018, Bayer notified the FDA of its decision to discontinue sales of Essure in the US market by the end of the year.[369]

390 In its communications with relevant regulatory bodies, Bayer maintained that the decision to discontinue sales of Essure internationally was commercial in nature and not based on safety or effectiveness concerns. Carney said decommercialisation was the result of a decline in sales of Essure globally that began in 2013. However, Turner submitted that at least a substantial reason for the decision to remove Essure from international markets from about mid-2017 was the growing regulatory and public concerns about the safety of the device and 'Bayer's ensuing fear of final adverse regulatory findings' (particularly from the NSAI, which had not yet completed its re-certification process).[370] In cross-examination, Carney agreed that the decline in Essure sales coincided with increased regulatory intervention and that the public's underlying safety concerns had directly impacted sales.[371]

***Jones v Dunkel* inferences**

391 Turner submitted that *Jones v Dunkel*[372] ('*Jones v Dunkel*') inferences should be drawn because of the defendants' unexplained failure to call a number of witnesses in relation to the decision to discontinue Essure in the context of the growing regulatory concerns from 2014 to 2017.

Manal Morcos, Alicia Lowery and Declan McGuinness

392 From January 2014, Manal Morcos was Director Group Head Essure and Device at

367 BAY-JCCP-0129197.
368 SBM.001.001.0004 at 238; BAY-EDPA-1564757.
369 BAY-JCCP-0137344.
370 SBM.001.001.0004 at 242, [788].
371 SBM.001.001.0004 at 240; T2356 (TRA.500.024.0001_2 at 0034).
372 (1959) 101 CLR 298 ('*Jones v Dunkel*').

Bayer HealthCare. From April 2016, Morcos' formal title was Director, Regulatory Affairs; Global Head, Essure and Devices.[373] Morcos ceased her employment with Bayer HealthCare in around October 2017.

393 Alicia Lowery was employed by Conceptus in Regulatory Affairs from 2008. She became Assistant Director Global Regulatory Affairs and remains employed by the Bayer defendants.

394 McGuinness was the Global Brand Manager, Essure, from November 2013, and was still employed by the Bayer defendants at the time of trial. McGuinness led an internal Bayer group known as the 'Women's Health Taskforce' from 2015, and was involved in the response to regulatory concerns raised about Essure.

395 Turner submitted that the failure to call Morcos and Lowery meant the following substantive inferences could be drawn with greater confidence:

(a) that the NSAI Essure suspension in 2014 did raise safety implications;

(b) that any 'compromise' by Bayer defendants in interactions with regulators involved a calculated consideration on the part of Bayer as to what commercial and regulatory consequences would flow if 'compromise' did not occur;

(c) that it was Bayer that was dilatory in not implementing warnings in Australia in 2016 equivalent to the FDA boxed warning, not the NSAI;

(d) that the failure by Bayer to appeal any of the adverse regulatory decisions of the NSAI and FDA is explained by at least a concern about wanting to control the 'narrative', which would not be available if appeals were lost; and

(e) that the decision to discontinue Essure was not entirely a commercial decision.

Turner relies on the failure to call Declan McGuinness only in respect of the fifth

373 LAY.001.002.0012 at 6; BAG.001.002.9773.

inference.

396 The rule in *Jones v Dunkel* does not require a party to call evidence that is merely cumulative or corroborative.[374] A very considerable volume of documentary and witness evidence was called by the defendants in this proceeding to explain the regulatory and commercial history of Essure. Each inference identified by Turner has been the subject of evidence. Turner did not bring a regulatory case. The inferences are peripheral to the case that was brought. In the circumstances, the failure to call Morcos, Lowery and McGuiness adds little if anything to consideration of the issues relevant to the inferences identified by Turner.

Christina Dixon

397 Christina Dixon was apparently the author of an internal Bayer note shown to Carney in cross-examination concerning the Bayer defendants' interactions with the NSAI in 2017. Turner did not identify any inference that should be drawn as a result of Dixon's absence. The note, and Carney's response to it, are in evidence. No matter was raised requiring some further explanation by Dixon.

Any current or former employee of Bayer Australia

398 Turner identified Prisca Drysdale and Teresa Lai, who were successively in the position of Regulatory Affairs Manager at Bayer Australia from December 2013 to March 2018. Turner relies on the failure to call Lai and Drysdale as being relevant to the substantive inference that the Bayer defendants delayed introduction of the enhanced boxed warnings in 2016. Chloe Perot was the National Sales Manager for Women's Health at Bayer Australia. Turner submitted that her failure to give evidence was relevant to inferences that should be drawn about discontinuation of Essure.

399 As explained above, the history of regulatory concerns and discontinuation of Essure was the subject of extensive evidence at trial. Bayer Australia had a relatively limited role in relation to Essure. The failure to call any witness from Bayer Australia is of

374 *Primrose Meadows Pty Ltd v River View Pty Ltd* [2019] VSC 263 at [23] (Croft J).

limited weight in relation to the inferences Turner identified.

400 In the period 2013 to 2017 Bayer faced significant public concern about the safety of Essure driven at least in part by social media, an associated substantial decline in sales, and the costs of responding to the concerns of regulators in multiple jurisdictions. Bayer's decision to discontinue sales of Essure is understandable in those circumstances. I accept Carney's evidence on this issue.

Post-discontinuance clinical evaluation

401 Bayer continued to prepare clinical evaluation reports in relation to Essure after decommercialisation. Carney prepared a report dated 28 September 2018 which annexed a biological risk assessment report prepared for Bayer by medical scientists from research organisation North American Science Associates ('NAMSA').[375] The report summary included:

> Based upon examination of the device materials, use of the Essure Insert would not be expected to result in an adverse biological response in patients. This risk assessment indicates that the likelihood of a toxic effect from the Essure Insert is negligible and that the device can be considered safe for use as intended. No further biocompatibility testing is recommended.
>
> The Essure Insert meets the requirements of ISO 10993-1:2009, EN ISO 14971:2012, FDA General Guidance on the Use of International Standard ISO 10993-1:2016, and the European Union Medical Device Directive 93/42/EEC for a permanent (>30 days) implant in contact with tissue and can be considered safe for use as a contraceptive when used as intended.[376]

The NAMSA report further stated:

> After an analysis of the materials used to construct the Essure Insert, it was apparent that all materials used are well characterized with a long history of clinical use in and of clinical use in similar or closely related, approved and marketed medical devices.[377]

The report stated, in relation to risk assessment and risk control:

> Based upon the risk analysis, use of the Essure Insert would not be expected to result in an adverse biological response in patients. This risk assessment indicates that the likelihood of a toxic effect from the Essure Insert is negligible

375 BAY-JCCP-1120549 at 978.
376 Ibid at 977.
377 Ibid at 985.

> and that the device can be considered safe for use as intended. Consideration has been given to all potential biological hazards for the materials and final product, and testing for each hazard is not necessary.[378]

2019 Metals Advisory Committee meeting

402 In November 2019, the FDA Center for Devices and Radiological Health ('CDRH') held a meeting of the Medical Devices Advisory Committee Immunology Devices Panel ('Metals Advisory Committee'). The panel included 22 experts from a variety of specialties including metallurgy, clinical practice and biomaterials science, including Badylak.

403 The FDA published a briefing paper in advance of the meeting. The purpose of the paper was described as follows:

> This paper presents FDA's review of currently available scientific information related to metals and their uses in medical implants, with focus on how metal materials are impacted by a physiological environment, expected and potential immune system responses to the metal associated with an implant, as well as subsequent clinical manifestations. It is the result of a collaborative effort amongst subject matter experts (SMEs) gathered from across the Center for Devices and Radiological Health (CDRH), the organization within the FDA that is charged with regulating medical devices. Just as importantly, this paper identifies where gaps exist in the scientific evidence related to immunological responses to metal-containing implants, and where opportunities for further research exist and will serve as a starting point for a public discussion on November 13 and 14, 2019 as part of an advisory panel meeting.[379]

404 In relation to inflammation, the paper identified that no FDA standards at that time provided:

> … all-inclusive guidance for comprehensive assessment of the overall inflammatory response that would incorporate nonclinical and clinical testing… because certain types of inflammatory responses to metals, and other select materials, in medical devices resulting in clinical manifestations (particularly systemic effects) had not been well-recognized in the past and are still the subject of debate, as described in this paper.[380]

405 On 28 October 2019, Bayer submitted a briefing document to the Metals Advisory Committee. Carney said that she 'considered [the document] to contain the most up-

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378 Ibid at 991.
379 PUB.001.001.3803 at 7.
380 Ibid at 19.

to-date information known to Bayer with regard to the Essure device and metal hypersensitivity issues,'[381] including:

(a) Essure metal release rate;

(b) clinical data of any nickel hypersensitivity that might be associated with Essure;

(c) the available epidemiological data/studies on matters such as pain and hysterectomy rates; and

(d) issues with relying on adverse event reports during post-marketing reporting.

406 Carney said that the Metals Advisory Committee did not publish any conclusions related to Essure.[382]

XI. PHYSIOLOGICAL RESPONSE TO ESSURE IMPLANTATION

407 An understanding of the physiological response to Essure implantation is critical to determination of Turner's claims.

408 Essure was designed to promote an inflammatory response intended to cause development of fibrosis and tubal occlusion. Insertion of the device disrupted the inner layers of the fallopian tube, causing a wound. The inflammatory response to this wound was promoted by the continued presence of the device as a foreign body in the fallopian tube, and by features including the PET fibres located between the outer and inner coils of the device.

409 Turner argued that biomedical devices should be designed to minimise the inflammation that occurs as part of the foreign body response to a device and the development of dysfunctional tissue. She argued that because Essure was designed

381 Carney at 95 (LAY.500.001.0008_2).
382 Ibid.

to have the opposite effect, there was an inherent risk that in a significant number of women, implantation would cause ongoing chronic inflammation that was pathological and inconsistent with optimal health.

410 The defendants submitted that there was no evidence on which the Court could find that insertion of Essure caused ongoing, pathological chronic inflammation.

411 It is necessary to say something about the immune system, foreign body responses to biomedical devices, biocompatibility and chronic inflammation before turning to consider the histological evidence relevant to Essure.

The immune system

412 The immune system plays a central role in wound healing and the foreign body response that follows implantation of a biomedical device.

413 The immune system consists of 'a diverse collection of cell types that patrol the body and reside in tissue to provide protection from threats including microbial infection, damage (e.g. a wound response), altered self (e.g. cancer, which derives from mutations altering the proteins expressed by a tissue), while at the same time preventing inappropriate activation against self-proteins, and regulating aspects of normal tissue turnover and remodelling (termed 'homeostasis')'.[383]

414 Immune cells may be pro-inflammatory or anti-inflammatory, depending on cell type and the processes occurring where they are located in the body.

415 The following table describes the major immune cells:[384]

	Cell Type		General Function
Adaptive Immune System	CD4* T cell	Th1	Cytokine* production targeted against viruses and intracellular bacteria
		Th2	Cytokine* production targeted against allergens and helminth parasites
		Th17	Cytokine* production targeted against extracellular bacteria and fungi
		Treg	Suppresses the activity of other CD4* T cells and CD8* T cells; produces anti-

383 Immunology JER at 5 (EXP.500.001.0004).
384 Sokol at 60 (EXP.001.002.0001).

		inflammatory cytokines*
	CD8* T cell	Kills infected or cancerous cells
	B cell	Antibody production
Innate Immune System	Eosinophil	Blood resident cell; involved in acute inflammation
	Neutrophil	Blood resident cell; involved in acute inflammation
	Natural Killer (NK) cell	Blood or tissue resident cell; kills infected or cancerous cells
	Dendritic cell	Tissue resident cell in immature state; activates CD4* and/or CD8* T cells
	Monocyte	Blood resident cell; involved in acute inflammation
	Macrophage	Long-lived tissue resident cell; either present from birth or generated from monocytes
	Foreign Body Giant Cell	Long-lived cell that forms by the fusion of macrophages in the tissue

* Cytokines are secreted factors that modulate immune cell phenotype or function.

416 The innate immune system monitors the body for evidence of infection or damage. When activated by pathogens or foreign materials, it will attempt to remove the substance and heal any damage. If a foreign material cannot be removed from the body, the innate immune system will attempt to wall off the substance through fibrosis.[385]

417 The adaptive immune system, once activated, is able to provide long-term memory and protection against pathogens. It can produce both pro-inflammatory T-cells which cause inflammation and damage to pathogens, and anti-inflammatory (regulatory) T-cells which prevent inflammation and protect tissue.[386]

418 The following definitions are not contentious:

(a) *leukocytes*: white blood / immune cells that emigrate to and accumulate in tissue as part of the inflammatory response, for example to a wound.[387] Leukocytes include the following cell types:

- Neutrophil (polymorphonuclear leukocyte, PMN): A type of white blood cell that is an important part of the immune system and helps the body fight infection. When microorganisms, such as bacteria or viruses, enter the body, neutrophils are one of the first immune cells to respond. They travel

385 Ibid at 7.
386 Ibid.
387 Robertson at 15 [24] (EXP.001.001.0127_2); Murdock at 5 [9.1] (EXP.001.002.0008).

to the site of infection, where they destroy the microorganisms by ingesting them and releasing enzymes that kill them. Neutrophils also boost the response of other immune cells.

- Eosinophil: A type of immune cell that has granules (small particles) with enzymes that are released during infections, allergic reactions, and asthma.
- Basophil: A type of immune cell that has granules (small particles) with enzymes that are released during allergic reactions, and asthma.
- Macrophages: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells.
- Lymphocytes: A type of immune cell that is made in the bone marrow and is found in the blood and tissue. The two main types of lymphocytes are B lymphocytes and T lymphocytes. T lymphocytes (more common in fallopian tubes than B lymphocytes…) help control immune responses. A lymphocyte is a type of white blood cell.
- Plasma cells: A type of immune cell that makes large amounts of a specific antibody. Plasma cells develop from B cells that have been activated.
- Mast cells: Found in connective tissues all through the body. They play an important role in how the immune system responds to bacteria and parasites.
- Natural killer (NK) cell: A type of immune cell that contains enzymes that kill tumor cells or cells infected with a virus.
- Dendritic cell: A type of phagocyte and antigen presenting cell that act as a communicator by presenting the antigen to other cells of the immune system[.][388]

(b) *fibroblasts*: a type of cell which contributes to the formation of connective tissue (a fibrous cellular material that supports and connects other tissues or organs in the body). Fibroblasts secrete collagen proteins that help maintain the structural framework of tissues and play an important role in healing wounds.[389]

(c) *neovascularisation***:** the development of new blood vessels that can be a feature of wound healing and an inflammatory response in tissue.[390]

388 Murdock at 5-6 (EXP.001.002.0008).
389 Ibid at 5-6 [9.2]-[9.6].
390 Ibid at 68 [253].

(d) *granulation tissue*: the new blood vessels and connective tissue that form as part of the wound healing process.[391] Granulation tissue is generated by the deposition of extra cellular matrix of fibroblasts and neovascularisation by proliferating endothelial cells.[392]

(e) *fibrosis*: connective tissue created by the proliferation of fibroblast cells.[393]

(f) *foreign body giant cell*: giant cells that may be found around the site of a foreign body that are the result of fusion of macrophages.[394]

(g) *phagocytes*: immune cells capable of phagocytosis (process of engulfing), which include monocytes, macrophages, dendritic cells, and neutrophils.[395]

Wound healing

419 The physiological process of wound healing involves a predictable sequence of four stages: first, *haemostasis* or blood clotting; second, an inflammatory response; third, fibroblast proliferation and scar formation; and fourth, tissue remodelling. A completely healed wound is characterised by the resolution of inflammation and then by fibrotic tissue and scar formation.[396]

420 In their expert reports, Sokol and Robertson each gave greater detail describing the wound healing response. Sokol said:

> Tissue damage leads to the release of pro-inflammatory cytokines from damaged cells that act alone or in concert with locally activated tissue resident innate immune cells (e.g., macrophages, mast cells), to induce immune cell entry to the site of the wound. This second phase is characterized by the influx of large numbers of innate immune effector cells (e.g., neutrophils, eosinophils, monocytes that can differentiate in the tissue into more macrophages). These innate immune effector cells share a common goal of removing damaged tissue and debris, while at the same time activating local structural cells (e.g., fibroblasts and myofibroblasts) to divide, differentiate, regenerate damaged vessels and supports, and heal the wound[.] This initial healing resolves the acute insult of tissue breakdown, but is often marked by a scar and disordered

391 Murdock at 24 [57] (EXP.001.002.0008).
392 Robertson at 83 [320] (EXP. 001.001.0127_2).
393 Ibid at 14, footnote 7 (EXP.001.001.0127_2).
394 Sokol at 17 (EXP.001.002.0001).
395 Immunology JER at 6 [275]-[285] (EXP.500.001.0004).
396 Ibid at 4 (EXP.500.001.0004).

fibroblasts and other structural cells[.] The second phase of wound healing then occurs, with local tissue resident macrophages (some descending from the monocytes that originally entered the tissue) secreting cytokines to promote the remodeling of myofibroblasts and supporting cells, with the goal of ultimately reducing or eliminating the scar and optimizing tissue strength[.][397]

421 Robertson described the four stages of wound healing as follows:

a. Haemostasis (<1 day). This is the rapid response to physical injury within the first hours after injury. It is necessary to control bleeding. It involves vasoconstriction, a platelet response, and a biochemical response. The intrinsic coagulation pathway is activated, initiating clot formation and haemostasis. This involves platelet activation and platelet degranulation, which elicit the acute inflammatory response by promoting neutrophil and macrophage recruitment[.]

b. Inflammation phase (0-4 days). Inflammation is the body's normal response to injury. This phase involves leukocyte recruitment, and activates vasodilatation leading to increased blood flow causing heat, redness, pain, swelling and loss of function[.]

c. Reconstruction phase (2-24 days) the time when the wound is healing. Granulation tissue is generated by deposition of extracellular matrix by fibroblasts and neovascularisation by proliferating endothelial cells. Fibroblasts produce collagen and other glycoproteins, as well as a range of growth factors and angiogenic signals, that stimulate proliferation of endothelial cells and direct formation of a new blood supply into the regenerating tissue. This phase results in formation of new blood vessels, tissue reconstruction and where appropriate, re-epithelialisation. The wound will progressively contain fewer leukocytes and usually become smaller as it heals[.]

d. Maturation phase (24 days-1 year) the final phase of healing. Tissue remodelling, fibrosis, and scar formation should be essentially complete by 4 weeks, and at most by 3 months. Shrinkage of the scar can continue for several months subsequently.[398]

422 The following diagram represents the wound healing phases as described by Robertson:[399]

397 Sokol at 8 (EXP.001.002.0001).
398 Robertson at 83 [320] (EXP.001.001.0127).
399 Ibid at 233.

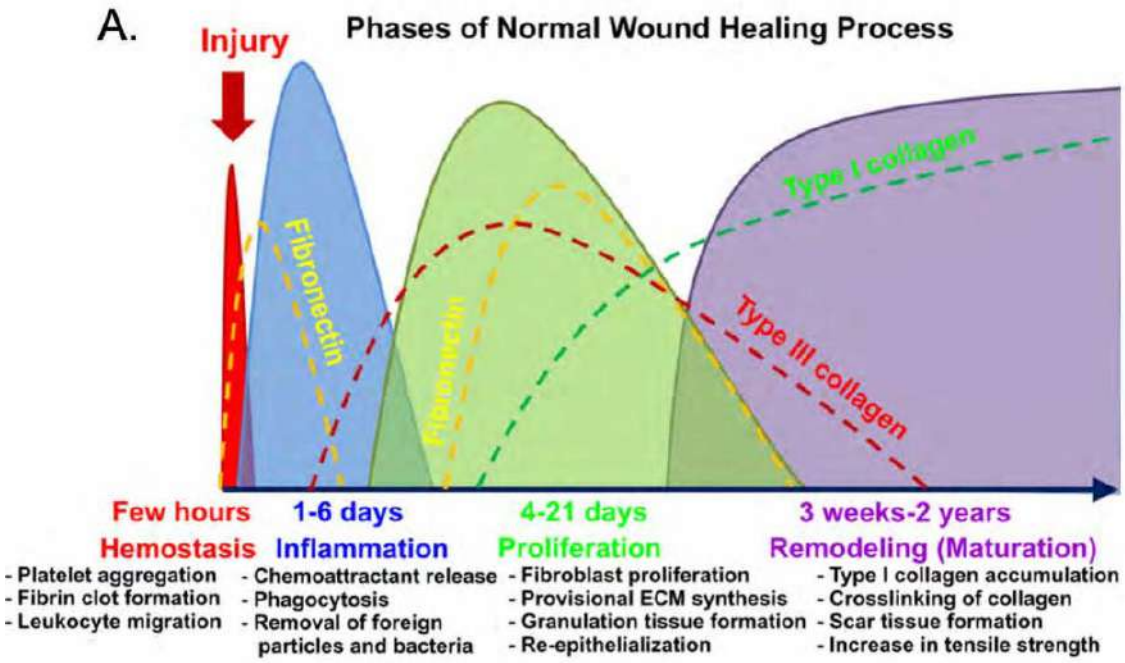

Figure 9. Diagrammatic representation of the phases and cellular processes involved in a healthy wound response. The four phases and approximate time course for a healthy wound response.

423 The experts agreed that the kinetics and final form of wound repair can vary depending on body location and individual characteristics, including genetics and other biological and health factors.[400] However, they disagreed about the timeframe for completion of the first three stages of wound healing. Robertson said that if wound healing up to the maturation or remodelling phase was not complete by three months, the wound would meet the definition of a 'chronic wound'.[401] Sokol said that there was no consensus in the medical literature on a precise timeframe by which a wound would be considered 'chronic'.[402] I will return to the issue of wound healing timing and kinetics later in these reasons.

424 The pattern of leukocyte infiltration during the wound healing stages is depicted in the following figure, taken from Robertson's primary report:[403]

400 Ibid at 83 [319].
401 Immunology JER at 4 (EXP.500.001.0004).
402 Ibid at 5.
403 Robertson at 235 (EXP.001.001.0127).

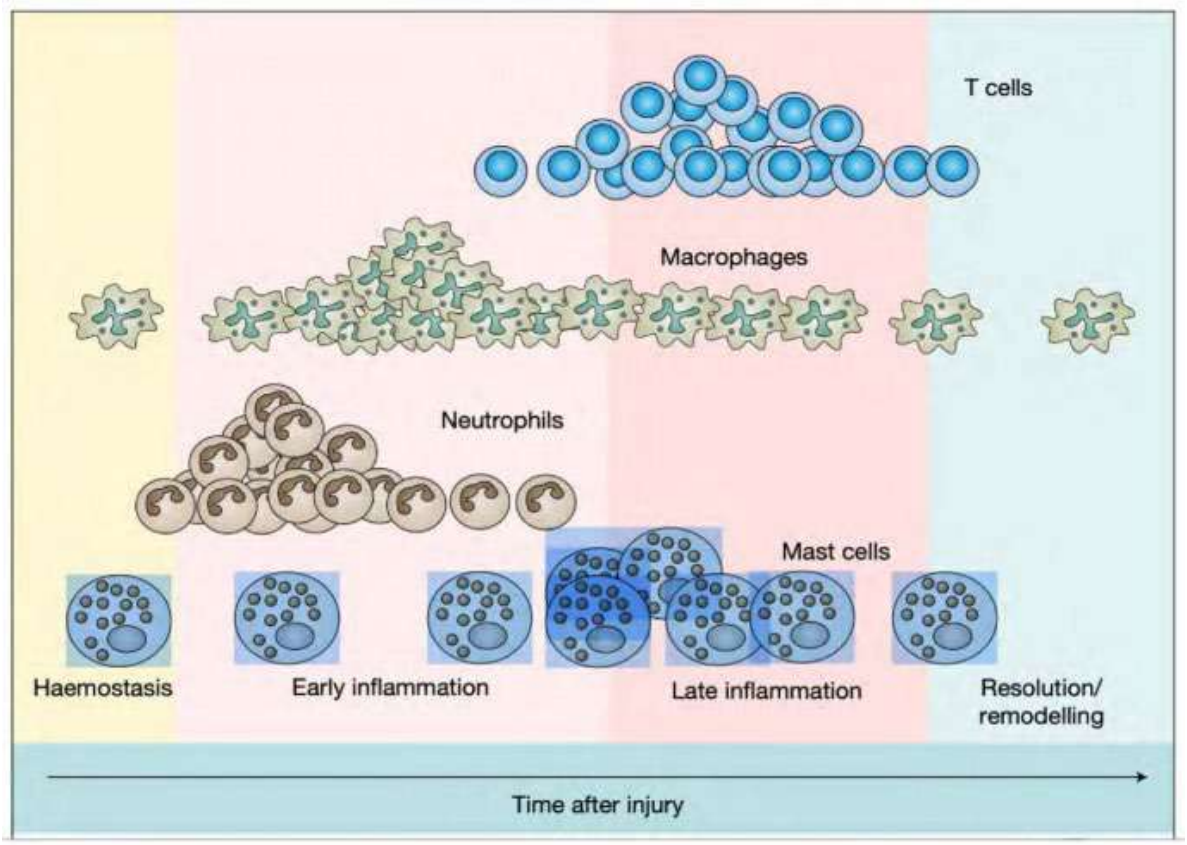

Figure 11. Pattern of leukocyte infiltration into wounds. Inflammatory cells are present during each of the phases of wound repair, represented here as haemostasis (yellow panel), acute (early) inflammation (light pink panel), chronic (late) inflammation (dark pink panel) and resolution/remodelling (blue panel). The relative density of the four most prominent types of leukocytes in wounds (mast cells, neutrophils, macrophages and T cells) is depicted. Whereas neutrophils and lymphocytes disappear, low numbers of resident mast cells and macrophages are present during the lengthy remodelling phase. T cells usually do not persist once inflammation has resolved.

425 The phenotype of a population of macrophages exists on a spectrum from pro-inflammatory macrophages ('M1' phenotype) to anti-inflammatory macrophages ('M2' phenotype). The average or net phenotype of a macrophage population may change over time depending on the function that the cells are engaged in. As Sokol explained:

> The process of wound healing is dependent on the function of macrophages, which generally act to first promote inflammation in the early stages of wound healing and then to resolve that inflammation in later stages.[404]

426 It is not in dispute that insertion of Essure caused damage and injury to the fallopian

[404] Sokol at 8 (EXP.001.002.0001).

tube and surrounding tissue. In the biomaterials JER, the participating experts agreed that deployment of Essure caused 'tissue injury, focal bleeding and damage to the internal lining of the isthmus and the SUTJ regions of the fallopian tube and uterus.'[405] The experts said:

> We agree that insertion of the Essure Device into a fallopian tube causes localised mechanical injury to the surrounding tissue. This is because the isthmus segment of the fallopian tube is a thin-walled, soft and fragile tissue. The SUTJ is also soft but has a thicker wall. Both parts have a very narrow internal diameter that is substantially less than the diameter of the Essure Device. At the time of insertion, in order to fit into the intended site and exert the desired effect, the Essure Device causes injury to the cells and tissue structures of the fallopian tube. This would happen to varying degrees in all women who receive it, because the tube is narrower than the device and has a limited ability to stretch without tissue[.]
>
> Once the Device is positioned in the isthmus and SUTJ regions of the fallopian tube, it is then deployed so that a spring-like action causes its external nitinol coil to be unwound, expand in diameter, and engage with the inner layers of the fallopian tube.[406]

The experts further agreed:

> In the days after insertion, the tissue injury caused by Device placement would begin a typical wound healing program[.] The ability of the Device to cause tubal occlusion and deliver its intended contraceptive effect depends on it provoking the surrounding tissues to undergo a typical wound healing response including fibrosis (the deposition of scar tissue). In most women the device placement causes short-lived inflammation followed by fibrosis and scar formation.[407]

Chronic wound

427 Robertson and Sokol agreed that a 'chronic wound' is a wound with ongoing inflammation and immune response activity which fails to heal.[408]

428 Robertson said that 'a chronic wound is a wound that has not proceeded through orderly and timely reparation to produce anatomic and functional integrity after three months'.[409] She said that a chronic wound will exhibit ongoing inflammation and

405 Biomaterials JER at 19 (EXP.500.001.0006).
406 Ibid at 22.
407 Ibid at 19.
408 Immunology JER at 4 (EXP.500.001.0004).
409 Pathology JER at 21 (EXP.500.001.0007).

immune response activity.[410]

429 Murdock said that a chronic wound 'stalls' in the acute phase of the wound response without significant progression to granulation tissue formation and fibrosis. She said that microscopically, a chronic wound is comprised of extensive acute and some chronic inflammatory cells, lacks any fibrosis, and is basically an abscess cavity. She said:

> Chronic wounds can be classified as vascular ulcers, diabetic ulcers, and pressure ulcers. Common features shared by each of these wounds include prolonged excessive inflammation, persistent infections, formation of drug resistant microbial biofilms, and the inability of dermal and/or epidermal cells to respond to reparative stimuli. Importantly, these features were not observed in relevant published literature of tissues adjacent to the Essure Device (Valle, 2001 and Banet, 2020)[.][411]

The literature Murdock referred to is discussed later in these reasons.

430 Robertson disagreed with Murdock's definition of a chronic wound for three reasons. First, Robertson said that a chronic wound may exhibit spatial heterogeneity in the degree of wound healing and fibrosis, with some parts of the wound showing more progress towards healing (including patches of fibrosis and granulation tissue) than others.[412] Second, she said that while vascular ulcers, diabetic ulcers and pressure ulcers are common types of chronic wounds, the term also incorporates surgical wounds, radiation wounds and ulcers that arise in response to infectious or sterile injuries.[413] Third, Robertson said that it was not necessary for a wound to exhibit all of the features referred to by Murdock in order to be classified as 'chronic'.[414] Robertson said that the critical feature of a chronic wound is inflammation, and that other features included neovascularisation, haemorrhage and tissue disruption.[415]

431 Murdock disagreed with Robertson's evidence about patchy fibrosis. She said she had

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410 Ibid at 21.
411 Ibid at 22.
412 Robertson at 138 (EXP.001.002.0015).
413 Ibid at 138.
414 Ibid at 139.
415 T2867 (TRA.500.030.0001_2 at 0073).

not seen fibrosis or attempts at wound healing when examining chronic wounds under the microscope.[416] Murdock did not agree that haemorrhage was necessarily a concerning feature. I will return to this debate later in these reasons.

Foreign body response

432 A 'foreign body' relevantly includes an implanted biomedical device or prosthesis. A 'foreign body response' to a biomedical device is a form of wound response complicated by the ongoing presence of the device.

433 Robertson and Sokol agreed that the foreign body response is the immune system's response to 'a foreign (non-self) substance, material or medical device embedded or implanted in the body'.[417] They agreed that 'the function of the foreign body response is to eliminate or physically segregate the foreign body and defend the body from the perceived or real threat it poses'.[418]

434 Robertson and Sokol agreed that:

> The foreign body response involves a cascade of molecular and cellular steps triggered when a foreign body causes tissue injury. This provokes inflammation – an altered tissue state characterized by immune cell accumulation and activation – that in turn causes activation of local fibroblasts. These cells proliferate to surround the foreign body, creating a barrier that when successfully completed, ultimately acts to 'wall-off' or cover the foreign body to prevent it from further provoking the immune response. When not successful – that is, when the foreign body is not walled-off – the unresolved foreign body response may cause the affected tissue to remain in a state of active inflammation.
>
> The foreign body response can be viewed as a form of wound response that is complicated by the ongoing presence of the non-self entity that cannot be removed by the usual process of engulfment by immune cells. The foreign body response has a comparable sequence of steps or phases to those of a standard wound healing response, but is modified and specialized by the presence of the foreign body and its effect on the immune response. Like a wound response, the foreign body response to medical implants includes four stages, which can be summarized as haemostasis, inflammation, fibroblast proliferation and scar formation, and finally scar maturation[.]
>
> We agree that this broad definition would be agreed upon by immunologists,

416 T2915 (TRA.500.030.0001_2 at 0122).
417 Immunology JER at 3 (EXP.500.001.0004).
418 Ibid.

pathologists and clinicians.

> We agree that when a foreign body response is elicited by a medical device, many host factors (the tissue site, host immune status, age, comorbidities) and device features (size, surface area, material and composition of the device) can affect the kinetics of the foreign body response.[419]

Badylak, Chrzanowski and Robertson expressed agreement in the same terms in the biomaterials JER.[420]

435 However, the experts did not agree on the expected timeline of this response.

436 Robertson said that the kinetics of a foreign body response should follow a similar timeframe to completion as the wound healing response.[421] She said that 'the wound response to a metal device is often never fully "healed" or "completed" in the same way as a standard wound usually is'.[422] She said this was because of the continued presence of the device, the resulting disruption of normal tissue architecture, and the ongoing engagement with (and effects on) the immune response caused by the device. She said that if wound healing in response to a medical device is not complete within three months and chronic inflammation is present, the wound around the foreign body would share features with a chronic wound.[423]

437 Robertson said that when inflammation associated with a wound or foreign body response does not resolve within a limited time, there is a high chance of persistent chronic inflammation that is damaging to ongoing health.[424]

438 In the biomaterials JER, Robertson and Chrzanowski said that resolution of inflammation associated with a foreign body response is crucial for wound healing, and echoed Robertson's view that inflammation which does not resolve within a limited time carries a high chance of becoming persistent and chronic.[425]

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419 Ibid.
420 Biomaterials JER at 3 (EXP.500.001.0006).
421 Immunology JER at 3 (EXP.500.001.0004).
422 Pathology JER at 22 (EXP.500.001.0007).
423 Ibid at 22.
424 Immunology JER at 4 (EXP.500.001.0004).
425 Biomaterials JER at 4 (EXP.500.001.0006).

439 Sokol said that the foreign body response is different to the wound healing response because it includes the complication of a foreign body. She said that a foreign body response can fully resolve, but that the foreign body may alter the timeline for complete resolution.[426] Sokol said that the goal of an acute inflammatory response during the foreign body response is to ultimately 'wall off' the device to separate it from the immune system and prevent chronic activation of the immune system, which would be indicated by the presence of continued neutrophils in the site. She said that with most foreign body responses this process takes time, and while acute inflammation can often transition into chronic inflammation at the six-week stage it is not a foregone conclusion that inflammation will always be active.[427] Sokol said that host and device factors can lead to widely disparate 'normal' kinetics that should be considered before speculating on whether a foreign body response has failed or stalled.[428] Sokol said there was no consensus in the medical literature on the precise timeframe for a chronic wound, and that chronicity could only be determined by comparison to the expected wound healing kinetics for the host and wound type.[429]

440 Badylak did not agree with the precise timelines specified by Robertson for resolution of the foreign body response. He agreed with Sokol that the timeline will vary with host and device factors.[430] In his expert report, Badylak said that the overall response to a foreign body transitions from an 'active pro-inflammatory' response to a 'pro-remodelling steady' state within a two to three month period after implantation, which is characterised by an abundance of fibrous tissue deposited by the recruited fibroblasts.[431] He said that the fibroblasts deposit collagen, which is the core substance of fibrous/scar tissue. He said:

> The end result of these cellular and tissue remodeling events is a dense fibrous (scar) tissue response with associated relatively small number of pro-remodeling mononuclear inflammatory cells adjacent to the metal materials

426 Immunology JER at 5 (EXP.500.001.0004).
427 T4043-4 (TRA.500.040.0001_2 at 0053_22-0054_2).
428 Immunology JER at 3 (EXP.500.001.0004).
429 Ibid at 5.
430 Biomaterials JER at 4 (EXP.500.001.0006).
431 Badylak at 15 [40] (EXP.001.002.0007).

> and PET fibers. This foreign body response reaches a steady state in which the tissue ingrowth process is essentially complete over a period of several months. The small number of mononuclear or multinucleate cells that are present after 3-4 months will likely persist for the life of the patient. It is inaccurate and misleading to characterize the presence of these cells as a persistent and active inflammatory reaction that causes continuous tissue damage.[432]

441 Murdock said that the foreign body response, or 'foreign body giant cell reaction' is a response to a foreign material in biological tissue.[433] Murdock said:

> Professor Robertson's argument that there must be a resolution of inflammation for "wound healing" (incorrect use of the term "wound," see my response to 2i), or scar formation and scar maturation, is incorrect. The response to the Essure Device was orderly and predictable and resulted in dense fibrosis (scar formation) and occlusion of the fallopian tube lumen in 100% of patients (Valle, 2001).[434]

She said that in the field of pathology she 'would not use the term "chronic wound" to describe the tissue response to a medical device'. She described the response as follows:

> The tissue response to implanted medical devices is a predictable tissue reaction that begins within minutes to hours and is characterized by an acute inflammatory cell infiltrate including polymorphonuclear leukocytes (neutrophils) and some mononuclear cells (monocytes and macrophages). Over time (variable for each patient), the tissue reaction develops into a chronic inflammatory response with granulation tissue formation, and eventually fibrosis… Regarding the Essure Device, the PMA data, as well as Rubin (2020), Banet (2020), and Valle (2001) all demonstrated at least loose, and most cases showing dense fibrosis and obliteration of the fallopian tube lumen ([scar formation] in 100% of patients, Valle) a normal tissue healing response (scar formation), and therefore, the term "chronic wound" does not apply and is misapplication of the term.[435]

442 Robertson, Sokol and Murdock agreed that the presence of foreign body giant cells adjacent to an implanted device, without other immune cells, was not sufficient to indicate active inflammation or an abnormal response to the foreign body.[436]

Biocompatibility

443 Robertson, Chrzanowski, Badylak and Eiselstein agreed in the biomaterials JER to the

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432 Ibid at 15 [42].
433 Pathology JER at 19 (EXP.500.001.0007).
434 Ibid.
435 Ibid at 22.
436 Immunology JER at 10, 13 (EXP.500.001.0004); Pathology JER at 20 (EXP.500.001.0007).

following definition of biocompatibility:

> Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, and to generate the most appropriate beneficial cellular or tissue response in that specific anatomic location, while mitigating any undesirable local or systemic effects in the recipient.[437]

The experts further agreed:

> We agree that an "ideal" biomaterial involves the overlapping properties of biocompatibility, safety and efficacy. "Inert" and "non-inflammatory" characteristics in biomaterials were identified as desirable and considered key features of biocompatibility several decades ago. However, it is now recognized that no biomaterial is absolutely inert or non-inflammatory.
>
> We agree that the act of introducing a biomaterial into the body, including the disruption to tissues of the implantation procedure, and the subsequent presence of the foreign material, will always elicit at least some degree of host tissue response. The response manifests as an inflammatory reaction and the associated subsequent formation of variable amounts of fibrous connective tissue. This fibrous connective tissue may be identified as dense collagenous connective tissue, scar tissue, or fibrous tissue, among other monikers, and is a consequence of the body's innate immune system response. The nature of this inflammatory response, with respect to both its temporal and spatial characteristics, is a determinant of the clinical outcome.[438]

444 Chrzanowski and Robertson said that over and above the issue of biocompatibility, a biomedical device should meet the following fundamental 'tenets':

> (1) an intention to repair a damaged tissue and/or treat a state of tissue pathology, and (2) an intention to not cause or increase dysfunction in the tissue. … [I]n the event of meeting neither of these fundamental tenets, the value proposition of a Device or intended Device is likely to be unreasonable. In their opinion, the Essure Device does not meet either of these fundamental tenets – that is, it does not (a) act to repair a tissue or repair a state of tissue pathology, and (b) it operates to cause tissue dysfunction, by virtue of its eliciting damage to otherwise healthy fallopian tube tissue.[439]

445 Chrzanowski further explained his opinion in relation to biocompatibility in oral evidence:

> … biocompatibility is the characteristic or property of the material which we frequently refer to as the biomaterial, to enable [it] to perform a desired function in respect to the medical therapy. I would like to highlight the word

437 Biomaterials JER at 2 (EXP.500.001.0006).
438 Ibid.
439 Ibid.

> 'therapy' here. Also biocompatibility refers to generating appropriate and beneficial cellular and tissue responses in the specific anatomic location, while mitigating any undesired localised or systemic effects in the recipient. So what it means, is that the material that is considered biocompatible will be the material which supports our body to regenerate its function. It is therapy. Therapy means regenerating, regaining the function or supporting the function. It is not about creating pathological tissue which does not have any function, what is a biological function, in the body. So biocompatibility means material which will support the organs or our body in regaining the actual physiological functions and supporting us in living and our longevity.[440]

446 Badylak did not agree with the 'fundamental tenets' described by Chrzanowski and Robertson. He said that the tenets were not found in any textbook or peer-reviewed publication of biomaterials or biocompatibility. He said:

> … the function of any particular biomaterial depends upon the choice of anatomic placement and the desired outcome which in the case of the Essure device is to cause permanent sterilization by occlusion of the fallopian tube with fibrous tissue. He further considers that integration of surrounding tissues with the biomaterial of choice, access of the biomaterial to the host vascular network, the presence of pores (holes) within certain biomaterials …, and the occurrence of a transient proinflammatory tissue response phase by the recipient are not only acceptable characteristics …, but in fact desirable and required characteristics.[441]

447 The cross-examination of Chrzanowski and the defendants' submissions on this issue proceeded on the basis that the tenets needed to be separately considered, and that both must be satisfied. Chrzanowski repeatedly said in oral evidence that the tenets were to be considered together. Further, Chrzanowski and Robertson expressly stated that the value proposition of a device was likely to be considered 'unreasonable' if it met 'neither of these fundamental tenets'. Robertson said that while there may be a 'serious problem' if a device fails to meet either tenet, there may be occasions where breaking the tenets is justified.[442]

448 The defendants also criticised the 'fundamental tenets' on the basis that their application would lead to the following absurd consequences:

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440 T3071 (TRA.500.032.0001_2 at 0039_1-19).
441 Biomaterials JER at 2 (EXP.500.001.0006).
442 T3090 (TRA.500.032.0001_2 at 0058).

(a) devices implanted for purely cosmetic purposes would be considered 'not biocompatible' or otherwise inappropriate to be implanted in the human body;

(b) nitinol coils, wires and stents delivered to the sites of cerebral aneurysms for the purpose of causing blood coagulation and occluding blood flow would not satisfy the fundamental tenets;

(c) devices used in tubal ligation to facilitate permanent contraception by interfering with the normal function of the fallopian tubes, such as Filshie and Hulka clips, would never satisfy either of the asserted tenets.

Further, the defendants criticised Chrzanowski and Robertson for proposing the tenets in the absence of any textbook or other authoritative support and, particularly in the case of Chrzanowski, for his adherence to and defence of the fundamental tenets in oral evidence.[443]

449 Chrzanowski and Robertson appear to have made a distinction between a biomedical device that is to be used for a medical purpose and a cosmetic device for an aesthetic purpose relevant to application of the tenets. It is not clear why this distinction should be made. It is not clear why tenets of biocompatibility would not apply to a cosmetic device that may have a therapeutic psychological purpose.

450 Chrzanowski rejected the defendants' proposition that nitinol coils and stents designed to treat cerebral aneurysms did not satisfy the tenets because they caused blood coagulation and occluded blood flow. Chrzanowski explained that the pathology the coils are intended to treat is altered blood flow associated with an aneurysm.[444] He said:

> I'm sorry, it does repair the damage because the tissue is damaged, it's a pathological state when your blood vessels are pathologically altered, they are completely changed. That's why the blood flow is circulating the completely wrong way and you are correcting pathology, the same way as you correct pathology in your heart when you have the

443 SBM.500.001.0003_2 at 650-2.
444 T3080 (TRA.500.032.0001_2 at 0048).

arrythmia.

> It's changed by creating dysfunctional tissue, isn't it?---Yeah, it is the dysfunctional tissue which allows you to restore the function, regain the proper blood flow and save lives.[445]

Chrzanowski explained that the vast majority of biomedical devices create a certain level of pathology in order to achieve the therapeutic purpose of restoring function. He said that blood coagulation caused by the nitinol coil results in a substantial plaque that acts as the plug to prevent dysfunctional blood flow.[446] Chrzanowski said that while the nitinol coils do cause a small amount of dysfunction, they do so in order to allow the entire tissue to overcome pathology and regain function.[447] I do not accept this aspect of the defendants' criticism.

451 There is merit in the defendants' submission that Filshie and Hulka clips used to achieve permanent contraception do not satisfy the fundamental tenets. Chrzanowski and Robertson's tenets were directed to treatment of tissue damage or pathology by medical therapy. Contraceptive choice does not involve the treatment of an illness, disease, tissue damage or pathology. Contraception may be better understood as an interference with biological function, rather than therapy directed to regaining or supporting that function. It is surprising that Chrzanowski and Robertson proposed as the main principles against which biocompatibility should be assessed tenets which could not be satisfied by tubal ligation, which is the obvious comparator to Essure when considering permanent sterilisation.

452 Chrzanowski and Robertson can also be criticised for proposing what they described as 'fundamental tenets' of biocompatibility without making any attempt to identify reputable and authoritative scientific literature that supported their proposition. Chrzanowski and Robertson did not even refer to other publications of their own in which they identified the tenets and argued in their support. I accept Badylak's evidence that the tenets could not be found in any textbook or peer-reviewed

445 T3080-1 (TRA.500.032.0001_2 at 0048-9).
446 T3082 (TRA.500.032.0001_2 at 0050).
447 T3081 (TRA.500.032.0001_2 at 0049).

publication. Save in the one respect referred to above, the defendants' criticisms of Chrzanowski and Robertson were warranted.

453 The defendants submitted that 'the extremity of the views expressed by Professor Chrzanowski is well demonstrated by the fact that, in all of the circumstances, he describes contraception as "a non-essential clinical outcome".'[448] This submission is a reference to the following statement by Chrzanowski in his first report:

> In my opinion it is an unorthodox strategy to achieve a nonessential clinical outcome – contraception – by forming a fibrotic tissue which does not perform any physiological function.[449]

The above sentence appears in the summary section of Chrzanowski's report in a paragraph dealing with the risks associated with the design approach to Essure, which he said intentionally maximised the foreign body response and promoted chronic inflammation contrary to accepted practice in biomedical engineering. Chrzanowski was not given an opportunity to further explain the context in which the sentence was made in cross-examination. It may be the case that Chrzanowski used the term 'non-essential' to distinguish Essure from a biomedical insert which is 'essential' in the sense of being necessary to maintain life. In the circumstances I make nothing of this criticism.

454 Robertson and Chrzanowski said that there is an inverse relationship between biocompatibility and the degree and duration of the inflammatory or immune response elicited by a device.[450] They said that:

> … any inflammatory response after placement of a medical device is undesirable, and should be time-limited and rapidly resolved … [A]n ongoing inflammatory response or immune response in the vicinity of an implanted medical device is not an acceptable characteristic of a medical device.[451]

Badylak disagreed that an inflammatory response to a biomedical device was undesirable. He said that without an inflammatory response and fibrous tissue

448 SBM.500.001.0003_2 at 652 [5.30].
449 Chrzanowski at 6 (EXP.001.001.0082).
450 Biomaterials JER at 2 (EXP.500.001.0006).
451 Ibid.

deposition, there would be no subsequent healing. He noted that inflammation and fibrous tissue deposition occur as part of all wound healing even in the absence of biomaterial.[452] I accept Badylak's evidence. However, the real issue is whether there was a risk that the immune response to implantation of a biomedical device such as Essure would fail to resolve and cause ongoing chronic inflammation.

Literature relied on by experts

455 Pathologist James Anderson, who authored a number of articles tendered into evidence, was cited by the experts as an authority in relation to the foreign body response to implanted biomedical devices.[453] In a 2013 text chapter titled 'Inflammation, Wound Healing, and the Foreign-Body Response' ('Anderson 2013'), Anderson described biocompatibility and implantation in the following terms:

> Implantation of a biomaterial, medical device, or prosthesis results in tissue injury that initiates host defense systems, e.g., inflammatory, wound healing, and foreign-body responses. The extent and time-dependent nature of these responses, in the context of the characteristics and properties of the biomaterial, form the basis for determining the biocompatibility or safety of the biomaterial. In addition to defining the biocompatibility of a biomaterial, a fundamental understanding of these responses permits their use as biological design criteria.[454]

456 Anderson described the temporal sequence of events following implantation of a biomaterial using the figure included below:[455]

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452 Ibid.

453 See for example Robertson at 17 (EXP.001.001.0127_2); Sokol at 28 (EXP.001.002.0001); Murdock at 5 (EXP.001.002.0008).

454 James Anderson, 'Inflammation, Wound Healing, and the Foreign-Body Response' in *Biomaterials Science: An Introduction to Materials in Medicine* (Elsevier, 3rd ed, 2013) 503, 1 (PUB.500.001.0841) ('Anderson 2013').

455 Ibid at 2.

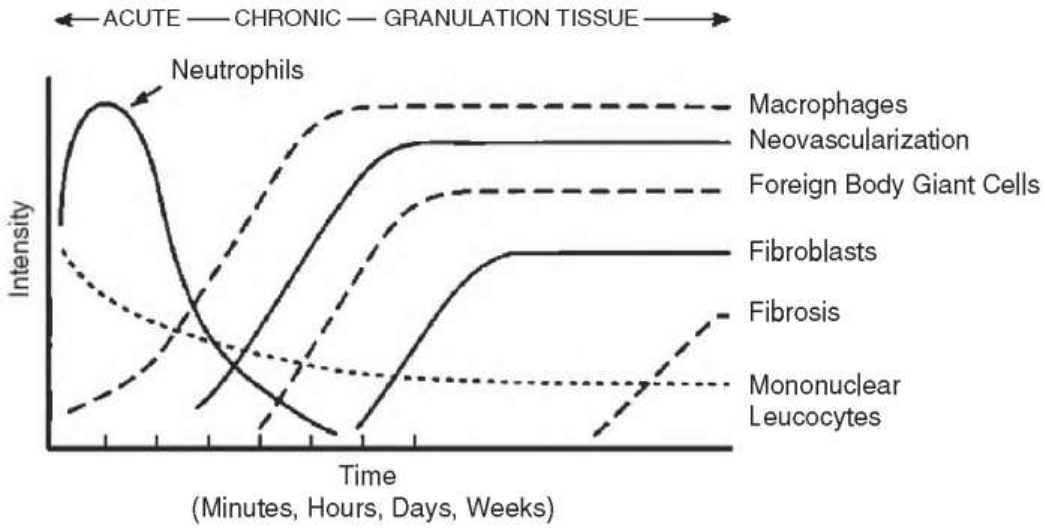


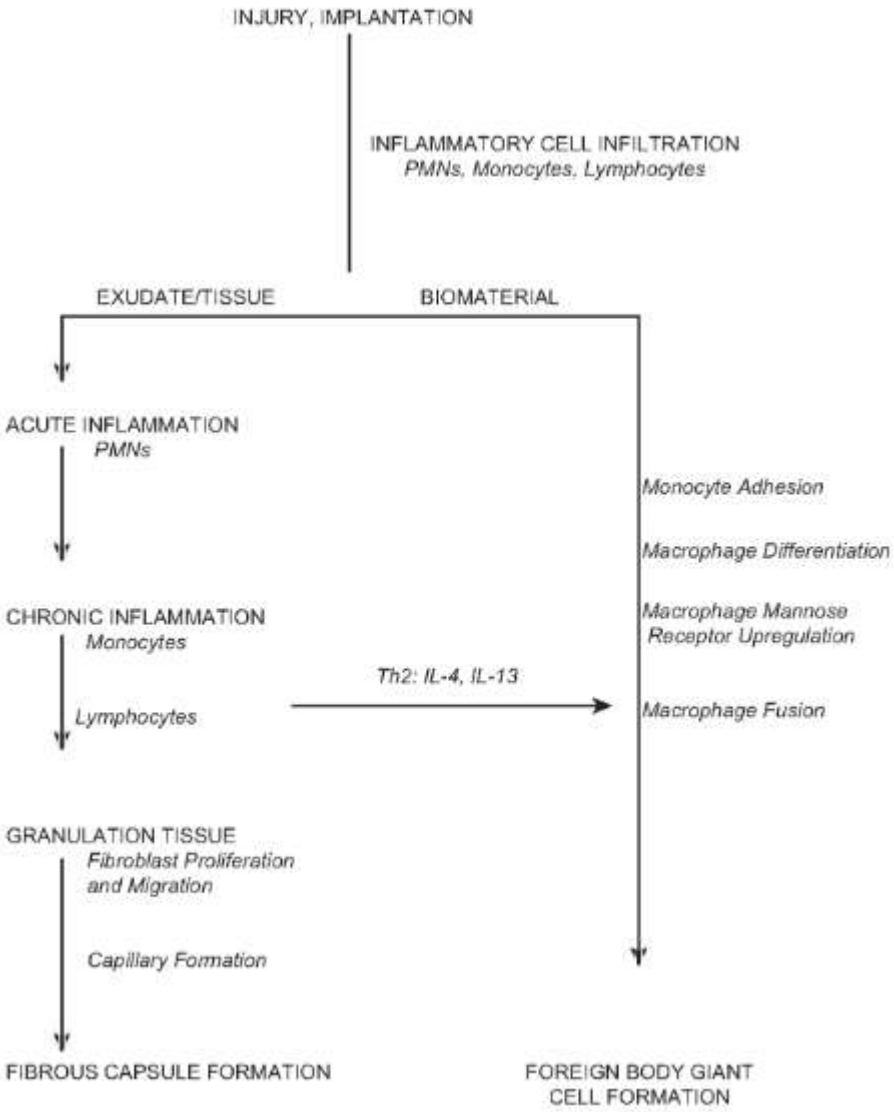
FIGURE II.2.2.1 The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign-body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

Anderson said:

> The size, shape, and chemical and physical properties of the biomaterial may be responsible for variations in the intensity and duration of the inflammatory or wound-healing process. Thus, intensity and/or time duration of the inflammatory reaction may characterize the biocompatibility of a biomaterial.[456]

457 Anderson used the figure reproduced below to demonstrate the sequence of events involved in inflammation and wound healing when medical devices are implanted:[457]

456 Ibid at 3.
457 Ibid at 8.



He said that, generally, the end-stage healing response to biomaterials is fibrosis or fibrosis encapsulation.[458]

458 Anderson 2013 described the foreign body reaction to a biomaterial as follows:

> The foreign-body reaction to biomaterials is composed of foreign-body giant cells and the components of granulation tissue (e.g., macrophages, fibroblasts, and capillaries in varying amounts), depending upon the form and topography of the implanted material.
>
> …
>
> The foreign-body reaction consisting mainly of macrophages and/or foreign-body giant cells may persist at the tissue-implant interface for the lifetime of the implant … Generally, fibrosis (i.e., fibrous encapsulation) surrounds the biomaterial or implant with its interfacial foreign-body reaction, isolating the

458 Ibid at 7.

implant and foreign-body reaction from the local tissue environment.[459]

459 In an earlier article published in 2001, Anderson defined biocompatibility as follows:

> Biocompatibility is generally defined as the ability of a biomaterial, prosthesis, or medical device to perform with an appropriate host response in a specific application, and biocompatibility assessment, i.e. evaluation of biological responses, is a measure of the magnitude and duration of the adverse alterations in homeostatic mechanisms that determine the host response. Practically speaking, the evaluation of biological responses to a medical device is carried out to determine that the medical device performs as intended and presents no significant harm to the patient or user. Thus the goal of biological response evaluation is to predict whether a biomaterial, medical device, or prosthesis presents potential harm to the patient or user by evaluating conditions that simulate clinical use.[460]

Key definitions

460 There were significant differences of opinion between the experts about the meaning of terms including 'inflammatory cells', 'acute inflammatory cells', 'acute inflammation', 'chronic inflammatory cells' and 'chronic inflammation'. The experts also differed in their views on how those terms were used in scientific literature by immunologists and pathologists, and in studies involving histological analysis of tissue following explantation of Essure inserts.

Acute inflammation

461 In the immunology JER, Robertson and Sokol agreed:

> We agree that acute inflammation is an immune response characterized by the infiltration or accumulation (entry out of the blood vessels and into tissues) of predominantly granulocytes (neutrophils and eosinophils), as well as lesser numbers of monocytes and macrophages. We also agree that this term is sometimes used to describe a chronic inflammatory response where neutrophils or eosinophils are the predominant infiltrating cells.
>
> We agree that this broad definition would be agreed upon by immunologists, pathologists and clinicians.[461]

In the biomaterials JER, Badylak, Chrzanowski and Robertson agreed to the same definition of acute inflammation.[462] Murdock agreed to the first sentence of this

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459 Ibid at 6.

460 James Anderson, 'Biological Responses to Materials' (2001) 31 *Annual Review of Materials Research* 82 (PUB.500.001.0715) ('Anderson 2001').

461 Immunology JER at 7 (EXP.500.001.0004).

462 Biomaterials JER at 4 (EXP.500.001.0006).

definition in the pathology JER.[463]

462 Robertson said that the acute inflammatory response in wound healing should be short-lived and progress rapidly with a characteristic sequence of different immune cell types passing into the wound. She said that this progression could be broken into 'early inflammation' and 'late inflammation' stages. By four weeks (or three months at the latest), the inflammatory response should be resolved and the immune cells should disappear by dying or exiting the wound.[464]

463 Sokol said that the standard meaning of 'acute inflammation' was any inflammation lasting up to six weeks after onset.[465]

464 In the biomaterials JER, Robertson, Chrzanowski and Badylak agreed:

> … that in all women, the wound healing response to placement of an Essure Device involves an acute inflammatory response phase. In most women, this phase will be short-lived and will be completely resolved within hours or days of Device placement, at which time it transitions to a chronic inflammatory response. We agree that in some women where the Device continues to elicit a chronic inflammatory response that is dominated by immune cells of the granulocytic type (neutrophils or eosinophils), the inflammatory response has been termed an 'acute inflammatory response', even though the Device was placed many weeks or months earlier (eg. Valle et al 2001).[466]

465 In the immunology JER, Robertson and Sokol agreed:

> … that the presence of a predominant neutrophil infiltrate surrounding the Essure device in the fallopian tube at 3 months or more after placement is consistent with active inflammation and not expected of the normal wound healing response.[467]

466 Robertson said that acute inflammation 'only occurs after it is elicited by a pro-inflammatory stimulus, and is not a feature of healthy quiescent tissue'.[468] She said that acute inflammation can be 'low grade' or 'high grade', and that low grade inflammation may not be readily detectable using standard clinical tests but can still

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463 Revised Pathology JER at 9 (EXP.500.001.0007_2).
464 Robertson at 98 [398] (EXP.001.001.0127).
465 Sokol at 11 (EXP.001.002.0001).
466 Biomaterials JER at 25 (EXP.500.001.0006).
467 Immunology JER at 12 (EXP.500.001.0004).
468 Pathology JER at 10 (EXP.500.001.0007).

adversely affect health if not rapidly resolved.[469] Sokol considered the 'low grade' and 'high grade' nomenclature to be descriptive without clear definition.[470]

467 Murdock said that in the clinical practice of pathology, 'acute inflammation' is a collective term that can mean the presence of one or more types of acute inflammatory cells, including neutrophils, eosinophils and/or basophils. She said that the presence of one or more of these cell types would usually be reported as 'acute inflammation'. She said that 'in general terms, acute inflammation is of relatively short duration, lasting from minutes to days, depending on the extent of injury'.[471] Murdock said:

> In clinical practice, when examining tissues adjacent to a medical device, the clinician responsible for the patient will request for us (pathologists) to specify in the pathology report if the inflammatory response to the medical device is composed of acute or chronic types. This is important information to the clinician taking care of the patient because if "acute inflammation" is present (i.e., neutrophils), then the patient may need clinical intervention (i.e., antibiotics). However, if "chronic inflammation" is present, this is an expected response to a medical device and no further clinical intervention is needed. This is why we (pathologists) specify acute versus chronic in the pathology reports of tissues adjacent to medical devices, but "chronic inflammation" is not meant as a systemic abnormal process, this is simply to communicate to the clinician that the inflammatory cell population is not comprised of acute inflammatory cells.[472]

468 This evidence demonstrates that the term 'acute inflammation' is used by immunologists and pathologists in a number of different but related ways. First, it describes an inflammatory response in which neutrophils, and sometimes eosinophils and basophils, predominate. This acute response occurs in the minutes, hours and days following injury.

469 Second, it may describe circumstances where neutrophils or eosinophils predominate in an inflammatory infiltrate that is present at a later point in time. This may also be described as a chronic inflammatory response.

470 Third, 'acute inflammation' may be used to describe inflammation that occurs in

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469 Ibid at 10.
470 Immunology JER at 7 (EXP.500.001.0004).
471 Ibid.
472 Pathology JER at 10-11 [32] (EXP.500.001.0007).

wound healing or as part of the foreign body response. The inflammatory response can be broken into 'early inflammation' and 'late inflammation' stages. Anderson described the early stage as 'acute inflammation' because neutrophils predominate. The later stage of the inflammatory response as part of normal wound healing can be called 'chronic inflammation' because macrophages predominate.

Chronic inflammation

471 In the immunology JER, Robertson and Sokol agreed:

> … that "chronic inflammation" in tissues is an inflammatory state usually characterized by an accumulation of leukocytes, predominantly macrophages and lymphocytes, in substantial excess of the numbers usually present in the tissue. Inflammation can be considered chronic when present for 6 weeks or longer since the initiating insult[.]
>
> We agree that the term chronic inflammation can apply to a specific tissue site, for example in the proximity of a foreign body response, and/or to a systemic state where many tissues of the body may be affected.
>
> We agree that the term "chronic inflammation" generally implies a pathological state of abnormal immune activation, as chronic inflammation is inconsistent with optimal health[.]
>
> We agree that this broad definition would be agreed upon by immunologists, pathologists and clinicians.[473]

Robertson, Chrzanowski and Badylak agreed on a definition of chronic inflammation in almost identical terms in the biomaterials JER.[474]

472 Sokol said that in the absence of activating stimuli, macrophages exist in tissues in a non-inflammatory quiescent state. Their simple presence in tissue does not indicate whether they are producing pro-inflammatory cytokines.[475] She said that the presence of other inflammatory cells that are consistent with an acute inflammatory reaction, including granulocytes such as neutrophils or eosinophils, can be used as a surrogate to indicate whether inflammation is occurring.[476] She said that 'since these granulocytes may also be present in normal uterine or fallopian tube tissue, it is

473 Immunology JER at 8 (EXP.500.001.0004).
474 Biomaterials JER at 3-4 (EXP.500.001.0006).
475 Sokol at 17 (EXP.001.002.0001).
476 Ibid.

essential to compare the numbers and proportion of these cells to those seen in normal tissue at the same locations'.[477]

473 Robertson and Sokol agreed that there were 'circumstances where the presence of inflammatory cells immediately adjacent to an Essure [d]evice means that "acute inflammation" or "chronic inflammation" are present.'[478] In the immunology JER, they said:

> … that the presence of immune cells, the number of immune cells, and the interval since Device placement, are relevant factors in designation of one or the other types of inflammation… [T]he presence of a predominant infiltrate of neutrophils immediately adjacent to an Essure Device would be consistent with active inflammation… [I]n the event that a neutrophil infiltrate immediately adjacent to an Essure Device was detected less than 6 weeks after placement, this would be considered "acute inflammation", and would be considered consistent with a normal foreign body response. In the event that neutrophils were identified immediately adjacent to an Essure Device 6 weeks or more after placement this would indicate active inflammation that could be termed "acute inflammation" or could be termed "chronic inflammation" as it is beyond the usual time frame for resolution of an acute inflammatory response… [W]hether the term "acute" or "chronic" is used in this circumstance and the precise time points for assigning these terms varies between investigators.[479]

474 During the immunology concurrent evidence session, I asked Sokol about this evidence and the agreed definition of 'chronic inflammation':

> So in the context of the Essure Device if there is a circumstance where neutrophils are identified immediately adjacent to the device six weeks or more after, placement, that would be indicative of active inflammation?---Yes.
>
> And could be termed chronic inflammation?---Depending on how the investigator is defining their terms. They could either refer to it as acute inflammatory cells or acute inflammation because of the presence of neutrophils, or they could refer to it as chronic inflammation because it is ostensibly going on for more than six weeks.
>
> Chronic inflammation, in the way that you have used that term in this report from line 380 onwards - so if we go to line 380 - in the four paragraphs under the heading 'Chronic inflammation' [see agreed definition at

477 Ibid at 17 [3.3.2]; T4092 (TRA.500.041.0001_2 at 0010_5).
478 Immunology JER at 13 (EXP.500.001.0004).
479 Ibid.

[471] above] ---Yes.[480]

475 In the biomaterials JER, Robertson, Chrzanowski and Badylak explained the chronic inflammatory response phase of the foreign body response to Essure as follows:

> We agree that in all women, the wound healing response to placement of an Essure Device involves formation of fibrotic tissue around the Essure Device. The formation of fibrotic tissue occurs as a consequence of the infiltration of immune cells (specifically macrophages) and fibroblasts into the vicinity of the device, as part of the chronic inflammatory response phase of the foreign body response. This formation of fibrotic tissue is an intended and desired component of the response to an Essure Device; it is what the Device is intended to elicit, in order to completely occlude the fallopian tube and cause a contraceptive effect. In most women, the fibrotic response will be extensive and will result in complete occlusion of the fallopian tube. In this event the laying down of fibrotic tissue may cease and become quiescent. We agree that there are many individual factors that affect the extent and duration of the fibrotic response, so these parameters will vary between women.
>
> …
>
> We agree that in all women, the wound healing response to placement of an Essure Device involves a chronic inflammatory response phase. In most women, this phase will be short-lived and will be completely resolved within 6 weeks, and at most 3 months of Device placement. We agree that in many women, the Device undergoes complete healing with resolution of inflammation and extensive fibrotic tissue/scar formation[.][481]

476 Badylak said that the acute inflammatory response is short lived — three to seven days —after which it transitions to a chronic phase that is dominated by macrophages and a small but variable number of foreign body giant cells. He said:

> This chronic phase is also accompanied by a progressive infiltration of fibroblasts that deposit collagen and contribute to the fibrous connective tissue component of the healing response. These events reach a "steady state" within 2-3 months. There is no scientific evidence that the cells remaining in the remodelled tissue that surrounds the Essure device are actively participating in an adverse "proinflammatory" process.[482]

477 The experts did not agree on the designation of chronic inflammation in clinical and scientific practice. This was an extension of their disagreement about the term 'inflammatory cells' (at [481]-[483] below). Robertson considered that when

480 T4232 (TRA.500.042.0001_2 at 0010_2-16).
481 Biomaterials JER at 24, 26 (EXP.500.001.0006).
482 Ibid at 26.

designating a state of chronic inflammation in tissue using histological analysis, immunologists and pathologists take into account other features of the tissue sample in addition to the number of immune cells. Those features include evidence of phagocytic activity, the presence of a pro-inflammatory stimulus, and the spatial proximity of immune cells to the stimulus.[483]

478 Sokol and Robertson agreed that the presence of immune cells in tissue does not, without more, indicate an active inflammatory response.

479 Sokol said it is necessary to know the numbers and types of infiltrating immune cells to determine whether there is active inflammation. She said that since evidence of phagocytic uptake can be seen in quiescent or active immune cells, there must be standard evidence of inflammation (that is, abnormal numbers of immune cells infiltrating into tissue) to conclude that inflammation is present. She considered that because there are different types of immune responses which lead to chronic inflammation, it is necessary to provide details of the cellular influx or markers used to diagnose chronic inflammation in histological analyses, instead of relying simply on the use of the term 'chronic inflammation'.[484]

480 The features of chronic active inflammation may include accumulation of leukocytes, swelling, heat, redness, fluid discharge, neovascularisation and pain.[485] Badylak said that a:

> chronic active inflammatory state does not occur as part of the foreign body response that accompanies permanently implanted devices such as the Essure device. If such a phenomenon did indeed occur, one would expect to see the hallmarks of an active, self-perpetuating process such as continued neovascularisation, foci of tissue necrosis with focal accumulations of neutrophils, and a robust fibroblast presence.[486]

481 Murdock said that in practice pathologists use the term 'chronic inflammation' as a collective term to describe 'the presence of one or more types of chronic inflammatory

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483 Ibid.
484 Ibid.
485 Robertson at 98 [390] (EXP.001.001.0127_2).
486 Badylak at 22 [71] (EXP.001.002.0007).

cells, including macrophages, lymphocytes, plasma cells, mast cells, natural killer (NK) cells and dendritic cells'. She said that chronic inflammatory cells can be found in normal fallopian tubes and that the term 'chronic inflammation' can also be applied to normal tissue if necessary. She said that when examining tissue adjacent to a medical device in clinical practice, pathologists will specify whether the inflammatory response to the device is composed of acute or chronic inflammatory cells.

482 Murdock said:

> It is clear from Professor Robertson's reports that she lacks the clinical training and experience in pathology, has misinterpreted the pathology literature, and misconstrues the presence of chronic inflammatory cells (chronic inflammation) adjacent to the Essure Device as a systemic chronic inflammatory process or causing a systemic changes in the immune response. When in fact, we know that chronic inflammatory cells (chronic inflammation) are present in normal fallopian tubes… and are expected to be in the tissue adjacent to the Device, in addition, normal fallopian tube histology was observed within 5 mm from the Device (Valle 2001).[487]

483 In response, Robertson said that she:

> …disagrees with Dr Murdock that inflammatory cells present in tissues adjacent to a medical device do not signify an abnormal tissue response. [Robertson] considers that existence of chronic inflammation associated with a medical device implies an abnormal state of immune activation and that ongoing chronic inflammation is inconsistent with optimal health[.] In her opinion, the persistence or duration of chronic inflammation associated with a medical device is a factor in the risk of adverse health impact[.][488]

484 Anderson 2013 described chronic inflammation in the following terms:

> Chronic inflammation is less uniform histologically than acute inflammation. In general, chronic inflammation is characterized by the presence of macrophages, monocytes, and lymphocytes, with the proliferation of blood vessels and connective tissue. Many factors can modify the course and histologic appearance of chronic inflammation.
>
> Persistent inflammatory stimuli lead to chronic inflammation. While the chemical and physical properties of the biomaterial in themselves may lead to chronic inflammation, motion in the implant site by the biomaterial or infection may also produce chronic inflammation. The chronic inflammatory response to biomaterials is usually of short duration, and is confined to the implant site. The presence of mononuclear cells, including lymphocytes and plasma cells, is

487 Ibid at 15 [52].
488 Ibid at 15 [56].

> considered chronic inflammation, whereas the foreign-body reaction with the development of granulation tissue is considered the normal wound healing response to implanted biomaterials (i.e., the normal foreign-body reaction). Chronic inflammation with the presence of collections of lymphocytes and monocytes at extended implant times (weeks, months, years) may also suggest the presence of a long-standing infection… The prolonged presence of acute and/or chronic inflammation also may be due to toxic leachables from a biomaterial.[489]

485 This extract was put to Murdock. She did not agree that the chronic inflammatory response to biomaterials is usually of short duration, because it may last for 'the lifetime of the device'.[490] Murdock agreed that chronic inflammation with the presence of collections of lymphocytes and monocytes for extended periods after implantation may suggest longstanding infection, but added that she would want to examine the tissue in such circumstances.[491]

486 Sokol expressed general agreement with the passages from Anderson 2013 extracted above. She agreed that the passages suggested that the prolonged presence of lymphocytes and monocytes indicated something 'out of the ordinary' or inconsistent with a normal foreign body response, but noted that a 'normal' response to one foreign body could differ from the 'normal' response to another and that data would be necessary to determine what was truly 'abnormal'.[492]

487 Again, the evidence demonstrates that 'chronic inflammation' is used by immunologists and pathologists in a number of ways. First, it can be used to describe the late inflammatory stage of wound healing or the foreign body response where the numbers of neutrophils have decreased and macrophages predominate.

488 Second, Murdock said that 'chronic inflammation' can be used as a collective term to simply describe the presence of certain types of immune cells, including macrophages, in tissue.

489 Third, it may describe an active inflammatory state that is present after the time when

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489 Anderson 2013 at 4 (PUB.500.001.0841).
490 T2839 (TRA.500.030.0001_2 at 0045_18).
491 T2841 (TRA.500.030.0001_2 at 0047).
492 T4046-7 (TRA.500.040.0001_2 at 0056_27-0057_19).

wound healing or the foreign body response should have resolved. In those circumstances, 'chronic inflammation' may be characterised by a predominance of macrophages and lymphocytes in substantial excess of the numbers usually present in tissue, or by a predominating neutrophil infiltrate. Other hallmarks or features would be expected in cases of active, self-perpetuating chronic inflammation.

490 Sokol said the presence of active chronic inflammation can be detected by standard laboratory tests including high sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and fibrinogen levels.[493] She said elevation in any one of these markers is indicative of inflammation, but that the results do not reveal the cause. Sokol said that if she suspected inflammation in a patient, she would request that these tests be performed. There is no evidence that these tests have been performed on Essure patients. Sokol said that this meant inflammation was not 'on the mind of the physician' as a differential diagnosis.[494]

491 Robertson said that like acute inflammation, chronic inflammation can be 'low grade' (and not readily detectable using standard clinical tests) or 'high grade'.[495] In her reply report, Robertson said that '[w]hile a positive score for one of these tests may be considered indicative of inflammation (high grade or low grade), absence of a positive result does not exclude low grade inflammation'.[496]

492 Robertson gave the following further explanation in her oral evidence:

> And the key element is inflammation, and I think that I have said that and, you know, I think that there are examples of inflammation that might not necessarily meet the grade at which a pathologist would diagnosis chronic salpingitis or chronic endometritis, but where there is change in the phenotype function pro-inflammatory disposition and inflammatory activation of immune cells in a tissue that are occurring to a level that causes injury and harm without necessarily changing the pattern of tissue that histologists or pathologists see in a microscope. There are many examples emerging. I was talking about inflammation earlier where a low grade or low level inflammation alters the immune cells in such a way as to have a considerable impact on the tissue and to elicit harm and injury. So I think I've made it clear

493 Sokol at 11 (EXP.001.002.0001).
494 T4227 (TRA.500.042.0001 at 0005).
495 Immunology JER at 8 (EXP.500.001.0004).
496 Robertson at 76 [196] (EXP.001.002.0015_2).

> that in my view, you know, it's not necessary to have chronic salpingitis or chronic endometritis for chronic inflammation to be there and to be a pathology and to be causing harm. Even if it's common or expected or usual, or perhaps normal even as part of a certain kind of response, that isn't inconsistent with it causing harm.[497]

493 Badylak said that while there can be degrees of intensity of the inflammatory response the terms 'low grade' and 'high grade' are not conventional in the field of pathology.[498] He said that a number of reliable laboratory tests are available to determine whether an active inflammatory process is occurring, but that these had not been done in the case of Essure.

494 In the immunology JER, Robertson and Sokol agreed:

> We agree that laboratory blood tests such as ferritin, fibrinogen, hsCRP, CRP, and ESR are methods used to diagnose the presence of either chronic inflammation or persistent chronic inflammation (Sokol report, lines 717-718). We also agree that it has not been proven whether or not scoring within normal ranges for these indicators rules out the presence of any inflammation causing an adverse health impact, although elevations in these indicators correlate with increased health risks.[499]

495 Despite this agreement, in her oral evidence Robertson said that her understanding was 'that there are examples of … where even the high sensitivity test wouldn't detect the presence of the low grade inflammation'.[500] It was put to Robertson:

> I suggest, Professor Robertson, that if there's a sufficient level of inflammatory process occurring in the human body so as to cause an adverse effect to a person's health, it would be capable of being detected by one or more of these tests?---I think you're wrong. I could quote to you from Harvard Health publishing if you like, 'Low-grade inflammation may continually simmer below the surface'. It's a type of persistent inflammation and I would say that 'simmer below the surface' implies unable to be readily detected, subclinical.
>
> What are you reading from, Professor Robertson?---One of the first definitions of low-grade inflammation that comes up when you look it up on - it's one of the pieces of information about a definition of low-grade inflammation.
>
> And where is that referred to in your report?---It's not in my report but I have

497 T3016 (TRA.500.031.0001_2 at 0090_3).
498 Biomaterials JER at 5 (EXP.500.001.0006).
499 Immunology JER at 22 (EXP.500.001.0004).
500 T4031 (TRA.500.040.0001_2 at 0041_20).

> in my report talked about low-grade inflammation as being subclinical. It's consistent with the statements I've made. It's part of my response to your question because you're persisting with the point that it should be able to be detected and I'm saying to you that it's common knowledge that it's not always possible to detect a low-grade inflammation, especially with those tests.[501]

496 In evidence the following day Sokol questioned Robertson's reliance upon the Harvard Health publishing website. She said the website did not mention CRP testing. It did mention low grade inflammation that can simmer below the surface in conditions including rheumatoid arthritis, lupus, ulcerative colitis, multiple sclerosis, cancer and cardiovascular disease. Sokol said CRP is elevated for all of those diseases.[502]

497 Robertson did not identify any other scientific literature to support her proposition that low-grade inflammation may not be detected by clinical tests. I accept Sokol's evidence that the Harvard Health website does not support Robertson's contention. I accept the evidence of Sokol and Badylak that standard and reliable laboratory tests are available to diagnose the presence of active chronic inflammation, and that there is no evidence that these tests have been performed in the case of Essure. I reject Robertson's evidence, which seemed imprecise and unscientific.

Persistent chronic inflammation

498 Robertson and Sokol agreed that 'persistent', when used in conjunction with 'chronic inflammation', is a descriptive term.[503] Robertson said that 'persistent' was an appropriate descriptor to specify chronic inflammation that persists for greater than three months and does not show indications of resolving. She said that the phrase 'persistent chronic inflammation' is commonly used in immunology literature. Sokol did not agree that use of the phrase was common or that it referred to a precise clinical entity.

499 Murdock said:

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501 T4032 (TRA.500.040.0001_2 at 0042_7).
502 T4125 (TRA.500.041.0001_2 at 0043).
503 Immunology JER at 9 (EXP.500.001.0004).

> The term persistent in the context of a medical device is misleading. We know that chronic inflammatory cells (chronic inflammation) may be present in the adjacent tissues for the lifetime of the device and does not signify an abnormal tissue response[.] In addition, chronic inflammatory cells are present in normal fallopian tubes.[504]

Pro-inflammatory response

500 Robertson and Sokol agreed:

> … that the term 'pro-inflammatory response' describes a type of immune response that provokes, facilitates, amplifies, or propagates an acute or chronic inflammatory response. A pro-inflammatory response involves certain types of immune cells or their molecular mediators after they are triggered by an activating stimulus. This is in contrast to the term 'anti-inflammatory response', which describes a type of immune response that suppresses, constrains and/or resolves an inflammatory response.[505]

Inflammatory cell infiltrate

501 Robertson said that 'inflammatory cell infiltrate':

> … is a term that is used to describe a distinctive pattern of immune cell accumulation or localisation in a tissue under circumstances where inflammation is occurring or inferred to be occurring, and infiltration of immune cells from the peripheral blood is indicated … The immune cells in an inflammatory infiltrate are usually but not always detected by histology, and may show other features indicative of an inflammatory activation state, such as phagocytic activity …
>
> In the context of an infiltrate, the term "inflammatory cell" may encompass a range of immune cell types including granulocytes (neutrophils, eosinophils), monocytes and macrophages, mast cells and lymphocytes. However, … [the] term "inflammatory cell" is not interchangeable with "immune cell" or "leukocyte" or any other term for immune cell subsets, as it only applies to immune cells located in a tissue site in which active inflammation is occurring or inferred to be occurring.[506]

502 Sokol said that the presence of chronic inflammatory infiltrate does not mean that the cells are active. She said that she would want to know whether there were neutrophils in the tissue or any other evidence of activation before reaching that conclusion.[507]

503 Murdock said:

> In pathology, "Inflammatory cell infiltrate" is used to describe a pattern of

504 Pathology JER at 16 (EXP.500.001.0007).
505 Immunology JER at 9 (EXP.500.001.0004).
506 Pathology JER at 20 [78], 21 [79] (EXP.500.001.0007).
507 T4113 (TRA.500.041.0001_2 at 0031_26).

> inflammatory cell localization in normal or abnormal tissue, where the inflammatory cells have infiltrated the tissue layers. This inflammatory cell infiltrate can be "acute" or "chronic" and would be specified and reported as such (e.g., "x tissue with acute inflammatory cell infiltrate"). It is important to note that the number of inflammatory cells is not quantified.[508]

504 In the immunology JER, Robertson and Sokol agreed:

> … that the presence of a predominant neutrophil infiltrate surrounding the Essure device in the fallopian tube at 3 months or more after placement is consistent with active inflammation and not expected of the normal wound healing response.[509]

Inflammatory cells

505 In the immunology JER, Sokol and Robertson agreed that 'inflammatory cells' is a non-specific term referring to immune cells that can promote inflammation. It can be used to describe a wide range of cells including granulocytes (neutrophils, eosinophils), monocytes and macrophages, mast cells and lymphocytes.[510]

506 Sokol and Robertson disagreed on whether the term 'inflammatory cells' necessarily indicates that the cells are actively engaged in or are promoting inflammation. [511] Sokol said that the term 'inflammatory cells' was:

> often used interchangeably with 'immune cells' in the medical literature. Because immune cells can have both pro-inflammatory and anti-inflammatory functions, she considers the presence of 'inflammatory cells' to not necessarily indicate active inflammation …[512]

507 Murdock agreed with Sokol. She said that in pathology, 'inflammatory cells' is a collective term and can refer to acute or chronic inflammatory cells.[513]

508 Robertson disagreed. She said that 'there is an important distinction between the term "immune cells" (which encompasses a wide range of functional states) and the term "inflammatory cells" which specifically relates to immune cells with pro-

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508 Revised Pathology JER at 21 [82] (EXP.500.001.0007_2).
509 Immunology JER at 12 (EXP.500.001.0004).
510 Ibid at 6.
511 Ibid.
512 Ibid.
513 Pathology JER at 21 (EXP.500.001.0007).

inflammatory activity.'[514] Robertson said that experienced immunologists and pathologists would not call immune cells in healthy tissue 'inflammatory cells', and that the term would only be used in the event of strong suspicion that the immune cells were engaged in inflammatory activity.[515] She explained:

> Unlike the term 'inflammatory cell', the term 'immune cell' is commonly used to describe leukocytes regularly found in most tissues of the body as part of normal tissue homeostasis, or 'house-keeping'. The housekeeping activities that immune cells undertake in healthy tissues (especially in mucosal tissues such as the uterus and fallopian tube) include (1) modulation of the behaviour of other cells, such as epithelial and decidual cells; (2) regulation of tissue turnover (removal of dead and dying cells); (3) remodelling of the extracellular matrix; and (4) surveillance for new foreign invaders (microbes, tumor cells, spermatozoa).
>
> …
>
> In histological analyses, a judgement on the likelihood of inflammatory activity would be made based on the pattern of tissue location of the cells – their numbers, identity, physical characteristics, and other indicators of their likely function in the tissue – for example their proximity to other types of cells that have specific biological functions in the tissue, such as epithelial surfaces or blood vessels. They would also take into account whether there was reason to suspect an inflammatory response – that is, whether there is evidence of tissue injury, destruction, disease or dysfunction.[516]

509 It is worth noting that Sokol is an experienced practising clinical immunologist and Murdock is an experienced practising clinical pathologist. Robertson has not practised as an immunologist or a pathologist.

Acute inflammatory cells and chronic inflammatory cells

510 Robertson said that 'acute inflammatory cells' and 'chronic inflammatory cells' are not scientific terms, nor are they commonly used in scientific literature to describe immune cells in a healthy quiescent uterus or fallopian tube.[517] She said that immune cells cannot have 'chronic' or 'acute' properties.[518] She said that when the terms are used, they are intended to connote the presence of immune cells in tissue in which

514 Robertson at 33 [55] (EXP.001.002.0015).
515 Ibid at 33 [56].
516 Ibid at 109-110.
517 Pathology JER at 11 (EXP.500.001.0007).
518 Ibid at 16.

active inflammation is occurring or inferred to be occurring. [519]

511 Murdock said that 'acute inflammatory cells' is a scientific term frequently used in pathology as a collective term to describe the presence of one or more types of acute inflammatory cells including neutrophils, eosinophils and/or basophils. She said that there are numerous examples in pathology literature describing 'acute inflammatory cells' in tissue, including in normal tissue.[520] Similarly, Murdock said that 'chronic inflammatory cells' is a collective term used to describe the presence of types of cells including lymphocytes, macrophages, plasma cells, mast cells, natural killer cells and dendritic cells. She said that the term was used to describe the presence of those types of cells, whether in normal or abnormal tissue.[521]

Scientific literature relevant to definitions

512 Murdock gave the following examples of texts and studies in support of her contention that 'chronic inflammatory cells' and 'chronic inflammation' are simply used to describe the presence of certain immune cells in tissue, including in normal tissue: the 1994 study by Wollen et al ('Wollen 1994');[522] extracts from the textbook *Blaustein's Pathology of the Female Genital Tract* ('*Blaustein*');[523] Ardighieri et al ('Ardighieri 2014');[524] and Hunt and Lynn ('Hunt 2002').[525]

513 Wollen 1994 involved histological examination of the fallopian tubes removed by laparoscopy from 60 healthy non-pregnant women without any history of salpingitis. Thirty-one of the women had used a copper IUD for a period of two to 10 years. The remaining 29 women, who were the control group for the purposes of the study, had

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519 Ibid at 11, 16.
520 Ibid at 12.
521 Revised Pathology JER at 17 (EXP.500.001.0007_2).
522 Anne-Lone Wollen et al, 'In situ characterization of leukocytes in the fallopian tube in women with or without an intrauterine contraceptive device' (1994) 73(2) *Acta obstetricia et gynecologica Scandinavica* 103 (PUB.500.001.0786) ('Wollen 1994').
523 RJ Kurman et al (eds), *Blaustein's Pathology of the Female Genital Tract* (Springer, 7th ed, 2019).
524 Laura Ardighieri et al, 'Characterization of the Immune Cell Repertoire in the Normal Fallopian Tube' (2014) 33(6) *International Journal of Gynecological Pathology* 581 (PUB.500.001.0670) ('Ardighieri 2014').
525 Jennifer L Hunt and Amy AA Lynn, 'Histologic Features of Surgically Removed Fallopian Tubes' (2002) 126(8) *Archives of Pathology & Laboratory Medicine* 951 (PUB.500.001.0723) ('Hunt 2002').

not used an IUD for the last 12 months.

514 Histological analysis of fallopian tissue revealed the presence of various types of immune cells in all of the tubes. The authors relevantly described the results as follows:

> In sections from the control group a moderate and variable number of mononuclear cells, interpreted as lymphocytes, were found both in the tubal epithelium, subepithelially, in the lamina propria, myosalpinx and the serosa. Granulocytes and plasma cells were also present, but in lower numbers and mainly localized in the center of the mucosal folds. Mast cells were present, but scarce, in the lamina propria and myosalpinx (Fig. I).
>
> When compared to the normal presence of leukocytes in the fallopian tube, biopsies with a subjectively increased infiltration of granulocytes, lymphocytes and/or plasma cells in the endosalpinx, were characterized as inflamed (Fig. 1). An inflammatory reaction was apparently present in 14% of the biopsies in the control group and in 68% the [IUD] users, a difference which was statistically highly significant (Table II). In both groups, the majority was of the chronic type of inflammation, with a predominance of mononuclear cells (Table II).[526]

Table II referenced above follows:[527]

Table II. Distribution of the morphological changes according to the histological evaluation

Tubal reaction	Control group *n*=29	IUCD users *n*=31
No inflammation	25 (86%)	10 (32%)
Inflammation	4 (14%)	21 (68%)
-acute	1 (3%)	1 (3%)
-subacute	1 (3%)	4 (13%)
-chronic	2 (8%)	16 (52%)

515 The authors only used the terms 'acute' and 'chronic' when describing the presence or type of inflammatory reaction. Where immune cells were seen, but not in increased numbers, they were identified by type and not by use of the collective terms 'acute inflammatory cells' or 'chronic inflammatory cells'. Murdock agreed that Wollen 1994 did not use 'chronic inflammation' to describe the normal presence of immune cells in

526 Wollen 1994 at 4 (PUB.500.001.0786).
527 Ibid at 5.

the fallopian tube.

516 In a chapter of *Blaustein* referred to by Murdock, 'chronic inflammation' and 'chronic inflammatory cells' are used in the context of a description of acute salpingitis.[528] However, the authors refer to 'a small number of acute or mixed acute and chronic inflammatory cells' being found in association with an asymptomatic form of acute salpingitis where attempts to culture for bacteria were unsuccessful.[529] Further, the authors note that where certain clinical information raises for consideration diagnosis of early tuberculosis salpingitis 'the mere finding of acute and chronic inflammatory cells should lead to consideration of staining for acid fast organisms'.[530] These extracts provide some support for Murdock's contention.

517 Another chapter of *Blaustein* used 'inflammatory cells' when discussing specific tumour types:

> Another pattern of necrosis that may be seen in ulcerated submucous leiomyomas features acute inflammatory cells and an associated zonal reparative process.[531]
>
> …
>
> Submucous leiomyomas, particularly if they protrude into the endometrial cavity, may display extensive necrosis, often with acute inflammatory cells, unlike the necrosis common in leiomyosarcoma.[532]
>
> …
>
> IMT is an uncommon uterine spindle cell tumor that typically has a prominent myxoid stroma that contains variable numbers of chronic inflammatory cells.[533]

518 Ardighieri 2014 describes the normal immune cell population in the fallopian tube.

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528 Russel Vang, 'Diseases of the Fallopian Tube and Paratubal Region' in Robert J Kurman et al (eds), *Blaustein's Pathology of the Female Genital Tract* (Springer, 7th ed, 2019) 649 (PUB.500.001.0843) ('Vang 2019').

529 Ibid at 20.

530 Ibid at 23.

531 Ibid at 7.

532 Ibid at 11.

533 Ibid at 78.

The study does not assist the consideration of this issue.

519 The purpose of Hunt 2002 was to document the frequency of histologic changes in fallopian tubes removed for all reasons or associations with clinical history. Two hundred and eighty-seven fallopian tube specimens were reviewed. In the summary of results, the authors said:

> Inflammatory cells were relatively common; 69% of specimens contained intramuscular mast cells, 19.9% had stromal plasma cells, 10.5% had neutrophils, and 2.1% had lymphoid follicles.[534]

In a more detailed description of results, the authors said:

> Beyond the ubiquitous intraepithelial lymphocytes, inflammatory infiltrates were not uncommon in our specimens. Inflammatory infiltrates were only included if they were composed of clusters of inflammatory cells occurring in significant numbers. Marginated neutrophils around vessels were specifically excluded; they were thought to be procedure- or pregnancy-related findings… Infiltration of neutrophils (acute salpingitis) in the epithelium was seen in 10.5% of specimens and was associated with a younger age. In addition, 69% of specimens demonstrated a minimum of 1 intramuscular mast cell per high-power field.[535]

Hunt 2002 used the term 'inflammatory cell' in a manner consistent with Murdock's evidence. Both authors are pathologists.

520 Robertson was cross-examined on the text 'Histology for Pathologists' by Stacey Mills ('Mills 2012') during her evidence.[536] She said that in the total of approximately 1,500 pages of the text, there were only one or two occasions when the term 'chronic inflammatory cells' was used in the context of normal tissue.[537]

521 Only 95 pages of Mills 2012 were tendered. My review of those pages shows that in most cases, the use of 'chronic inflammatory cells' was related to specific pathologies. This is hardly surprising as the text is directed to the identification of pathological

534 Hunt 2002 at 1 (PUB.500.001.0723).
535 Ibid at 2.
536 Stacey E Mills (ed), *Histology for Pathologists* (Lippincott Williams & Wilkins, 4th ed, 2012) (PUB.500.003.0040) ('Mills 2012').
537 T2772 (TRA.500.029.0001_2 at 0118).

processes. However, the portion of the text I reviewed also included the following:

> Microscopic periductal aggregates of chronic inflammatory cells and duct dilatation are not uncommon findings in the normal esophagus.
>
> …
>
> The superficial gastric lamina propria normally contains some chronic inflammatory cells. It is often a [matter] of judgment whether these are considered normal or increased in number because there is no simple satisfactory method of objective measurement.[538]

522 This limited review of pathology literature did reveal some examples where 'inflammatory cells' and 'chronic inflammatory cells' were used in a manner consistent with Murdock's evidence. I accept that pathologists may use those terms in a similar way when reporting histological analysis of tissue.

XII. HISTOLOGY

Histology of the uterus and fallopian tubes

Uterus

523 In the immunology JER, Robertson and Sokol said:

> We agree that the human non-pregnant uterus normally contains a wide variety of immune cells including, but not limited to, monocytes/macrophages, mast cells, dendritic cells, innate lymphoid cells including uterine natural killer cells (uNK), and lymphocytes (B cells, CD4+ T cells and CD8+ T cells). The uterus and the fallopian tubes are mucosal tissues with immune cells similar to other mucosal sites, but with three key distinctive features relating to their function: (1) the numbers, composition, and functional properties of these immune cell populations vary in their composition over the course of the menstrual cycle, (2) they play a critical role in the remodeling of the uterine lining over the course of the menstrual cycle, and (3) they play a critical role in permitting and regulating embryo implantation.[539]

524 Robertson said:

> Each of these immune cell subsets has a remarkable capacity to undergo a range of programmed functions (so-called 'phenotype flexibility'). Different phenotypes confer different effects on wound healing, on promoting and resolving inflammation, in generating immune tolerance or immune defence,

538 Mills 2012 at 19-21 (PUB.500.003.0040).
539 Immunology JER at 16 (EXP.500.001.0004).

and in regulating hemostasis and remodelling of blood vessels.[540]

She said that immune cell populations are spatially and temporally regulated by molecular cues in the functionalis tissue microenvironment that respond to sex hormones and other signals. She said that '[fertility] and healthy pregnancy depend on a remarkable ability of the uterine immune response to cycle between pro-inflammatory (estrogen dominated) and anti-inflammatory (progesterone dominated) states'.[541] She said that sophisticated discriminatory capabilities allow the uterus 'to sense and respond selectively to gametes, embryos, microbes and foreign entities or noxious stimuli' at appropriate stages of the menstrual cycle, thus conferring what she described as a 'hypervigilant immune capacity'.[542]

525 Robertson said:

> In the proliferative phase and at ovulation, when under the predominant influence of estrogen, the uterus is generally disposed towards activating inflammatory and effector responses, and will only elicit tolerance in the context of strong permissive signals. In the luteal phase after ovulation, when progesterone is the dominant sex hormone, the uterine immune response becomes disposed towards immune tolerance and tissue remodelling, and requires a stronger degree of stimulation to sustain an inflammatory response. When pregnancy occurs, this pro-tolerogenic and anti-inflammatory state continues, to support maternal tolerance of the fetus and its placenta. This is state is not the absence of inflammation, but rather the presence of a controlled inflammatory response that is kept in check by anti-inflammatory checks and balances.[543]

526 Robertson said that the uterine immune response is highly sensitive to environmental disturbances, and that:

> In women with a chronic wound response and persistent chronic inflammatory response to the Essure Device, the ongoing pro-inflammatory stimulus would be expected to change the behaviour (phenotypes) of immune cells not just in the immediate vicinity, but also more broadly in the tissue. This happens because the pro-inflammatory mediators affect the proliferation and function of immune cells in the lymph nodes draining the fallopian tube and uterus, and the cells produced in this site then recirculate to become disseminated in nearby tissue sites in the female reproductive tract (elsewhere in the uterus,

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540 Robertson at 66 [245] (EXP.001.001.0127).
541 Ibid at 67 [248].
542 Ibid.
543 Ibid at 67 [249].

fallopian tubes and ovaries) and elsewhere in the body.[544]

527 Robertson said that uterine immune cells modulate the uterine vasculature to ensure bleeding associated with menstruation is time-limited and resolves rapidly, allowing the blood vessels to close over and repair once bleeding is complete.[545]

528 Robertson said:

> In some aspects the events of menstruation resemble a tightly-controlled, self-limited inflammatory response. Just prior to menstruation, immune cells infiltrating into the decidualized endometrium to facilitate tissue breakdown, and allow it to be followed by vasoconstriction and an efficient hemostatic response (to allow bleeding to cease). The predominant infiltrating cells are macrophages and uNK cells.
>
> Macrophages recruited into the endometrium prior to and during menstruation initially acquire a pro-inflammatory phenotype, but a finely controlled modulation of their function and progression to an anti-inflammatory phenotype must occur in a timely manner so that tissue breakdown rapidly gives way to tissue repair, with cessation of bleeding followed by endometrial proliferation.
>
> Macrophages present in the tissue at menstruation play a key role in initiation of endometrial shedding by secreting matrix metalloproteinases (MMPs). Specifically, secretion of MMP-12, MMP-9, and MMP-14 are required for the breakdown of the functionalis layer. If the phenotype of uterine macrophages is incorrectly controlled or not correctly synchronised over the entire endometrial surface of the uterus (for example due to an excessive inflammatory activation (M1 phenotype) in regions adjacent to the SUTJ), this would be expected to contribute to bleeding at inappropriate stages of the cycle, or heavy bleeding in menstruation.
>
> Both uNK cells and macrophages are essential to allow menstrual bleeding to occur in a temporally- and spatially-controlled manner. uNK cells are critical for menstruation, through their ability to actively promote cell death of uterine decidual cells when progesterone withdrawal occurs. If uNK cells are insufficient in number, decidual breakdown may be compromised. If uNK cells are dysregulated in their phenotype or functional behaviour, this could contribute to bleeding at inappropriate stages of the cycle, or heavy bleeding in menstruation.
>
> These observations imply that sufficient numbers and precise functions in uterine immune cells are required to prevent uterine bleeding disorders such as menorrhagia (abnormally heavy or prolonged bleeding at menstruation), dysmenorrhoea (intense uterine cramping and pain), amenorrhea (abnormal

544 Ibid at 68 [251].
545 Ibid at 68 [252].

absence of menstruation), and irregular bleeding.[546]

529 Murdock said that acute and chronic inflammatory cells may be identified in the normal endometrial stroma depending on the phase of the menstrual cycle.[547] She said:

> In menstrual endometrium, where the endometrium is breaking down and sloughing away, numerous acute inflammatory cells including neutrophils are present, as well as a lesser degree of lymphocytes. In proliferative endometrium, (when the endometrial glands and stroma are building back up again), there are scattered stromal lymphocytes (chronic inflammatory cells) and during the late secretory phase, the predominant chronic inflammatory cell within the stroma is the lymphocyte.[548]

530 Sokol said that the uterine immune cells play different functions during the menstrual cycle, 'with macrophages dominating during menses, neutrophils infiltrating during the proliferative phase, and uNK cells proliferating during the secretory phase'.[549] She said that monocytes and monocyte-derived macrophages that enter endometrial tissue during breakdown and menstruation have been shown to be largely anti-inflammatory 'based on surface marker expression and the constitutive production of reparative cytokines'. She said that expression of low levels of antigen presentation molecules indicates that uterine macrophages are not only anti-inflammatory, but are likely deficient in their ability to initiate an adaptive immune response.[550] Sokol made further observations about the roles of neutrophils and uterine Natural Killer ('uNK') cells in the uterus that she said supported the concept that the uterine immune response was reparative and anti-inflammatory in nature.[551]

531 Robertson disagreed. She said that there is considerable evidence that uterine macrophages can be involved in initiation of an adaptive immune response.[552] She said there was compelling data in studies showing that uterine macrophages express elevated levels of pro-inflammatory cytokines and regulators during the peri-

546 Ibid at 69.
547 Revised Pathology JER at 9 (EXP.500.001.0007_2).
548 Ibid.
549 Sokol at 13 (EXP.001.002.0001).
550 Ibid.
551 Ibid at 14.
552 Robertson at 79 (EXP.001.002.0015).

ovulatory phase and late luteal phase, compared to the time of receptivity to embryo implantation in the mid luteal phase.[553]

532 Sokol and Robertson agreed that the uterus had the capacity to develop a chronic inflammatory response, but disagreed on the nature of such a response in the context of Essure. Robertson said:

> there is a strong biological rationale for the uterus to respond with a pro-inflammatory response to an Essure Device, especially considering the Device is designed to provoke an inflammatory response.[554]

Sokol said that:

> while pre-clinical studies indicate that the human uterus can mount a proinflammatory response, there are no data to suggest that the human reproductive tract is primed to specifically mount an inflammatory response to the Essure device.[555]

Fallopian tubes

533 Robertson said that under normal circumstances, the fallopian tube would not have anywhere near the number of immune cells that are found in the uterus, and that the types of immune cells are different. She said that there are some macrophages in the fallopian tubes but not as many as in the uterus. She said there are predominately lymphocytes located just below the epithelium in the inner mucosal lining of the fallopian tube and lamina propria.[556] She said that PMNs (neutrophils, eosinophils and basophils) are rare in the fallopian tube, and when present engage in 'housekeeping' functions under normal circumstances. She said that depending on the identity and nature of specific triggers, the epithelial and immune cells in the fallopian tube secrete a wide array of both pro-inflammatory and anti-inflammatory cytokines.

534 Robertson said that the 'dynamic and selective' immune response of the fallopian tube, which is similar to the uterus, 'is relevant to the Essure device as it will promote

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553 Ibid at 79 [208].
554 Immunology JER at 17 (EXP.500.001.0004).
555 Ibid.
556 T2685 (TRA.500.029.0001_2 at 0031_2).

the likelihood of a robust pro-inflammatory immune response to the presence of the device and noxious materials leached from it'.[557]

535 Murdock said that a normal fallopian tube contains 'a heterogeneous population of innate (first line of defence in the immune response) and adaptive immune cells (activated when the innate immune response is insufficient) including lymphocytes, macrophages, NK cells and dendritic cells'.[558] She said:

> Lymphocytes, macrophages, dendritic cells, and NK cells are types of chronic inflammatory cells. The most common cell type identified in the normal fallopian tube is the T cell, which is a lymphocyte and type of chronic inflammatory cell. When chronic inflammatory cells are present in an abnormally increased amount, this is termed chronic salpingitis. Importantly, when the cells described in [Ardighieri 2014] (lymphocytes, macrophages, etc.) are observed in the fallopian tube, they would be described by pathologists as "chronic inflammation," if necessary.
>
> … One of the most important points in my report is that chronic inflammatory cells may be identified in normal fallopian tubes, this includes innate and adaptive types (see previous paragraph). From my clinical practice and everyday microscopic examination of human fallopian tubes, there are chronic inflammatory cells including lymphocytes, which can be found in the muscular wall (MW), lamina propria (LP) and intraepithelial (IE) parts of the normal fallopian tube. In addition, it is worth stressing that in [Ardighieri 2014] they examined normal fallopian tubes and found chronic inflammatory cells (including those involved in both the innate and adaptive immune response) including CD8+ T cells (lymphocyte), CD4+T cells (lymphocyte), [natural killer] cells, and macrophages in all three parts (IE, LP and MW) of the fallopian tube[.]CD8+ T cells (lymphocytes that participate in adaptive immunity) would be just one cell type expected to be in the tissues adjacent to a medical device and are also the dominant lymphoid subset in the normal fallopian tube tissues.[559]

Murdock gave similar evidence in relation to the uterus.

536 Robertson said that like the uterus, the SUTJ region of the fallopian tube is primed towards a pro-inflammatory immune response at the periovulatory and late secretory phases of the menstrual cycle.[560] She said that this is by virtue of its responsiveness to fluctuating ovarian sex hormones, particularly estrogen. She said that this

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557 Robertson at 77 [287] (EXP.001.001.0127).
558 Pathology JER at 8 (EXP.500.001.0007).
559 Ibid.
560 Immunology JER at 15 (EXP.500.001.0004).

responsiveness enabled a selective regulation of embryo implantation and menstruation.

537 Sokol considered that there was no convincing human data to suggest such a state of priming in the fallopian tubes under homeostatic conditions or conditions of tissue injury.[561] In cross-examination, Sokol agreed that the fallopian tube has a highly functional immune response.[562] She agreed that the uterus and fallopian tubes are not always anti-inflammatory and that they are capable of eliciting a strong inflammatory response.

538 Robertson and Murdock agreed that very few neutrophils were found in a healthy fallopian tube, and that most cells that were present were found in blood vessels, not in tissue.[563]

539 I deal with Robertson's contention that the fallopian tubes and uterus are primed towards a pro-inflammatory response, and the relevance of that evidence to ongoing chronic inflammation and Essure, in Chapter XIV.

Essure histological studies

540 The relevant experts considered six primary histological studies which each involved analysis of fallopian tube tissue following explantation of Essure inserts. These studies are:

(a) the pre-hysterectomy study together with a report on that study by Rafael Valle et al ('Valle 2001');[564]

561 Ibid at 5.
562 T4180 (TRA.500.041.0001_2 at 0098).
563 T2755 (TRA.500.029.0001_2 at 0101_18-24).
564 Rafael F Valle et al, 'Tissue response to the STOP microcoil transcervical permanent contraceptive device: results from a prehysterectomy study' (2001) 76(5) *Fertility and Sterility* 974 (PUB.500.001.0100) ('Valle 2001')

(b) 'Removal of Essure sterilization devices: a retrospective cohort study in the Netherlands' by Maassen et al ('Maassen 2018');[565]

(c) 'Pathologic findings in fallopian tubes of woman with chronic pelvic pain after Essure placement' by Rubin et al ('Rubin 2020');[566]

(d) 'Clinical and histopathologic characteristics of patients undergoing surgical excision with Essure coils: Longitudinal experience at a women's speciality hospital' by Natalie Banet ('Banet 2020');[567]

(e) 'Symptomatic Bilateral Granulomas after Essure Sterilization' by Hoogendam et al ('Hoogendam 2020');[568] and

(f) 'Confirmation of the systematic presence of tin particles in fallopian tubes or uterine horns of Essure implant explanted patients: A study of 18 cases with the same pathological process' by Catinon et al ('Catinon 2022').[569]

I have also included in this section the 12-week rabbit study and a 24-week rabbit study conducted for Conceptus; histological analysis of post-hysterectomy tissue from four women published in the annual PMA reports; and a 2012 Conceptus study of a proposed new Essure model ('Essure 505 study').

541 Turner relied heavily on the histopathological evidence reported in the studies to establish that Essure was a cause of ongoing chronic inflammation in the fallopian

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565 Liselotte W Maassen et al, 'Removal of Essure sterilization devices: a retrospective cohort study in the Netherlands' (2018) 26(6) *The Journal of Minimally Invasive Gynecology* 1056 (PUB.500.001.0066) ('Maassen 2018').

566 Alexandra Rubin et al, 'Pathologic findings in fallopian tubes of woman with chronic pelvic pain after Essure placement' (2020) 102(2) *Contraception* 133 (PUB.500.001.0247) ('Rubin 2020').

567 Natalie Banet, 'Clinical and histopathologic characteristics of patients undergoing surgical excision with Essure coils: Longitudinal experience at a women's speciality hospital' (2020) 46 (June) *Annals of Diagnostic Pathology* (PUB.001.001.3744) ('Banet 2020').

568 Jacob P Hoogendam, Celien PH Vreuls and Sebastiaan Veersema, 'Symptomatic Bilateral Granulomas after Essure Sterilization' (2020) 27(6) *Journal of Minimally Invasive Gynecology* 1237 (PUB.001.002.0123) ('Hoogendam 2020').

569 Mickaël Catinon et al, 'Confirmation of the systematic presence of tin particles in fallopian tubes or uterine horns of Essure implant explanted patients: A study of 18 cases with the same pathological process' (2022) 69 (January) *Journal of Trace Elements in Medicine and Biology* (PUB.001.001.3758) ('Catinon 2022').

tubes of a not insignificant number of women. She submitted that while the defendants' experts initially disputed that the studies contained findings of active chronic inflammation caused by Essure, Murdock and Sokol accepted that proposition after cross-examination, leaving Badylak isolated on this issue.

542 In her expert reports, Robertson said that the histological studies showed compelling evidence of a chronic inflammatory response which extended beyond three months from the date of implantation in women with Essure. Robertson's evidence is summarised in the following statement taken from the pathology JER:

> Individually and collectively these studies demonstrate a high incidence of chronic inflammation in fallopian tubes of women with Essure Devices of more than 3 months duration. Importantly, each of these studies clearly uses the term "inflammation" or "chronic inflammation" (not just "presence of immune cells"). We can therefore infer that in the judgement of the investigators, the features of the tissue — including the abundance, types, and locations of immune cells — met the common understanding of constituting inflammation. Designating chronic inflammation requires more than the simple presence of immune cells. If it were simply the presence of a few immune cells, to a degree that was not different to healthy tissue, this would be expected in all the examined tissues.[570]

Robertson said that it was implicit in the conclusions of the investigators in each study that the observed patterns of leukocyte abundance and composition were different to those seen in healthy fallopian tubes.[571]

543 In her primary report, Sokol said:

> Robertson raises [Banet 2020], which supposedly showed types of inflammation in the fallopian tubes caused by the Essure Device. As I previously discussed…, since the fallopian tubes normally contain immune cells, it is essential to not only quantify the number of immune cells seen in these pathological samples, but to compare them to normal control tissue. If there were more or less immune cells as compared to healthy controls, it could indicate that Essure was associated with that difference. Unfortunately [Banet 2020] neither quantified the immune cell infiltrate nor did it include a normal control comparison, making it impossible to interpret in any meaningful manner. Furthermore, [Banet 2020] did not show any correlation of supposed inflammation with patient symptoms, making any clinical correlation impossible. Although it also did not quantify the immune cell infiltrate, [Rubin 2020] did compare the fallopian tubes of women who had Essure with those

570 Revised Pathology JER at 26 [105] (EXP.500.001.0007_2).
571 Robertson at 97 [248] (EXP.001.002.0015_2).

> who did not. Acute inflammation, as indicated by the presence of neutrophils, was only seen in one of the control patients and was not associated with active disease since it did not correspond with any symptoms in that patient. Macrophages and giant cells were detected in two of the three Essure patients, but there was no evidence of acute inflammation indicating that these cells were not active[.] [Rubin 2020] underscores the importance of including controls in any study, but both [Rubin 2020 and Banet 2020] are limited in the number of samples evaluated. Thus, it remains to be determined whether the Essure Device is associated with chronic inflammation in the fallopian tubes.[572]

Sokol disagreed with Robertson's evidence that the studies demonstrated a high incidence of chronic inflammation in response to Essure. She said that it was normal and expected to see increased numbers of macrophages and foreign body giant cells at the site of a foreign body response.[573] She said that the simple presence of immune cells at the site did not indicate an active inflammatory response. In the immunology JER Sokol said:

> Furthermore, in these same studies Dr. Sokol considers there to be a lack of quantitative data on the immune cell infiltrates and a lack of criteria provided to define the inflammatory state. None of the studies cited by Prof. Robertson define or provide the criteria by which investigators determined the presence of "inflammation". Furthermore, each study uses different terms to describe "inflammation", indicating that the investigators are not using a shared and standard nomenclature. Based on this, Dr. Sokol considers it absolutely necessary for the investigators to then define or provide quantitative data on the immune cell infiltrate so that their data can be properly interpreted, and their conclusions on the presence of "inflammation" verified.
>
> Finally, Dr. Sokol considers there to be a lack of evidence suggesting active inflammation. [T]he presence of foreign body giant cells alone does not indicate acute or chronic inflammation. However, the presence of foreign body giant cells was considered to be indicative of "inflammation" in [Banet 2020 and Rubin 2020]. For these reasons, Dr. Sokol considers these studies to be flawed, fundamentally limiting their generalizability to patients.[574]

544 Robertson disagreed with Sokol's opinion in her reports. She said that healthy control tissue was often difficult to access in histological studies and it was common for such studies to designate chronic inflammation in its absence. She said further that studies often use a qualitative or semi-quantitative analytical approach to reporting immune cell prevalence and designating chronic inflammation.[575] Robertson said that the

572 Sokol at 17-18 (EXP.001.002.0001).
573 Ibid at 19.
574 Immunology JER at 10-1 (EXP.500.001.0004).
575 Robertson at 30 [43] (EXP.001.002.0015_2).

reported findings of chronic and acute inflammation in the vicinity of the device, photomicrographs from several studies which indicated a clear spatial relationship between the surface of a device and immune cell infiltrates, and a statement in Valle 2001 that PET fibres elicited a strong fibrotic inflammatory tissue response supported a causal connection between the observed inflammation and Essure. She said that the numbers of women studied and the similarities in the reported findings across the studies indicated that chronic inflammation was not an uncommon event in women with Essure.[576]

545 Murdock said that it was incorrect to say that the findings of chronic inflammatory cells in tissue adjacent to the Essure device reported in Banet 2020, Rubin 2020 and Valle 2001 equated to an abnormal process. She said Robertson's interpretation of the histological studies was incorrect because:

> … 1) chronic inflammatory cells are present in the normal fallopian tubes, 2) the chronic inflammatory cells were not present in an excessive amount to warrant a diagnosis of chronic salpingitis, and 3) [the] conclusion statement [in Rubin 2020] is "Given the minimal and bland inflammation in the Essure cases, symptoms may more plausibly be ascribed to confounding gynecologic conditions or other mechanisms." The Essure Device causes a predictable and orderly tissue response and chronic inflammatory cells may be present for the lifetime of the device.[577]
>
> …
>
> A pathological (abnormal) tissue response to the Essure Device does not occur. The Essure Device followed a normal and localized tissue response confined to the inner layers of the fallopian tube and normal histology was observed within 5 mm of the distal end of the Device. The Device causes a tissue response that is similar to other medically implanted devices. The response begins with an acute inflammatory cell infiltrate, followed by a chronic inflammatory cell infiltrate and fibrosis. This tissue response to the Device is appropriate and should not be considered pathological. This opinion is based on the [pre-hysterectomy study], the Annual [PMA] Reports (2003-2007), PMDA studies, and the peer reviewed medical literature including [Valle 2001, Banet 2020 and Rubin 2020]. In addition, chronic salpingitis (abnormal chronic inflammatory response in the fallopian tube was not identified in any study.[578]

546 In his primary report, Badylak said Valle 2001 concluded that Essure appeared to be

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576 Revised Pathology JER at 26 (EXP.500.001.0007_2).
577 Ibid at 29 [117].
578 Ibid at 33 [134].

'feasible, safe and well accepted by patients'.[579] He said that the Banet 2020 findings were 'consistent with the expected foreign body response', with inflammation characterised as acute in patients with a shorter implant time and chronic in patients with a longer implant time.[580] Badylak noted that Rubin 2020:

> … concluded that "changes in the Essure patients were bland and showed only minimal chronic inflammation, in the form of foreign-body reaction, and no acute inflammation, suggesting that pain is unlikely to be due to an ongoing localized inflammatory process".[581]

547 Badylak said that it was inaccurate and misleading to characterise the presence of macrophages and foreign body giant cells as a persistent and active inflammatory reaction that causes continuous tissue damage in the context of a foreign body response.[582]

Twelve-week rabbit study

548 As referred to earlier in these reasons, the 12-week rabbit study was conducted in 2000 by NAMSA. The purpose of the study was to evaluate the potential for a local irritant or toxic response to Essure materials implanted in direct contact with muscle tissue.

549 A minimum of four sections of the Essure insert ('test articles') were implanted in three male rabbits. Control articles made from USP negative control plastic were placed in three control male rabbits. Histopathology results were recorded at one, four and 12 weeks. The microscopic irritant response to the articles was graded as 'non-irritant', 'slight', 'moderate' or 'severe'.

550 The table of scores following histopathological examination by a pathologist at 12 weeks is as follows:[583]

	TEST			USP NEGATIVE CONTROL PLASTIC		
Rabbit Number:	60218	60222	60223	60218	60222	60223

579 Badylak at 11 (EXP.001.002.0007).
580 Ibid at 10 [21].
581 Ibid at 11 [22].
582 Ibid at 16 [42].
583 Ibid at 1093.

Inflammation						
Polymorphonuclear	1	2	2	1	0	2
Lymphocytes	1	3	3	1	0	2
Plasma Cells	2	0	2	0	0	0
Macrophages	2	2	2	2	1	1
Giant Cells	3	3	3	0	0	0
Necrosis	2	3	2	0	0	0
SUB TOTAL (X2)	22	26	28	8	2	10
Fibroplasia	2	2	2	2	2	2
Fibrosis	0	0	0	0	0	0
Fatty Infiltrate	0	0	0	0	2	0
SUB TOTAL	2	2	2	2	4	2
TOTAL	24	28	30	10	6	12
GROUP TOTAL	82			28		
AVERAGE* TEST 27.3 (−) CONTROL 9.3 = 18						
*Used to determine Irritant Ranking Score shown below as the Conclusion. A negative difference was recorded as zero.						
Traumatic Necrosis	2	2	2	0	0	0
Foreign Debris	2	2	2	0	0	0
No. Sites Examined	4	4	4	3	4	4

On the basis of this data, the NAMSA pathologist rated the Essure test articles as a 'severe irritant' compared to the control articles.

551 After receiving the NAMSA results, Conceptus sought a second opinion on the histology from a pathologist at a different organisation.[584] The second pathologist observed two types of changes in rabbit muscle, the first associated with the PET fibres and the second associated with the coil. In relation to the PET fibres, the pathologist stated (original emphasis):

> Overall the test article appears well tolerated after 12 weeks in rabbit skeletal muscle and does not elicit any host reaction considered to be adverse. There is a low severity grade foreign body reaction to the [PET fibre] without evidence of encapsulation or necrosis.
>
> The foreign body reaction is *spatially limited* to the areas where [PET fibre] is present and *does not extend in adjacent tissues*. In my experience, the severity of the foreign body response to the [PET fibre] observed in this study is at the *lower end of the range of severity typically observed with this type of material* when placed in animal tissues (across species, including the rabbit). I have seen other devices causing marked irritation characterized by dense inflammatory infiltrate encroaching upon adjacent tissues with formation of a thick wall of granulation tissue and sometimes necrosis of the host tissue within and around the device. These features are clearly *absent* from the sections examined for the

584 Ibid at 1099.

"STOP Device".[585]

In relation to the coil, the pathologist found:

> In all samples there is a focal nodular accumulation of acellular amorphous and partially mineralized material. This material appears well tolerated and stable, and is not associated with significant inflammation. This material is probably derived from sequestered proteinaceous body fluid and inflammatory cells that accumulated inside the device coil and was prevented from organization by the presence of the coil around it. I do not regard this feature as evidence of necrosis. This interpretation is supported by the near absence of inflammation at the interface between this material and host tissue. In addition, these accumulations have a diameter comparable or slightly smaller to that of the outer coil of the device and would fit entirely within their inner compartment.[586]

552 The pathologist said that changes elicited by the test articles extended less than 0.5 mm in all three animals. The pathologist concluded that the tissue response to the test articles was minimal to mild, and irritation associated with the device was low.

553 Badylak said that the second pathologist's description of the test results as showing an accumulation of inflammatory cells around the PET fibre, but not extending further, was consistent with the expected findings.

Twenty-six week rabbit study

554 Covance Laboratories Inc conducted a 26-week rabbit intramuscular implant study for Conceptus in 2002 ('26-week rabbit study').[587] The purpose of the study was to evaluate the subchronic toxicity of Essure. Two devices and two control strips were implanted in the muscle tissues of 20 female rabbits. The study pathologist found minimal or mild granulomatous inflammation in more sites containing the device than in sites containing the control strip. The pathologist noted that the inflammation was largely associated with the small fibres within the device and was characterised by the presence of macrophages and multinucleated giant cells.[588] There was no adverse effect on the rabbits associated with the inflammation.

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585 Ibid at 1099–1100.
586 Ibid at 1100.
587 Ibid at 643.
588 Ibid at 699, 702.

555 Badylak said that rabbits were used in the muscle implantation studies because they are hypersensitive.[589]

556 Badylak agreed that the 26-week rabbit study showed granulomatous inflammation. He was asked:

> In those circumstances where the device was to be permanently implanted into the body of a woman for her lifetime, would you agree that it would have been reasonable to study the consequences of this inflammatory effect beyond the 26 week timeframe that was studied?---That's not a simple answer. It would depend upon the type of inflammation that was present. By type what I mean is was there an active component to it, were there other signs of a systemic inflammation? So it would depend upon the device. I think in some cases you're right, it would be. In others you have to look at the whole story.
>
> In this case?---I don't believe so. I'm trying to put myself in the position of the people who, you know, came to this conclusion. It's hard, though, when you know the rest of the story. As I mentioned just a few minutes ago, you will always see an accumulation of inflammatory cells, macrophages, around the device. If that is called granulomatous inflammation, like it may be in this report, then that's not surprising, it's expected, and I'm not sure anything further is needed.[590]

Pre-hysterectomy study and Valle 2001

557 As outlined at [206] above, Conceptus conducted the pre-hysterectomy study of Essure on 63 women scheduled for a hysterectomy from 1998 to 2001.[591] Forty-six women had bilateral placement and eight women had unilateral placement.[592] There was a failure to implant any device in the remaining women. Participants wore inserts for up to 16 weeks (and in the case of one woman for 30 weeks) prior to explantation by hysterectomy.

558 Forty-nine women were enrolled through investigator Rafael Valle in Mexico and 14 through a second investigator in the US.[593] Valle 2001 is based on the histology findings for 27 of the study participants.

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589 T4357 (TRA.500.043.0001_2 at 0075).
590 T3478 (TRA.500.035.0001_2 at 0053_10–29).
591 BAY-ESSURE-0006158 at 1286.
592 Ibid at 1292.
593 Ibid at 1290.

559 Care was taken at the time of hysterectomy to remove the uterus and fallopian tubes en bloc whenever possible, without cutting into the Essure insert. The uterus and fallopian tubes were x-rayed to determine the position of the insert. The uterine cornuae and fallopian tubes were then excised for histological examination.

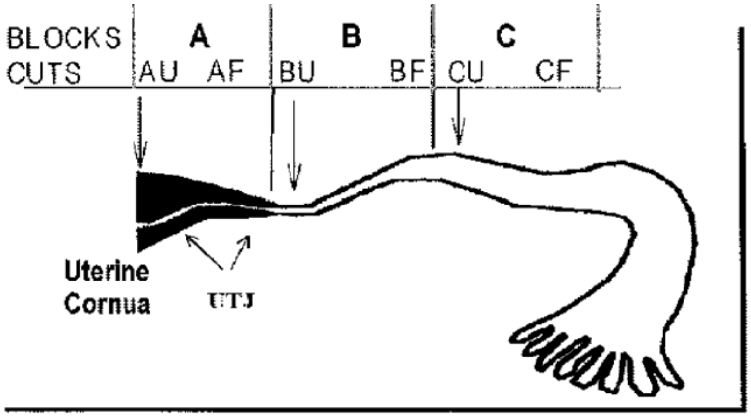
560 After x-ray, the fallopian tubes were divided into three blocks according to the insert position:

a. Block A included the uterine cornua up to the utero-tubal junction (UTJ),

b. Block B included the UTJ to the proximal isthmic portion of the tube, and

c. Block C included the proximal isthmic portion to a point within 5 mm distal to the end of the Micro-insert.[594]

The following figure illustrates the three blocks:[595]



561 Two cross-sections were then taken from the uterine end of each block (indicated by 'AU', 'BU' and 'CU' on the figure above), and from the fimbrial end of Block C ('CF' on the figure above).[596]

562 Below is an example of how microscopic assessment of histological sections was reported by the pathologists, in this case for the participant identified as '826' who had a wearing time of 13.86 weeks before hysterectomy.[597] The assessing pathologists

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594 Ibid at 1299.
595 Ibid.
596 Ibid.
597 Ibid at 1695–1702.

were blinded to participant wear time. The histological response for each assessed characteristic was rated on a scale of 0–3, with '0' meaning absent, '1' mild, '2' moderate and '3' severe.[598] No further information or guidance was provided about the grading system. In most cases the assessing pathologist was Dr Thomas Wright.

[598] Ibid at 1300.

Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI 826
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections A-U: – Right Tube

Histologic section A-U: Uterine end of block A containing cornua

Which slides evaluated (list numbers): 826 R AU

Stains used: H+E, TRI

1. Describe the presence of the device in the slides:

   A. Not present (B. inner and outer coils) C. Inner only D. Outer only

2. Describe the presence of Dacron fibers

   ~~A. Not present~~ B. Present between the two coils only C. Extend outside the outer coil (D)

TCW 6/4/02

3. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	1
Chronic	3
Foreign body giant cells	1
Fibrosis	
Loose	3
Dense	2
Neovascularity	0
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

loose fibrosis with lymphocytes, macrophages, plasma cells, some PMN's

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 (2) 3 4 5

Minimally Completely

RECEIVED
MAR 1 1 2002
BY:

Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI 826
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections A-U: – Left Tube

Histologic section A-U: Uterine end of block A containing cornua

Which slides evaluated (list numbers): S26 L A4

Stains used: H+E, TRI

4. Describe the presence of the device in the slides:

   A. Not present (B.) inner and outer coils C. Inner only D. Outer only

5. Describe the presence of Dacron fibers

   (A.) Not present B. Present between the two coils only C. Extend outside the outer coil

6. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	1
Chronic	3
Foreign body giant cells	1
Fibrosis	
Loose	2
Dense	1
Neovascularity	1
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

Lots of lymphocytes, plasma cells, macrophages. some PMNs.

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 2 3 4 (5)

Minimally Completely

RECEIVED
MAR 1 1 2002
BY:

Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI 826
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections B-U: – Right Tube

Histologic section B-U: Uterine end of block B containing UTJ or isthmic portion of tube

Which slides evaluated (list numbers): 826 R BU

Stains used: H+E TRI

7. Describe the presence of the device in the slides:

   A. Not present (B.) inner and outer coils C. Inner only D. Outer only

8. Describe the presence of Dacron fibers

   A. Not present B. Present between the two coils only C. Extend outside the outer coil (D)

9. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	1
Chronic	2
Foreign body giant cells	3
Fibrosis	
Loose	3
Dense	2
Neovascularity	0
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

Fibroblasts, PMN's, lymphocytes, macrophages, plasma cells.

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 2 3 (4) 5

Minimally — Completely

Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. initials: PHI 826
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections B-U: – Left Tube

Histologic section B-U: Uterine end of block B containing UTJ or isthmic portion of tube

Which slides evaluated (list numbers): 826 L - BU

Stains used: H+E, TRT

10. Describe the presence of the device in the slides:

A. Not present (B.) inner and outer coils C. Inner only D. Outer only

11. Describe the presence of Dacron fibers

A. Not present B. Present between the two coils only C. Extend outside the outer coil (D)

12. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	2
Chronic	2
Foreign body giant cells	2
Fibrosis	
Loose	3
Dense	2
Neovascularity	1
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

PMN's, lymphocytes, Plasma cells, macrophages, fibroblasts.

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 2 3 (4) 5

Minimally Completely

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Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI 526
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections

Sections C-U: – ~~Left Tube~~ RIGHT TUBE

Histologic section C-U: Uterine end of block C containing device in distal part of tube

Which slides evaluated (list numbers): S26R - CU.

Stains used: H+E / TRI

16. Describe the presence of the device in the slides:

A. Not present (B) Inner and outer coils C. Inner only D. Outer only

17. Describe the presence of Dacron fibers

(A) Not present B. Present between the two coils only C. Extend outside the outer coil

18. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation Acute	~~0~~ 1	TW 8/8
Chronic	1	
Foreign body giant cells	0	
Fibrosis Loose	1	
Dense	3	
Neovascularity	~~0~~ 1	TW 8/8.
Granulation tissue	0	
Disruption of epithelium	2	
Disruption of lamina propria	3	
Hemorrhage	0	

Describe the cell types present

Dense fibrosis around device -
Some PMN's + lymphocytes present

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 2 (3) 4 5
Minimally Completely

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Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI 826
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections C-U: – Left Tube

Histologic section C-U: Uterine end of block C containing device in distal part of tube

Which slides evaluated (list numbers): 826 L - CU

Stains used: H+E, TRF

16. Describe the presence of the device in the slides:

A. Not present (B.) Inner and outer coils C. Inner only D. Outer only

17. Describe the presence of Dacron fibers

A. Not present B. Present between the two coils only C. Extend outside the outer coil (D)

18. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	1
Chronic	3
Foreign body giant cells	3
Fibrosis	
Loose	3
Dense	2
Neovascularity	0
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

PMNs, lymphocytes, plasma cells, fibroblasts,

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 2 3 (4) 5

Minimally Completely

Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI 826
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections C-F: – Right Tube

Histologic section C-F: fibrial end of block C containing distal tube without device

Which slides evaluated (list numbers): 826 R - CF

Stains used: H+E TRI

19. Describe the presence of the device in the slides:

A. Not present (B) inner and outer coils C. Inner only D. Outer only

20. Describe the presence of Dacron fibers

(A) Not present B. Present between the two coils only C. Extend outside the outer coil

21. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation Acute Chronic Foreign body giant cells	1 1 0
Fibrosis Loose Dense	0 3
Neovascularity	1
Granulation tissue	0
Disruption of epithelium	2
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

Dense fibrosis, normal elastin,
Some PMN's + lymphocytes

Does the lumen of the tube appear to be obliterated by the device and reactive tissue:

0 1 2 (3) 4 5

Minimally Completely

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MAR 1 1 2002
BY:

Conceptus

Safety and Principles of Operation of the STOP Device	Pt Study #: S6- Pt. Initials: PHI S26
Conceptus Protocol: STOP 06 Pathology & Histology	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections C-F: – Left Tube

Section C-F: fibrial end of block C containing distal tube without device

Which slides evaluated (list numbers): S26 L CF

Stains used: H+E, TRI

22. Describe the presence of the device in the slides:
    (A.) Not present B. inner and outer coils C. Inner only D. Outer only
23. Describe the presence of Dacron fibers
    (A.) Not present B. Present between the two coils only C. Extend outside the outer coil
24. Describe the histologic reaction of the tube to the device:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	1
Chronic	1
Foreign body giant cells	0
Fibrosis	
Loose	1
Dense	2
Neovascularity	2
Granulation tissue	0
Disruption of epithelium	2
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

F: basophils, lymphocytes, PMN's

Does the lumen of the tube appear to be obliterated by the device and reactive tissue

0 1 2 (3) 4 5
Minimally Completely

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BY:

STOP 06, Rev 08
January 22, 1999

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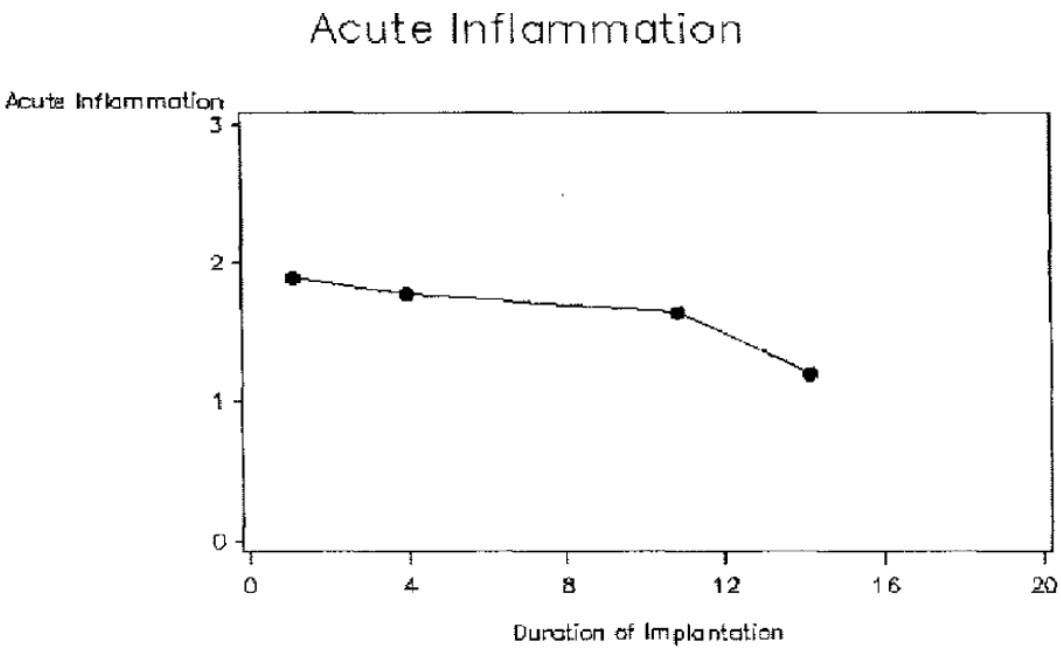
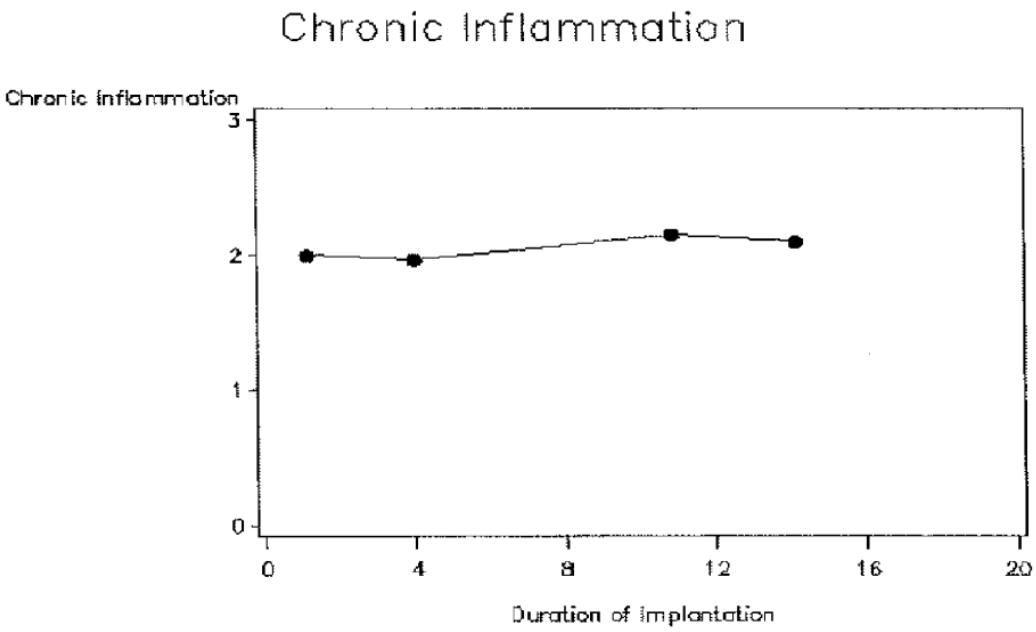
563 The cell types recorded by the examining pathologist on the right and left B-U cross-sections were PMNs (neutrophils), lymphocytes, plasma cells, macrophages and fibroblasts. Similar findings were made at other cross-sections.

564 The following graphs from the pre-hysterectomy study provide some of the information derived from the histology slides of the study participants. The

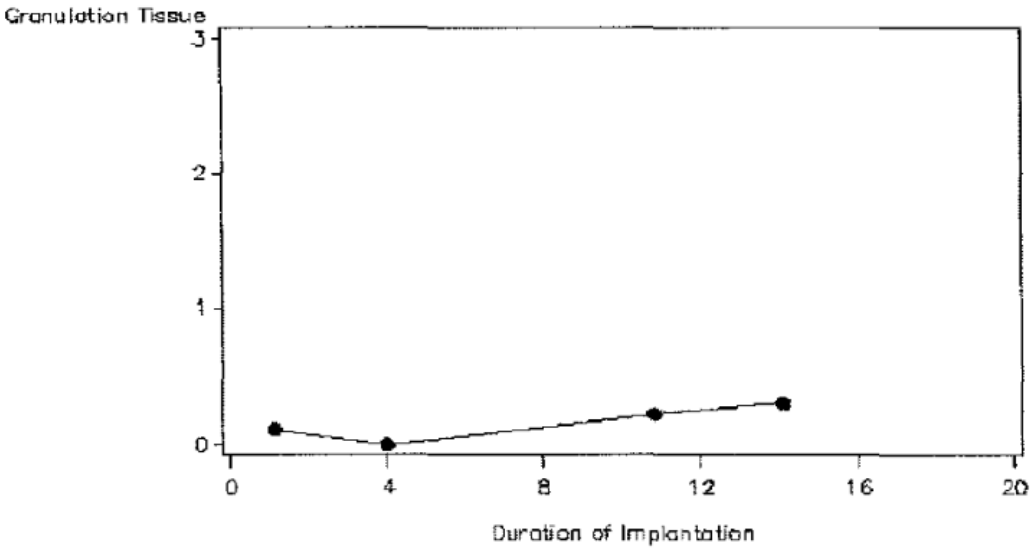
histological response for each assessed characteristic on the '0-3' grading scale is represented on the Y-axis. The X-axis shows the wearing time in weeks. For each characteristic, the histological rating for each fallopian tube within the same timeframe was averaged to develop a mean score which was plotted.[599]



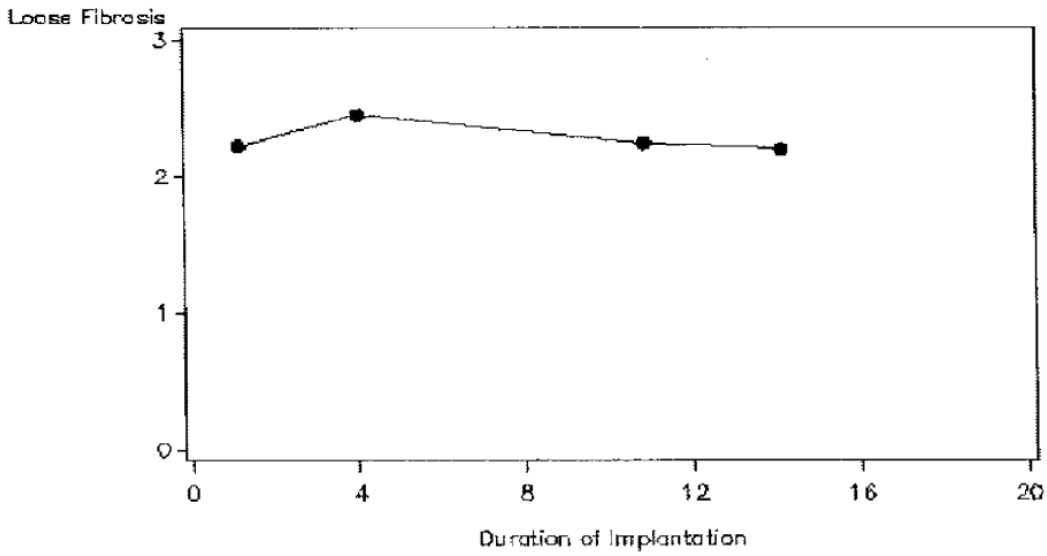


[599] Ibid at 1301-8.

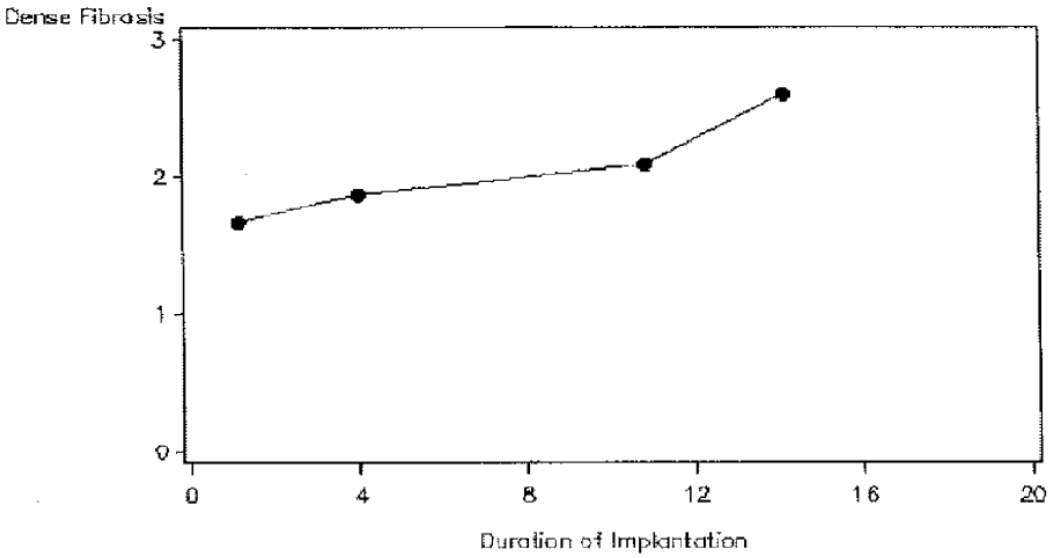
Granulation Tissue



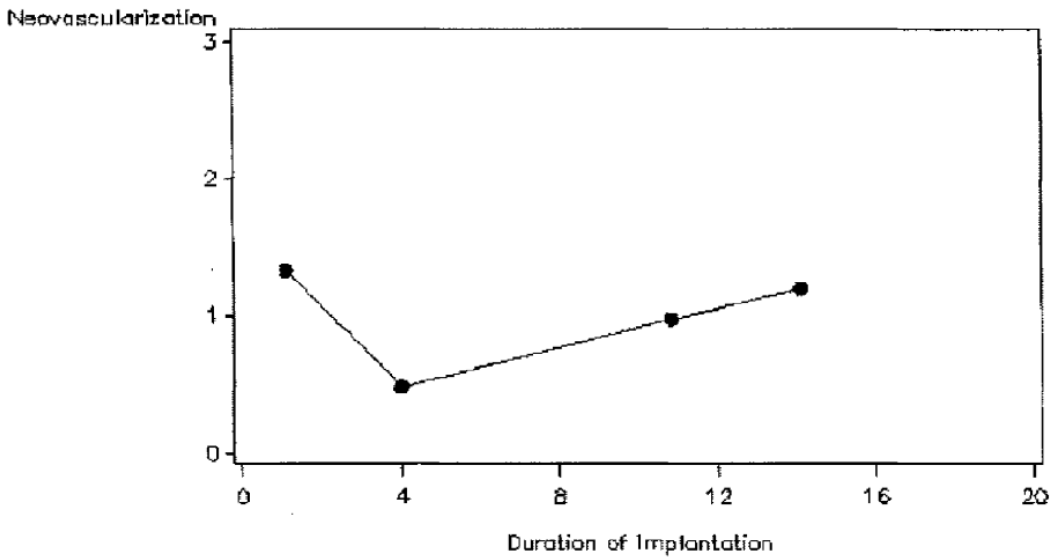
Loose Fibrosis

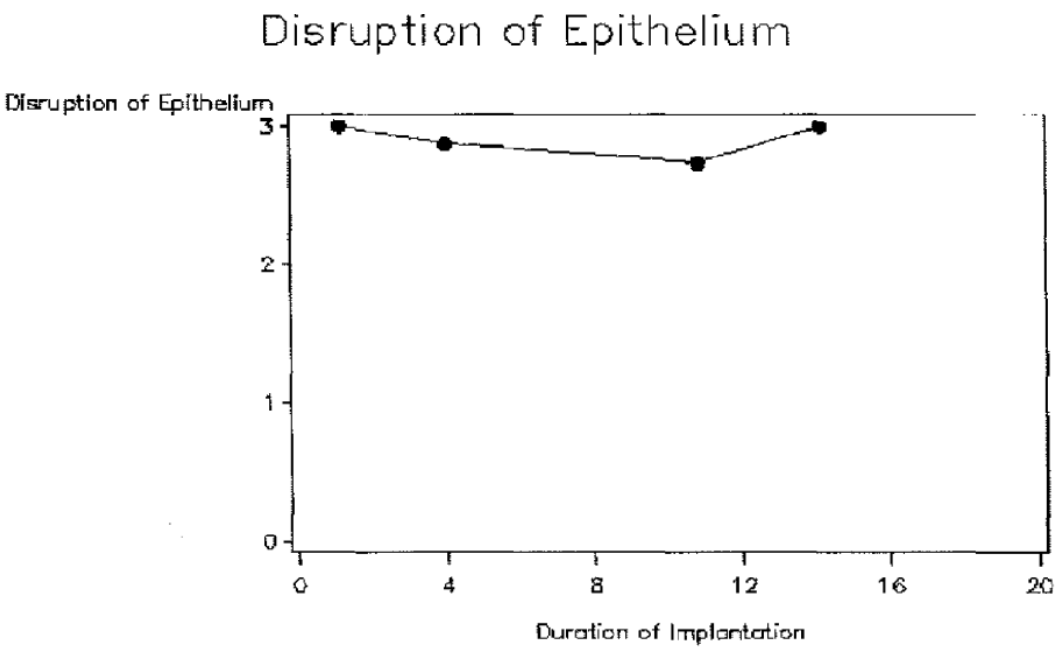


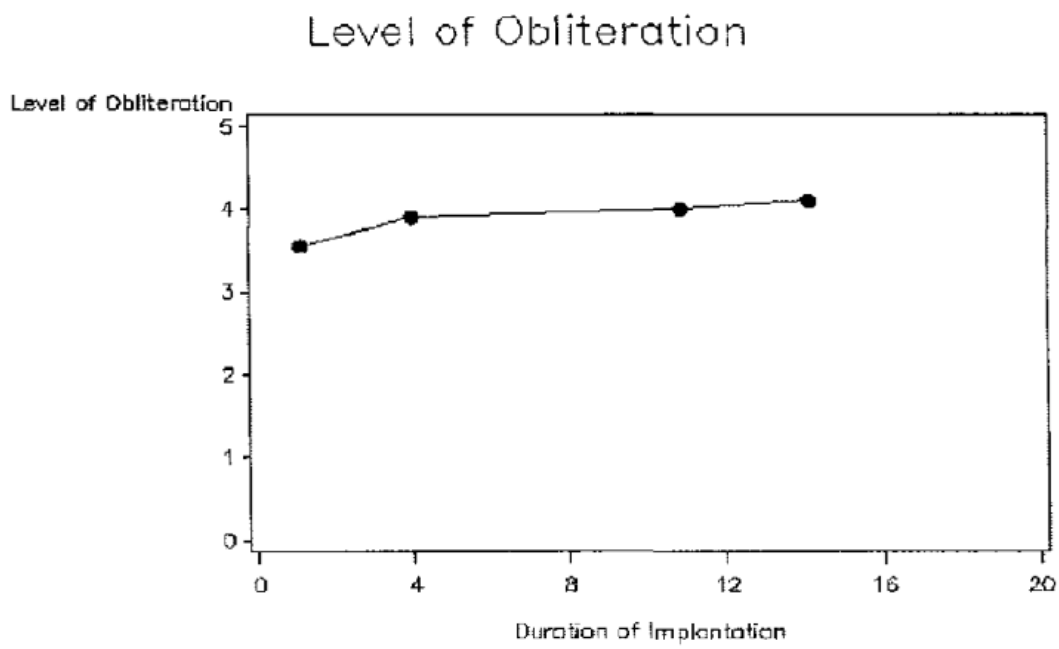
Dense Fibrosis



Neovascularization







565 The study authors summarised the findings in the graphs as follows:

> The histological response to the Essure Micro-insert is characteristic of the histological response observed with the use of PET fibers in other anatomical sites. Specifically, the PET fibers appear to elicit a strong fibrous and inflammatory tissue response that extends into the space between the inner and outer coils of the Essure Micro-insert. The tissue response consists predominantly of macrophages and lymphocytes, with some foreign-body type giant cells seen in women who wore the devices for longer periods of time (12 weeks or longer), and larger numbers of polymorphonuclear cells (PMNs) seen in shorter wearing times (less than 12 weeks). The fibrous response consists of both loose and dense fibrous tissue, with moderate loose fibrosis apparent as soon as one week after implantation, and dense fibrosis becoming

> moderate to severe after four weeks of wearing. In some specimens, smooth muscle cells are also observed migrating from the fallopian tube wall into the space between the inner and outer coils, more commonly in women who wore the devices for longer periods of time, 12 weeks or longer.
>
> …
>
> Normal tubal architecture was present within 5mm distal to the end of the Micro-insert. The histological analysis of slides taken past the ball tip of the Essure Micro-insert, revealed normal tubal segments that were absent of inflammatory cells.[600]

566 The authors drew the following conclusions:

> The procedure was found to be safe with minimal post-procedure discomfort and sequelae and minimal adverse events. The short-term wearing of the Micro-insert, from one to 30 weeks was also found to be acceptable, with no side effects reported in the participant diaries.
>
> …
>
> The local, occlusive, benign tissue response demonstrated by histological evaluation of the specimens supports the theorized mechanism of action. The acute inflammatory response and low level chronic inflammatory response is consistent with other devices that have used PET fibers. The reaction is confined, however, to the area immediately adjacent to the Micro-insert and does not extend beyond the tubal wall. Also, immediately distal to the Micro-insert, the tube resumes its normal appearance.
>
> Based on the histological observations from this study, it is apparent that the response to the Essure™ Micro-insert is occlusive in nature and should provide for long-term Micro-insert retention as well as pregnancy prevention. This study demonstrated that the tissue in-growth reaction is predictable, occurred in all fibered specimens collected, was localized to the Micro-insert, and did not result in adverse clinical sequelae.[601]

Valle 2001

567 Valle 2001 evaluated patient tolerance and recovery from device placement; patient safety and comfort during device wearing; occlusion of the fallopian tube up to 12 weeks after device placement; and fallopian tube histologic information in order to confirm the theorised mechanism of action.[602]

568 The authors commented on the histology findings as follows:

---

600 Ibid at 1309.
601 Ibid at 1312-3.
602 Valle 2001 at 1 (PUB.500.001.0100).

> The PET fibers appear to elicit a strong fibrotic and inflammatory tissue response that extends into the space between the inner and outer coils of the STOP device. The reaction is localized to the inner portion of the fallopian tube wall, with normal tubal architecture present within 5 mm of the distal end of the device. There is no evidence that fibrosis induced by the device extends into the wall of the fallopian tube or causes peritubal adhesions or serositis.
>
> The tissue response consisted predominantly of macrophages and mononuclear cells, with some foreign-body–type giant cells and acute inflammatory cells. The fibrous response consisted of both loose and dense fibrous tissue. In some specimens, smooth muscle cells were also observed migrating from the fallopian tube wall into the space between the inner and outer coils. This is clearly demonstrated in Figure 4.
>
> The tissue response varied according to the elapsed time after placement. Acute inflammation was predominant in early specimens whereas chronic inflammation and fibrosis was more extensive in the fallopian tubes of patients who had worn the device for 8 to 30 weeks. The overall reaction to the device and fibers was more pronounced over time.[603]

The authors continued:

> The histologic evaluation of the specimens supported the hypothesized mechanism of action, namely that long-term anchoring and occlusion are achieved with fibrosis into the device. The acute inflammatory response and low-level chronic inflammatory response were consistent with other devices that have used PET fibers. The reaction was confined to the area immediately adjacent to the device and did not extend into the tube wall. Immediately distal to the device, the tube maintained its normal appearance.[604]

569 The histology results were summarised in the following table:[605]

603 Ibid at 4.
604 Ibid at 5.
605 Ibid.

TABLE 2

Histology results by tube.

Tissue reaction	Wearing time (weeks) 1–4 n = 9 tubes	4–8 n = 5 tubes	8–12 n = 3 tubes	12–16 n = 29 tubes	>16 n = 1 tube	Total n = 47 tubes
Moderate/extensive acute inflammation	7/9	2/5	0/3	17/29	0/1	26/47
Moderate/extensive chronic inflammation	8/9	4/5	3/3	26/29	1/1	42/47
Moderate/extensive loose fibrosis	7/9	3/5	3/3	26/29	1/1	40/47
Moderate/extensive dense fibrosis	7/9	2/5	3/3	25/29	1/1	38/47
Moderate/extensive disruption of epithelium	7/9	4/5	3/3	29/29	1/1	44/47
Moderate/extensive disruption of lamina propria	7/9	4/5	3/3	28/29	1/1	43/47
80–100% obliteration of tubal lumen	4/9	5/5	3/3	26/29	1/1	39/47
Overall reaction to device = extensive	3/9	1/5	3/3	26/29	1/1	34/47
Overall reaction to device = moderate	2/9	3/5	0/3	1/29	0/1	6/47
Overall reaction to device = mild	4/9	1/5	0/3	2/29	0/1	7/47

Valle. Tissue response to STOP microcoil. Fertil Steril 2001.

570 Figure 4 in Valle 2001 contained four tubal cross-section images with the following description:

> Microscopic view of cross section of tube containing the STOP device. (A), One week: fibrosis and acute inflammation cells migrating into device. (B), Four weeks: fibrosis replacing tube, acute and chronic inflammatory cells present. (C), Eight weeks: dense fibrosis filling the tube. Epithelium destroyed. Tubal lumen occluded. (D), Thirty weeks: dense fibrosis replacing tubal lumen; scant acute inflammatory cells present.[606]

571 The authors concluded:

> The STOP transcervical approach to tubal sterilization, evaluated in this prehysterectomy study, appears to be feasible, safe, and well-accepted by patients. It holds promise as a new female sterilization procedure that offers a transcervical alternative to incisional methods of tubal sterilization.
>
> Based on the histologic observations from this study, it is apparent that the tissue response to the STOP device is occlusive in nature, providing long-term anchoring of the device. This study demonstrates that the tissue in-growth reaction was predictable, occurred in all fibered specimens collected, and was localized to the device.
>
> This demonstration of the feasibility of this approach prepares the way for clinical trials to evaluate long-term safety and effectiveness of the STOP device for tubal sterilization.[607]

606 Ibid at 6.

607 Ibid at 5-6.

Oral evidence of experts

Robertson

572 Robertson said that the '0-3' grading scale used in the pre-hysterectomy study was 'semi-quantitative', meaning it was not quite as precise as a fully quantitative measure. She was asked:

> And there's nothing to indicate that it's more than in a sense an assessment of the number of cells it seems?---Well, there is an assessment of inflammation which integrates inflammation relating to numbers of cells, types of cells, their positions in the tissue, the relative balance of the different types of cells and their proximity to a suspected inflammatory stimulus.[608]

573 Robertson was challenged about whether there was a causal connection between the device and the inflammation identified on histological examination:

> But there's nothing to identify what the source of the inflammation in this woman 39 and a half [months] after device placement was, is there?---When a pathologist or an immunologist or another skilled person looks at a tissue with an inflammatory stimulus sitting a matter of micrometres away from the very high accumulation of inflammatory cells, it's colloquially known as a no-brainer that the suspected stimulus is the cause of the inflammatory reaction, and I would expect that any sensible pathologist engaged in a study like this would have the same opinion.[609]

Robertson added that the histology assessments of tissue further away from the Essure inserts had lower inflammatory scores. She said that a very strong inflammatory score a matter of microns away from the insert, and a '0' score some further distance away from the insert, is irrevocable evidence that the insert was the cause of the inflammation.[610] Robertson said that while this inflammatory response is localised, it could cause major impacts.[611]

574 Robertson said that the most sensible interpretation of the inflammation data graphs set out in the pre-hysterectomy study was that the level of inflammation did not change over time. She posited that the mean value would move slightly if the data

608 T2883 (TRA.500.030.0001_2 at 0089_9-15).
609 T2884 (TRA.500.030.0001_2 at 0090_13-23).
610 T2884-5 (TRA.500.030.0001_2 at 0090-1).
611 T2885 (TRA.500.030.0001_2 at 0091).

was plotted with their standard deviations, but that statistically there would be no difference in the proportion of women with acute or chronic inflammation.[612] She said that this was worrying, as it indicated the wound was not changing character from two weeks to 16 weeks and hence was not healing.[613]

575 In relation to Valle 2001, Robertson said it was very significant that 17 out of 29 women were still experiencing acute inflammation beyond 12 weeks after Essure placement. She said that this data indicated the presence of neutrophils, which should only be present for a couple of days, and again indicated that a wound was not healing well.[614] She said that moderate extensive chronic inflammation was likewise present in 26 out of 29 women after 12 weeks, and in the woman who wore the inserts for 30 weeks.[615] Robertson said that there was no evidence that the foreign body response was resolving.[616]

576 Robertson said that there was evidence of fibrosis in all of the study samples. She said that this was to be expected as part of the foreign body response to a device, but that the inflammation was inconsistent with resolution of the response and more consistent with elements of a chronic wound.[617] She disagreed that the evidence of fibrosis was inconsistent with a chronic wound response, and repeated that chronic wounds may have patches of fibrosis and granulation tissue.[618]

577 It was put to Robertson that the most important purpose of Valle 2001 was to assess the efficacy of the development of fibrosis and occlusion of the fallopian tube, and that there was nothing in the article to suggest that the authors were concerned that the healing process was not proceeding as expected and intended.[619] Robertson noted that the authors appeared encouraged by their observations. However, she said that

612 T2898 (TRA.500.030.0001_2 at 0104).
613 T2898-9 (TRA.500.030.0001_2 at 0104_31-0105_3).
614 T2874 (TRA.500.030.0001_2 at 0080).
615 T2874 (TRA.500.030.0001_2 at 0080_24-6).
616 T2891 (TRA.500.030.0001_2 at 0097).
617 T2890 (TRA.500.030.0001_2 at 0096_22-7).
618 T2890 (TRA.500.030.0001_2 at 0096).
619 T2892 (TRA.500.030.0001_2 at 0098).

the authors did not disclose their conflict of interest as the inventors and developers of the pre-hysterectomy study, and that this raised concerns about their ability to reflect objectively on the conclusions to be drawn from the data.[620] Robertson said it was not possible to expect that the authors had given adequate and unbiased consideration to the balance of interpretations.[621] Robertson said that she expected a stronger statement from the authors about the concerning observation of ongoing inflammation, which she considered a 'red flag', and a conclusion that this warranted further investigation.[622]

Murdock

578 Murdock said that the finding of occlusion in 100% of cases in the pre-hysterectomy study indicated fibrosis. The fibrosis was found to be localised in the inner portions of the fallopian tube, without extending into the smooth muscle or further than 5 mm distally beyond the insert itself.[623] Smooth muscle cells were integrating into the fallopian tube lumen and migrating into the insert, which indicated to Murdock that the insert was not destructive of the smooth muscle on the outside of the device.[624] Murdock said that, importantly, the insert did not cause any peri-tubal adhesions or serositis.[625] She said that the finding of some moderate or loose fibrosis as soon as one week after implantation, and dense moderate to severe fibrosis after four weeks, was consistent with a normal reaction to a medical device.[626] She said that the tissue was still healing despite the inflammatory response.

579 Murdock interpreted the inflammation graphs as showing acute inflammation decreasing over time; chronic inflammation peaking around 10 to 14 weeks post-implantation; and loose fibrosis decreasing and dense fibrosis increasing over time. She said that the reference to granulation tissue was consistent with healing and that

620 Ibid.
621 T2893 (TRA.500.030.0001_2 0099).
622 Ibid.
623 T2895 (TRA.500.030.0001_2 at 0101).
624 T2878 (TRA.500.030.0001_2 at 0084_23-6).
625 T2878 (TRA.500.030.0001_2 at 0084).
626 T2896 (TRA.500.030.0001_2 at 0102).

there was no evidence of an abnormal foreign body response or development of a chronic wound.[627]

580 Murdock agreed that the histological assessments demonstrated that Essure could cause acute inflammation in the fallopian tubes lasting for at least 30 weeks.[628] In relation to chronic inflammation, Murdock said:

> I think that chronic inflammation is present… in the lymphocytes - lymphocytes are present in the normal fallopian tube so, yes, they are present around this device as well.[629]

Murdock said it was fair to infer that Essure was causally related to the inflammation observed.[630]

581 Murdock was then asked about the table of histology results in Valle 2001, set out at [569] above:

> But this particular table is histological evidence that the Essure Device can cause chronic inflammation up to at least 29 weeks?---Yes, there is chronic inflammation there. What I mean by that is as a pathologist there are chronic inflammatory cells.
>
> You say the presence of chronic inflammatory cells?---M'hmm.
>
> But you've already answered that when categorised on a rate of 2, in the scale of 0 to 3, that that's of more significance, it's a severity on the quantitative analysis; isn't that right?---And 2 is moderate.
>
> That's right, out of 3?---Yes.
>
> So it's not simply, for example, one floating leukocyte, is it?---No, but we also don't know what they quantified as moderate.
>
> I understand that. But you assume, wouldn't you, on a scale of 0 to 4, you would assume, wouldn't you, that there is some significance attached to the 2 category out of 3, right?---Yes.[631]

Badylak

582 Badylak said that the '0-3' grading system in the pre-hysterectomy study should be

627 T2897 (TRA.500.030.0001_2 at 0103).
628 T2911 (TRA.500.030.0001_2 at 0117).
629 T2912-3 (TRA.500.030.0001_2 at 0118–9).
630 T2913 (TRA.500.030.0001_2 at 0119).
631 T2914-5 (TRA.500.030.0001_2 at 0120_25–0121_11).

considered either qualitative or semi-quantitative, as he did not know how the corresponding descriptors of 'mild', 'moderate' and 'severe' were being measured. [632] He said that a grading scale in these types of studies can be set up in one of two ways. The first method, which Badylak said was not used in the pre-hysterectomy study, is to specify different grades based on the number of particular types of cells present, and then examine the histological evidence and allocate grades accordingly. The second method is to view the histological evidence and allocate grades based on the relative characteristics of the samples (for example, the level of accumulation of certain types of cells compared to a normal sample). However, the second grading method would not necessarily indicate that a finding of '3' on the scale was clinically relevant, because the grade is relative to the specific samples and not to an objective scale. [633]

583 Badylak said that while the acute inflammation graph did not make clear the amount of inflammatory cells present at each plotted point, it did indicate a 'drop off' between two and three months. He said this was to be expected in the foreign body response, but agreed that he might have expected the reduction in acute inflammatory cells to occur earlier.[634]

584 In his primary report, Badylak said that a focal accumulation of neutrophils is consistent with an active inflammatory response. When cross-examined about that evidence and the findings of acute inflammation made in the pre-hysterectomy study, he said:

> You're going to always have neutrophils. There will always be some. They're part of the normal cell population of - you do find them in normal tissues occasionally. So the presence of them there is normal. When you're talking about neutrophils as part of an active inflammatory response, the active part, they dominate. They're the most. That would be notable at whatever this was, 12, 13 weeks. The fact that they're there is not surprising at all. We again don't know what a 2 means. So I think he or she is identifying the types of cells that are present. Every one of those cell types in the tissue at this point is expected.[635]

632 T3507 (TRA.500.035.0001_2 at 0082).
633 T3508 (TRA.500.035.0001_2 at 0083).
634 T3512 (TRA.500.035.0001_2 at 0087).
635 T3525-6 (TRA.500.035.0001_2 at 0100_26-0101_7).

It was put to him that if the active inflammatory response had reached a 'steady' state, one would not expect the second most severe grading for neutrophils. He said:

> I know what you mean. What does a 2 mean for neutrophils versus macrophages? Neither of us can answer that question, we don't know. It's a qualitative assessment. If this was an active response, an active inflammatory response, your neutrophils would be dominating here.[636]

585 Badylak was asked whether a rating of '3' for chronic inflammation would indicate an ongoing inflammatory response. He said:

> Like I said, I assume what he means by chronic inflammation is the presence of mononuclear cells like macrophages. So if you have a lot of macrophages that's, you know, going to be present when you're out longer than a couple of months and you're going to have typically very few neutrophils. In order for it to be chronic active explanation I would expect large numbers of both maybe even with a dominance of neutrophils.[637]

586 Badylak was asked about a histological assessment for a patient who wore Essure inserts for 14 weeks where the pathologist assessed acute inflammation as '2' and chronic inflammation as '3'. Badylak said:

> Then there's 3 for chronic, which would be that the dominant cell type here is the macrophage. And if you notice there's also foreign body giant cells starting to form at this point. In a chronic active inflammatory response the giant cells don't form because there too much going on.
>
> Professor Badylak, 3, severe chronic inflammation, I suggest to you at this point suggests an ongoing inflammatory response?---And you're using the term inflammation and what I've tried to do is to distinguish between the cells that are present and the process of inflammation as it's been interpreted for a very long time.[638]

It was put to Badylak that the word 'severe' in the rating system must be given some meaning, and he said:

> A scoring system was set up that goes from the least to the most and the most is given the term severe. What does the most mean with respect to an adverse pathologic response? Neither you nor I could answer that question but we could get some idea if we look at how things change over time.[639]

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636 T3526 (TRA.500.035.0001_2 at 0101_21–26).
637 T3532-3 (TRA.500.035.0001_2 at 0107_29-0108_5).
638 T3533-4 (TRA.500.035.0001_2 at 0108_22-0109_2).
639 T3534 (TRA.500.035.0001_2 at 0109_14–19).

587 It was put to Badylak that Valle 2001 showed both acute and chronic inflammation in a number of women at around 12 to 16 weeks. He said that this conclusion could not be reached simply by examining the histological results table and 'matching up' which patients had more neutrophils and which had more macrophages. He said that an acute inflammatory response would be evidenced by images of micro-abscesses and accumulations of neutrophils around the Essure insert, of which none were published. He said the conclusion was therefore that Essure was safe and effective. When it was put to Badylak that the descriptors 'moderate' and 'extensive' were more likely to indicate an active inflammatory response, he said:

> Well we just don't know, do we, because we aren't in the mind of the pathologist. But I can tell you that if a pathologist sees a consistent presence of acute active inflammation occurring at time points at, you know, four months out, 12 to 16 weeks, they're not going to come up with a conclusion that it's safe and effective. Those are inconsistent with each other.[640]

Badylak agreed that the study did not record data in the long-term, but said there were aspects of the authors' conclusion that were worthy of note:

> The first paragraph, 'it appears to be feasible, safe and well accepted by patients'. The second paragraph, 'it's occlusive in nature providing long-term anchoring and demonstrates tissue ingrowth'. You know, if there were - if one of the conclusions that there was an active ongoing acute inflammatory response that would have also been in the conclusion.[641]

588 In his primary report, Badylak said:

> This chronic active inflammatory state does not occur as part of the foreign body response that accompanies permanently implanted devices such as the Essure device. If such a phenomenon did indeed occur, one would expect to see the hallmarks of an active, self-perpetuating process such as continued neovascularization, foci of tissue necrosis with focal accumulations of neutrophils, and a robust fibroblast presence. These processes simply do not occur with implanted medical devices such as the Essure device. The prehysterectomy study provides hard data to support the foreign body response to the Essure device and the lack of an aggressive, chronic active inflammatory process. [642]

Badylak said, in relation to neovascularisation, that the relevant question was the

640 T4300 (TRA.500.043.0001_2 at 0018_18–25).
641 T4301 (TRA.500.043.0001_2 at 0019_23–29).
642 Badylak at 22 (EXP.001.002.0007).

proportion of *new* blood vessels. He said that this could not be answered by reference to the graph in the pre-hysterectomy study, which only showed how vascular the tissue was. Badylak said that during active inflammation, neovascularisation should be rated at '3' (adopting the grading system) and that he'd expect six to 10 times the number of blood vessels than at an earlier point.[643] Badylak said that some neovascularisation would be expected during the early acute inflammatory stage, but said that the injury caused by Essure insertion 'basically destroy[s] everything', disrupting blood vessels and causing haemorrhage. He said that the graph showed that at the one-week point, a certain number of blood vessels had formed and that this level of neovascularisation was consistent with an acute inflammatory response to injury.[644] He said of the later stage:

> …even in the absence [of] quantitative data to help with these data points, the shape of the graph is definitely not consistent with an active inflammatory response because it would be way up. You'd have blood vessels everywhere. Literally there are almost too many blood vessels to count in an active inflammatory response. Whatever 1 means, this is more consistent with the body coming to some sort of an equilibrium with the tissue that's there.[645]

Badylak did not agree that a neovascularity rating of '2' was evidence of an active inflammatory response.[646]

Sokol

589 Sokol repeated that the term 'chronic inflammation' is used in some of the studies to refer to 'any sort of immune cells'.[647] In relation to Valle 2001, she said:

> … they are saying that they're seeing inflammatory cells. In some cases they see acute inflammatory cells, which I assume would be neutrophils there, that last for more than six weeks. So [Valle 2001], if it was quantified, if we actually knew how many cells were there, although I think it is reasonable to expect that there would still be inflammation after six weeks in that case, just like there's inflammation in response to any foreign body being placed after six weeks. This is expected, this is expected for any type of medical device placement or

643 T3520 (TRA.500.035.0001_2 at 0095).
644 T3521 (TRA.500.035.0001_2 at 0096).
645 T3521 (TRA.500.035.0001_2 at 0096_21–29).
646 T3531-2 (TRA.500.035.0001_2 at 0107-8).
647 T4088 (TRA.500.041.0001_2 at 0006).

any type of foreign body, even a tattoo.

But you accept that in [Valle 2001] there was verified inflammation extending well beyond six weeks, up to about at least 16 weeks, you accept that?--They only went up to 16 weeks. Again, that's less than six months and we would expect continued inflammation from a medical device through six months at least.[648]

590 Sokol accepted that the pre-hysterectomy study data established that in some cases there was an active inflammatory state for up to at least 16 weeks.[649] She said:

> It would overall decrease over time, although the amounts of time that we see active inflammation would at least be through six months for standard foreign body responses.[650]

Submissions

Turner

591 The pre-hysterectomy study and Valle 2001 are compelling evidence of ongoing chronic inflammation in a significant proportion of the women studied.[651]

592 The assessment in Valle 2001 that Essure is 'safe' must be understood in context. Success in the pre-hysterectomy study was determined by the ability to place an insert in a fallopian tube and the occlusion of the tube over time, not by any assessment of long-term safety. Safety was only considered in the context of the placement procedure and assessments of post-procedure discomfort, sequelae and adverse events.[652]

593 The only reasonable interpretation of the '0-3' grading system is that it was a semi-quantitative analysis that assessed the number and type of cells, the relative balance of different types of cells, and their proximity to the suspected inflammatory stimulus. That approach was ultimately accepted by Sokol and Murdock, leaving Badylak isolated on this issue. Badylak's unwillingness to accept that there was any evidence of an active inflammatory state based on the histopathology results, a position which

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648 T4088-9 (TRA.500.041.0001_2 at 0006-7).
649 T4102 (TRA.500.041.0001_2 at 0020).
650 Ibid.
651 SBM.001.001.0004 at 59 [157].
652 Ibid at 59 [156].

entirely contradicted his own expert report, means that his evidence in relation to this study should be rejected.[653]

594 The only reasonable interpretation of the case reports which rate the presence of chronic immune cells at level '2' or '3', is that chronic inflammation is at a level which is elevated above normal. Similarly, given that all the relevant experts agreed that neutrophils are rarely found in normal healthy fallopian tubes, their presence (even when assessed at a '1' or '2') supports this interpretation. That position is reinforced by the findings in Valle 2001 that inflammation (including acute inflammation) was 'moderate/extensive' and described as a 'strong inflammatory response'.

595 The data points in the graphs of the histological characteristics over time are an average of all cross-sections and all individual patients. As Robertson said, the most reasonable interpretation of the graphs showing active and chronic inflammation is that the levels of each respectively did not change over time. Further, the case reports show that reactive features (including acute and chronic inflammation, and fibrosis) are graded highest for those sections of the fallopian tube where the insert and PET fibres were present.[654]

Defendants

596 Valle 2001 is an example of a scientific paper which uses the terms 'acute inflammatory cells' and 'chronic inflammatory cells' to describe the presence of particular types of cells observed in histopathology samples. This directly contradicts Robertson's opinion that these are not 'scientific' terms.[655] The terms are used to refer to the normal and expected stages of the foreign body response, rather than a pathological and persistent chronic inflammatory process as Robertson contends. This is confirmed by:

653 Ibid at 66 [168].
654 Ibid at 30 [93].
655 SBM.500.001.0003_2 at 525 [a].

(a) the trends over time demonstrated by the histological data, including the reduction of acute inflammatory cells, the slight increase in chronic inflammatory cells, increased formation of granulation tissue and loose and dense fibrosis, and a relatively unchanging level of neovascularisation;

(b) the strong fibrotic response and obliteration of the fallopian tube; and

(c) Murdock's evidence that the 12 to 16 week period post-procedure was possibly 'the timeframe where [the] inflammatory response peaks', beyond which the inflammatory response begins to decrease.[656]

597 Valle 2001 records the presence of 'chronic inflammatory cells' in the tissue adjacent to the Essure insert. Murdock's evidence is that this, without more, is not evidence of an active inflammatory process occurring, and that had such a process been identified in any sample, one would expect the authors to have also identified chronic salpingitis in that sample.[657]

598 The pre-hysterectomy study does not record any features of a chronic wound in any of the patients.[658] To the extent that chronic wounds are characterised by a lack of fibrosis, the results of the study show the opposite. It should be inferred that if signs of developing chronic wounds had been observed in any samples, the authors would have expressly noted this in the study.[659]

599 There is no indication in Valle 2001 that chronic inflammatory cells were present in an abnormally increased amount to warrant the diagnosis of a pathologic process.[660] The longest wear time considered in the study was 13 weeks. In this regard, at its highest the study is evidence of chronic inflammatory cells being detected in the vicinity of an Essure insert up to that period of time from the date of implantation.[661] Even if it is

656 T2877 (TRA.500.030.0001_2, at 0083_5–11).
657 Revised Pathology JER at 29 [117] (EXP.500.001.0007_20); SBM.500.001.0003_2 at 528.
658 SBM.500.001.0003_2 at 529 [f].
659 Ibid.
660 Ibid at 530 [g].
661 Ibid.

accepted that the study is evidence of an active inflammatory process occurring, there is no evidence that this process would not have ultimately resolved.[662] Further, the study contains no evidence of any patient harm or adverse events associated with chronic inflammation.[663]

600 Robertson's opinion that Valle 2001 is evidence of persistent, pathologic chronic inflammation is inconsistent with the authors' own conclusions that the device procedure is 'feasible, safe and well accepted by patients'. It is implausible that the authors would have described Essure in this way if their findings were consistent with Robertson's conclusions.

Analysis

601 The pre-hysterectomy study does not explain the grading system or what is meant by the descriptors 'mild', 'moderate' and 'severe'. In the histologic section assessments, the presence of immune cells at any level and in any location resulted in a grading for inflammation. Foreign body giant cells, which are not inflammatory and do not indicate that an active inflammatory process is occurring, were graded for inflammation. The presence of macrophages graded as 'mild' in a section of a fallopian tube distal to the device is unlikely to indicate that an active inflammatory process is occurring at that point. I conclude that the grading for inflammation in the histologic section assessments reflects the presence of certain types of immune cells. It is unlikely that the grading distinguishes between the mere presence of immune cells and those cases where active inflammation is occurring.

602 The purpose of the assessments was to assess the histologic reaction in the fallopian tube to the device. I infer that, in most instances, the examining pathologist reported features that were considered to be causally related to the device. As Robertson said, it is a 'no brainer' that the Essure device, which was designed to cause a particular tissue reaction, was in fact the cause of that reaction observed in tissue immediately

662 Ibid at 531 [h].
663 Ibid at 931 [i].

adjacent to it.

603 The experts agreed that the foreign body response to implantation of a biomedical device will involve an inflammatory response in tissue adjacent to the device. The pre-hysterectomy study covered the period during which the inflammatory response to the Essure device was expected to occur. This means that at least some of the histologic section assessments record findings that reflect an active inflammatory response to Essure.

604 Murdock and Sokol both agreed that the histologic section assessments were evidence, in some cases, of an ongoing active inflammatory response to the device up to at least 16 weeks post-implantation. Murdock said the 12 to 16-week timeframe was consistent across participants, indicating that this was probably when the inflammatory response peaked.[664] Sokol said that you may see an active inflammatory response to a biomedical device for at least six months.[665]

605 The next question is whether the pre-hysterectomy study data demonstrates any relevant trends.

606 The graph of acute inflammation reduces from a mean of 1.9 at less than four weeks to 1.2 at greater than 14 weeks. Chronic inflammation is graphed as remaining relatively constant, ranging from 2 at less than four weeks to 2.1 at greater than 14 weeks.

607 Both the pre-hysterectomy study and Valle 2001 state that acute inflammation was predominant in specimens with shorter wear times, with chronic inflammation becoming predominant in those with longer wear times. The authors reported moderate loose fibrosis after one week, with dense fibrosis becoming moderate to severe after four weeks.

608 Table 2 in Valle 2001 records that at 1–4 weeks, the tissue reaction in seven out of nine

664 T2877 (TRA.500.030.0001_2 at 0083).
665 T4102 (TRA.500.041.0001_2 at 0020).

tubes was assessed as showing moderate/extensive acute inflammation (see [569] above). At 12–16 weeks, 17 out of 29 tubes were assessed as showing moderate/extensive acute inflammation. For moderate/extensive chronic inflammation, the assessments were eight out of nine at 1-4 weeks, and 26 out of 29 at 12–16 weeks. Loose fibrosis was assessed as moderate to extensive in seven out of nine participants at 1–4 weeks and 26 out of 29 participants at 12–16 weeks. Dense fibrosis was assessed as moderate to extensive in seven out of nine participants at 1–4 weeks and 25 out of 29 participants at 12–16 weeks.

609 I conclude that the pre-hysterectomy study data shows:

(a) some reduction in acute inflammation by 12–16 weeks when compared with shorter wear times;

(b) no discernible change in chronic inflammation over the study period; and

(c) no discernible change in loose fibrosis, but an increase in dense fibrosis over the study period.

610 The pre-hysterectomy study is evidence that Essure causes ongoing active inflammation in the fallopian tubes of some women at 12-16 weeks after implantation. This conclusion is supported by cases where acute inflammation (neutrophils) was assessed at '2' or '3', and by the evidence of Robertson, Sokol and Murdock.

611 The more important issue is whether the presence of inflammation in some cases more than three months after implantation of Essure was, as Sokol, Murdock and Badylak said, consistent with the normal resolving foreign body response to Essure, or whether it was, as Robertson contended, inconsistent with a resolving foreign body response and more consistent with development of a chronic wound.

612 The following matters are relevant. First, there is no evidence in the histological assessments or from macroscopic examination of tissue reported in the pre-hysterectomy study that hallmark signs or features of a chronic wound were present.

There were no reports of swelling, redness, fluid discharge, pain associated with inflammation, tissue necrosis or other physical signs of a chronic wound or abscess.

613 Robertson said haemorrhage was an indication of a chronic wound that was not resolving or healing.[666]

614 Badylak was cross-examined about haemorrhage grading in the histologic section assessments. He said that the haemorrhage was very likely caused by surgical removal with hysterectomy. It was put to Badylak that he was speculating, and he responded:

> If I was speculating I would say so. This is more than speculation. This is informed interpretation. I mean this is almost, I don't know, it's going to be close to 100 per cent of samples that I've looked at as a diagnostic pathologist have some small haemorrhage in it. It's a result of harvesting.[667]

Badylak's evidence is difficult to accept. If his explanation were correct, haemorrhage would be observed on assessment of most if not all histologic sections. Review of the pre-hysterectomy study data shows that this is not the case. Further, the histologic section assessment required the pathologist to grade haemorrhage as a reaction to the device. It is unlikely that experienced practitioners would grade haemorrhage as a histologic reaction to the device if it was in fact caused by surgical removal.

615 Murdock agreed that a grading of '2' indicated haemorrhage was occurring in the tissue. She said this was not a matter of concern because the development of scar tissue could disrupt vessels in the lamina propria and possibly granulation tissue. While Murdock agreed that haemorrhage indicated that the device was continuing to have an effect on tissue, she did not agree it was indicative of a chronic wound.[668]

616 The evidence in relation to haemorrhage was limited. In their evidence in chief the expert witnesses did not refer to haemorrhage as a relevant feature indicating the presence of a chronic wound. I am not satisfied that the reported observations of

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666 T2867 (TRA.500.030.0001_2 at 0073).
667 T3524 (TRA.500.035.0001_2 at 0099_14–19).
668 T2909 (TRA.500.030.0001_2 at 0115).

haemorrhage are of significance.

617 Second, the pre-hysterectomy study in Valle 2001 described the tissue response to Essure as 'benign' and 'predictable', and the chronic inflammatory response as 'low level'. Further, the study said that the localised response to Essure did not result in adverse clinical sequelae. I do not accept Robertson's criticism that the authors of the pre-hysterectomy study or Valle 2001 failed to disclose a conflict of interest as investigators of Essure. The pre-hysterectomy study was part of the PMA application by Conceptus to the FDA. Valle 2001 acknowledged that Essure was limited to investigation or use, and that he was part of the pre-hysterectomy investigator group. The findings and conclusions of the pre-hysterectomy study and Valle 2001 are consistent with the examining pathologists not having made observations or findings that raised for them a concern that in the case of some participants the foreign body response to Essure was stalled or failing to resolve, or that there were signs or features of a chronic wound developing.

618 Third, the histologic response may suggest a resolving foreign body response to Essure. Acute inflammation was trending down over time. While chronic inflammation remained relatively consistent, macrophages that were present may not always have been in a pro-inflammatory state. Granulation tissue increased, though not by much. Dense fibrosis increased markedly and the fallopian tubes were almost completely obliterated. I accept Murdock's evidence that the development of dense fibrosis is consistent with a resolving foreign body response, and is not indicative of a chronic wound. Neovascularisation was graded as mild. I accept Badylak's evidence that a chronic active inflammatory state would be associated with severe neovascularisation.

619 Disruption of the fallopian tube epithelium is consistently reported as severe. I accept Badylak's evidence that disruption was caused by insertion of the device into the fallopian tube. Without more, this feature is not indicative of a chronic wound.

620 The above analysis refers to the mean score for all participants for each feature as recorded in the graphs from the pre-hysterectomy study. Of course, individual participant assessments may vary above or below the mean. However, I note the agreement by the experts that the kinetics of a normal foreign body response will depend on the features of the biomedical device, where it is implanted in the body, and factors that are subjective to the individual recipient. As Sokol said, host and device factors can lead to widely disparate normal kinetics for a foreign body response that must be taken into account before concluding that the response has failed or stalled.

Hysterectomy data from annual PMA reports

621 As part of the Phase II study and Pivotal trial follow-up, Conceptus asked participants scheduled for surgical removal of Essure to allow histological evaluation of their fallopian tube tissue. The histological findings from four of these hysterectomies were published in the 2003 annual PMA report.[669] Histologic examination was performed by a pathologist using the same process for fallopian tube tissue sectioning and analysis as in the pre-hysterectomy study.

622 The report records in relation to the first patient:

> A hysterectomy for the diagnosis of "heavy periods" was performed on 12/13/02, making the patient's wearing time 39.5 months. Upon histological examination both tubes showed focal total occlusion by dense fibrosis and the micro-insert. The histologic reaction of the fallopian tubes to the micro-insert showed mild to moderate acute and chronic inflammation with severe disruption of epithelium and lamina propria. Uterine histology showed the cervix was unremarkable. Adenomyosis was present in the myometrium.[670]

623 For the second patient, the report records:

> She subsequently had a hysterectomy on 10/3/02 after a wearing time of 21 months. The hysterectomy was performed for chronic pelvic pain and heavy bleeding which began in May 2002. The patient's previous history was significant for endometriosis. Because of the unicornuate uterus, only one tube (left side) was evaluated. This tube showed focal total occlusion. There was no acute or chronic inflammation present. There was severe disruption of the

669 BAY-ESSURE-0028999_R at 572.
670 Ibid at 573.

epithelium and lamina propria.[671]

624 The third patient ceased oral contraceptives in mid-July 2001, and reported heavier menstrual periods than normal by October of that year. The report records:

> Heavier periods continued and in September 2002 the patient was diagnosed with uterine fibroids. Hysterectomy was performed on 10/03/02 for the diagnosis of uterine fibroids. This made the wearing time for the left side 22 months and 20.5 months for the right side. Histology showed almost total occlusion in both tubes. There was mild acute inflammation and mild to moderate chronic inflammation seen. There was also severe disruption of the epithelium and lamina propria in each tube.[672]

625 The fourth patient reported heavy periods which commenced about six months after Essure implantation. Hysterectomy was performed after 27 months. Histology was reported as follows:

> The uterine specimen showed the cervix to be unremarkable. There was chronic endometritis with focal breakdown of the endometrium. The myometrium was unremarkable. Both fallopian tubes revealed dense fibrosis with near total to total occlusion. There was mild chronic inflammation and no acute inflammation. Severe disruption of the epithelium and lamina propria was present in both tubes.[673]

626 The results were summarised as follows:

> Results of these 4 cases were discussed with Dr. Wright who indicated that the extent of the histological response of the tubes was what would be expected based on the previous histology work performed. There were no cases in which the Essure micro-insert ulcerated the exterior of the fallopian tube, Fibrosis was confined to the portion of the tube containing the micro-insert.[674]

627 Robertson commented on the first patient's right tube B-U histologic section, which is reproduced below: [675]

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671 Ibid.
672 Ibid at 574.
673 Ibid.
674 Ibid.
675 Ibid at 580.

Histology of Essure Micro-inserts from women relying on Essure for Contraception	Pt Study #: S 7 - 251- Pt. Initials:
Conceptus Protocol: STOP 2000 STOP 7 STOP 10 (Circle one)	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections B-U: – Right Tube

Histologic section B-U: Uterine end of block B containing UTJ or isthmic portion of tube

Which slides evaluated (list numbers): 1-2-1 ; 1-2-2

Stains used: H+E ; Trichrome

7. Describe the presence of the Micro-insert in the slides:

A. Not present (B) inner and outer coils C. Inner only D. Outer only

8. Describe the presence of Dacron fibers (circle all that apply)

A. Not present (B.) Present between the two coils only C. Extend outside the outer coil (D.) Inside the inner coil

9. Describe the histologic reaction of the tube to the Micro-insert:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	2
Chronic	2
Foreign body giant cells	1
Fibrosis	
Loose	2
Dense	3
Neovascularity	1
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	1

Describe the cell types present

PMN's, lymphocytes, macrophages, fibroblasts

Does the lumen of the tube appear to be obliterated by the Micro-insert and reactive tissue:

0 1 2 3 (4) 5

Minimally Completely

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Robertson said the findings of inflammation, neovascularity, haemorrhage, and severe disruption of the epithelium and lamina propria indicated that the tissue had

not healed. She considered that these were indications of a chronic wound.[676]

628 The first patient's left tube B-U histologic section assessment is reproduced below:[677]

[676] T2867 (TRA.500.030.0001_2 at 0073).
[677] BAY-ESSURE-0028999_R at 581.

Histology of Essure Micro-inserts from women relying on Essure for Contraception	Pt Study #: S7-251- Pt. Initials:
Conceptus Protocol: STOP 2000 STOP 7 STOP 10 (Circle one)	Dr.: Thomas Wright

Microscopic Assessment of Histologic Sections
Sections B-U: – Left Tube

Histologic section B-U: Uterine end of block B containing UTJ or isthmic portion of tube

Which slides evaluated (list numbers): 1-2-2 1-2-1

Stains used: _____

10. Describe the presence of the Micro-insert in the slides:
    A. Not present (B.) Inner and outer coils C. Inner only D. Outer only
11. Describe the presence of Dacron fibers (circle all that apply)
    A. Not present (B.) Present between the two coils only C. Extend outside the outer coil
    (D.) Inside the inner coil
12. Describe the histologic reaction of the tube to the Micro-insert:

Grade: 0=absent; 1= mild; 2= moderate; 3= severe

Inflammation	
Acute	1
Chronic	1
Foreign body giant cells	2
Fibrosis	
Loose	2
Dense	3
Neovascularity	0
Granulation tissue	0
Disruption of epithelium	3
Disruption of lamina propria	3
Hemorrhage	0

Describe the cell types present

Lymphocytes, Fibroblasts, macrophages, PMN's,

Does the lumen of the tube appear to be obliterated by the Micro-insert and reactive tissue:

0 1 2 3 (4) 5
Minimally Completely

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629 Murdock interpreted the histologic assessments in the annual PMA reports as showing the presence of chronic inflammatory cells 'but importantly, not in an abnormally increased amount to warrant the diagnosis of a pathologic process (i.e., a

chronic salpingitis or chronic wound/abscess)'.[678] Murdock accepted that the report included histological evidence that Essure can cause acute and chronic inflammation for up to 39 months post-implantation. She accepted that a grading of '2' meant the pathologist identified inflammation of moderate severity. She agreed this meant that chronic inflammatory cells were present. She did not dispute the pathologist's identification of a 'moderate' state of chronic inflammation.[679]

630 Sokol accepted that a grading of '2' indicated an elevated level of inflammation and that the presence of neutrophils indicated an inflammatory state, but said that its cause and extent were unclear. It was put to Sokol that sections of the fallopian tube furthest from the device where no or minimal inflammation was detected provided control tissue relevant to causation. She agreed, but said that sections from the same area of tissue in multiple women with the device present would be the better control in order to understand the long-term changes caused by the device in asymptomatic women.[680]

631 Sokol accepted that the first patient's assessments showed active inflammation of the right tube, but said that the assessment of the left tube did not. She said that one would expect the same inflammatory reaction to the device on both sides. Sokol agreed that the difference between the tubes may be explained by micro-injury or some other sort of irritation, but said there would need to be evidence of this to be certain.[681] She said it was also possible that there was an alternate cause of the inflammation of the right tube.[682] Sokol agreed that a mild amount of neutrophils was identified in the left tube.[683] Sokol said that the presence of PET fibres did not correlate with the active inflammation observed in the first patient. She said that inflammation was not localised around the entire device, but was present in patchy spots.

632 In cross-examination, Badylak gave the following evidence about the histologic

678 Murdock at 16 [36] (EXP.001.002.0008).
679 T2921 (TRA.500.030.0001_2 at 0128_17-8).
680 T4094 (TRA.500.041.0001_2 at 0012).
681 T4097 (TRA.500.041.0001_2 at 0015).
682 T4096 (TRA.500.041.0001_2 at 0014_25-8).
683 T4098 (TRA.500.041.0001_2 at 0016_9-11).

assessment of tissue from the first patient:

> I'm not surprised to see any of these cell types present. … I can't remember the exact scoring but the fibrosis was, you know, more advanced, 2s and 3s or something like that. And the dense would be the more mature fibrous connective tissue. This is simply, as we talked about before, describing the different types of cells that are present in the inner tissue section that's examined. This is not surprising, it's expected … [T]he thing that one would worry about is if there was some sort of an active progressive inflammatory response leading to pathology. I've tried to explain how you would recognise something like that, both locally and systematically. These types of cells, there aren't clear cut-offs. There's not, you know, 17 per cent of this is okay and 18 per cent is not, and so forth. That's just not the way tissues respond, that's not biology. The presence of all of these types of cells is part of the body's recognition that there's a foreign material present there. You would see the exact same type of characterisation if you were looking at an insulin pump, a pacemaker, an artificial hip, a total knee joint … this is the way the body responds to it. It's a localised nonpathologic tissue response that's present. There's nothing here that concerns me.[684]

Submissions

Turner

633 The granular histological analysis of tissue reaction to Essure after a lengthy period of time is of particular relevance to the issues in this proceeding. The data clearly demonstrates that the device has elicited an ongoing active chronic inflammatory response in some women years after insertion, some with accompanying acute inflammation.[685]

Defendants

634 Badylak's evidence that the presence of immune cells in the histopathology was part of the body's recognition of a foreign material, rather than evidence of pathology precipitated by an active inflammatory response, should be accepted.

635 The assessments provide extremely limited support for Turner's case, even if it is accepted that they contain evidence of active inflammation. First, they lack the broader clinical context necessary for proper interpretation of the assessment findings.[686] As Badylak said, '[i]f there's a chronic active inflammatory response this

684 T4319-20 (TRA.500.043.0001_2 at 0037–38).
685 SBM.001.001.0004 at 68 [177].
686 SBM.500.001.0003_2 at 586.

patient is going to have pain, a fever, a high white blood cell count and other indicators of active inflammation'.[687] It is not possible to conclude that the the PMA annual reports are evidence of pathologic inflammation in the absence of such observations or test results.

636 Second, the assessments are a point-in-time analysis. It is not possible to conclude that any active inflammation would not have resolved pursuant to the altered (but still normal) kinetics of a foreign body response to a medical device.

637 Third, there is nothing in the annual PMA reports that identifies the source of the inflammation particularly in circumstances where, as Sokol observed, there was a difference in the reaction observed in the first patient's right and left tubes and patchy inflammation not associated with the presence of PET fibres. There is insufficient information in the assessments to conclude that Essure caused the observed inflammation.[688]

638 Fourth, there is no evidence linking the observed inflammation to any harm suffered by any of the patients.

Analysis

639 It is difficult to know what to make of the histologic assessments in the annual PMA reports. Robertson and Sokol agreed that the right tube assessment in the case of the first patient showed the presence of active inflammation. Murdock and Badylak said, in effect, that the grading did no more than identify a presence of certain immune cells.

640 There was no evidence of any adverse sequelae suffered by any of the four patients connected to Essure. The assessing pathologist said that the observed histological responses were expected. No observations that were consistent with a chronic wound or other pathology related to the devices were recorded.

641 Robertson referred to neovascularity, disruption of the epithelium and haemorrhage

687 T3534 (TRA.500.035.0001_2 at 0109).
688 SBM.500.001.0003_2 at 583.

as being indications of a chronic wound. I accept Badylak's evidence that damage to the epithelium occurs when the Essure device is inserted. Neovascularity and haemorrhage were graded '1' in the right B-U histologic section of the first patient. The same gradings were given for neovascularity and haemorrhage in other sections where no inflammation was present,[689] and where acute inflammation was absent and chronic inflammation was graded '1'. I do not accept that a grade of '1' for neovascularity and haemorrhage indicates the presence of a chronic wound.

642 I accept Badylak's evidence that there were no other signs or clinical features recorded in respect of the first patient to indicate the presence of an pathologic chronic inflammatory response to Essure.

643 Sokol questioned the causal connection between the observed inflammatory response and the Essure devices. The purpose of the histologic assessment was to describe the reaction of the fallopian tube to the device. The pathologist said that the reaction observed in these four cases was expected. Badylak gave similar evidence. I conclude it is likely that the inflammatory reaction observed by the pathologist was related to the devices.

644 I accept Badylak's evidence that there is no clear cut-off, in terms of the numbers of immune cells present, between a normal response and an active progressive inflammatory response leading to pathology. Consideration of other features is necessary to determine whether an active chronic pathological inflammatory response is present.

645 Murdock characterised pathological chronic inflammation in the fallopian tubes as salpingitis. She was asked the following questions about the spectrum of chronic inflammation:

> You've also accepted, haven't you, that chronic inflammation is on a spectrum, you'd accept that?---A spectrum for normal, yes.

689 BAY-ESSURE-0028999_R at 593.

> Even for abnormal there's a spectrum, isn't there?---Sure.
>
> At the most extreme you'd have one cell and the other extreme you'd have chronic salpingitis, wouldn't you agree with that?---Yes and no, because there are other tissue changes that happen along with chronic salpingitis that you have to look for.
>
> Certainly. But you do accept that in relation to those what you call chronic inflammatory cells would be the spectrum between the one cell at the one end and the chronic salpingitis at the other end, would you agree with that?---Sure, yes.
>
> The fact that chronic salpingitis hasn't been identified doesn't mean that there was no chronic inflammation at some point on that scale, does it?---To me there's a spectrum of normal and then once you cross that line of normal, which again is a gestalts, that pathologist, through training and through evaluation of clinical information, then they would diagnosis that as a chronic salpingitis once it crosses that threshold.[690]

I accept Murdock's evidence that pathological chronic inflammation is recognised by a unified configuration or pattern of elements or features. It is not recognised merely by the presence of certain immune cells.

Essure 505 Study

646 Conceptus undertook a multi-centre prospective study in 2012 to measure the histological response of fallopian tubes to the new proposed Essure 505 insert model ('ESS505'), compared to the existing ESS305 model.[691] Sixty-six patients who were already scheduled to undergo a hysterectomy were enrolled in the study.

647 The Essure 505 study consisted of two phases. In Phase 1, 25 patients had ESS505 inserts placed in at least one fallopian tube. Histological responses were assessed after one hour, 30, 60 and 90 days post-procedure. In Phase 2, 31 patients had an ESS505 insert placed in one fallopian tube and an ESS305 insert placed in the other, with the same follow-up procedure as in Phase 1.[692]

648 Acute inflammation was defined in the study as 'the presence of neutrophils within or surrounding the insert', and was scored using the following graded scale:

690 T3014-5 (TRA.500.031.0001_2 at 0088_12-0089_2).
691 BAY-EDPA-5063983.
692 Ibid at 13.

0 = None, Essential absence of tissue neutrophils.
I = Minimal, Rare individual neutrophils.
2 = Mild, Scattered neutrophils without clustering.
3 = Moderate, Neutrophils with focal clustering.
4= Extensive, Neutrophils with more confluent infiltration.[693]

Chronic inflammation was defined as 'the presence of lymphocytes, histiocytes, eosinophils and/or plasma cells within or surrounding the insert', and was graded as follows:

0 = None, Essential absence of chronic inflammatory cells.
1 = Minimal, Occasional scattered chronic inflammatory cells.
2 = Mild, Frequent scattered or focally clustered chronic inflammatory cells.
3 = Moderate, Multifocal chronic inflammatory cell clusters.
4 = Extensive, More confluent chronic inflammatory cell infiltrate.[694]

649 For the purposes of this proceeding, the histological results for the patients with ESS305 inserts are of utility. The study found mild acute inflammation for those patients with ESS305 inserts who were assessed at 90 days post-procedure, with mean scores ranging from 0 to 2. Chronic inflammation was assessed as mild to moderate for those patients with mean scores ranging from 1 to 2.5.[695] There also appeared to be a gradual increase in chronic inflammation over the 30, 60 and 90-day period.

650 Murdock agreed that the Essure 505 study showed that Essure could cause 'mild' inflammation for at least 90 days. She agreed that the description 'moderate, multifocal chronic inflammatory cell clusters' in the chronic inflammation grading scale suggested an active inflammatory process. She agreed that a mean score of 2.5 for chronic inflammation meant there must have been some inflammation assessed at '3'. She said that this meant the inflammatory cells '[were] there doing an active duty', rather than merely being present.[696]

693 Ibid at 168.
694 Ibid.
695 Ibid at 190.
696 T3004 (TRA.500.031.0001_2 at 0078_28).

Submissions

Turner

651 This study is of less relevance to the current proceeding as the devices were not worn beyond 90 days. Nevertheless, it is of some utility to demonstrate that there was still an active inflammatory response to the device at 90 days, and that that the response did not decrease over the 30, 60 and 90 day timeframe. To the contrary, there was an increase in chronic inflammation scores over the period.

Defendants

652 All Murdock was asked in relation to the Essure 505 study was whether the data reflected the fact that 'the Essure Device can cause chronic inflammation for at least 90 days in the wearer of the Essure Device to that mid-level' (being a reference to the 'mild' category), to which she answered 'yes'. Murdock's response reflects the words of the document to which she was taken. She was not asked whether she agreed with the use of the term 'chronic inflammation' in the document in question, or what implications she considered that a finding of 'mild' (as that term was defined in that study) chronic inflammation meant. This cross-examination ultimately did not achieve any aim other than asking Murdock to confirm the express words used in the document in question.[697]

Analysis

653 The 505 Study demonstrates that in some cases there was still an active inflammatory response to the device in the fallopian tube at 90 days post-implantation. However, there is nothing in the study to indicate that, in those cases where an active inflammatory response was present, the foreign body response would not resolve or that the inflammation had become or risked becoming pathologic chronic inflammation that was adverse to health.

Maassen 2018

654 Maassen 2018 is a retrospective cohort study of Essure in the Netherlands to '[analyse]

697 SBM.500.001.0003_2 at 580 [5.31].

short-term effectiveness and symptom resolution after surgical removal of Essure sterilization devices'.[698] The study included 93 patients who had Essure removed during the period between January 2009 and December 2015. The authors investigated patient records to collect data on patient characteristics, symptoms, insertion and removal procedure, and the results of pathological and follow-up assessments. Based on the patient records, the two most disabling symptoms were noted.

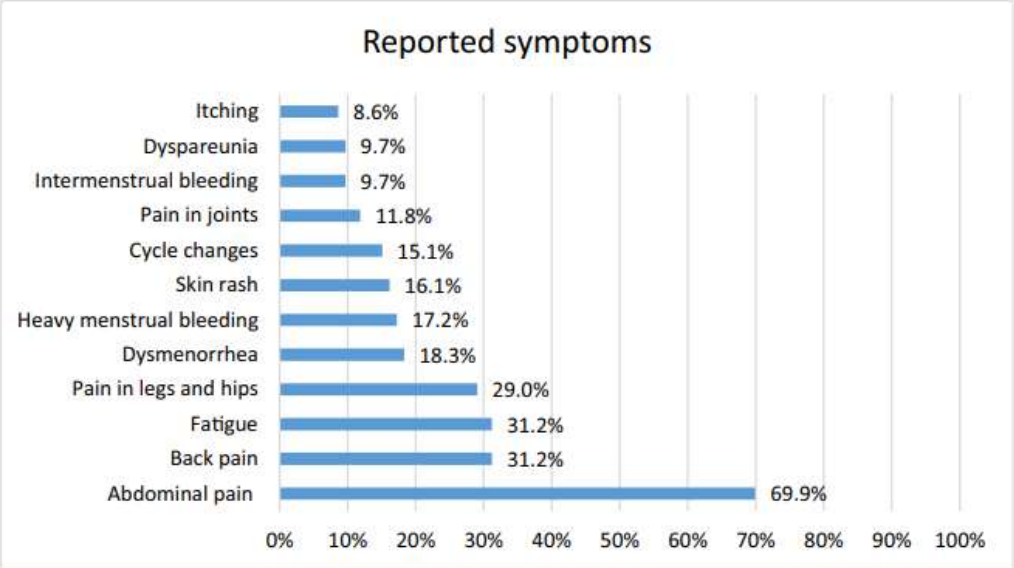
655 The average time between implantation and removal was 43 months, with time ranging from zero to 125 months. The time between sterilisation and insert removal was less than three months for six patients, and between three months and one year for a further 16 patients.

656 Twenty-two patients (23.7%) reported the onset of symptoms immediately after Essure placement. Fifteen patients (16.1%) reported the onset of symptoms more than one year post-placement.[699] Most patients reported more than one symptom. The most frequently reported symptoms leading to surgical removal were recorded in the following figure:[700]

698 Maassen 2018 at 3 (PUB.500.001.0066).
699 Ibid at 6.
700 Ibid at 3.

Fig. 1

The most frequently reported symptoms at the first outpatient clinic visit. Symptoms were extracted from patients' files. The data are presented as percentages of the total patients experiencing the symptom.

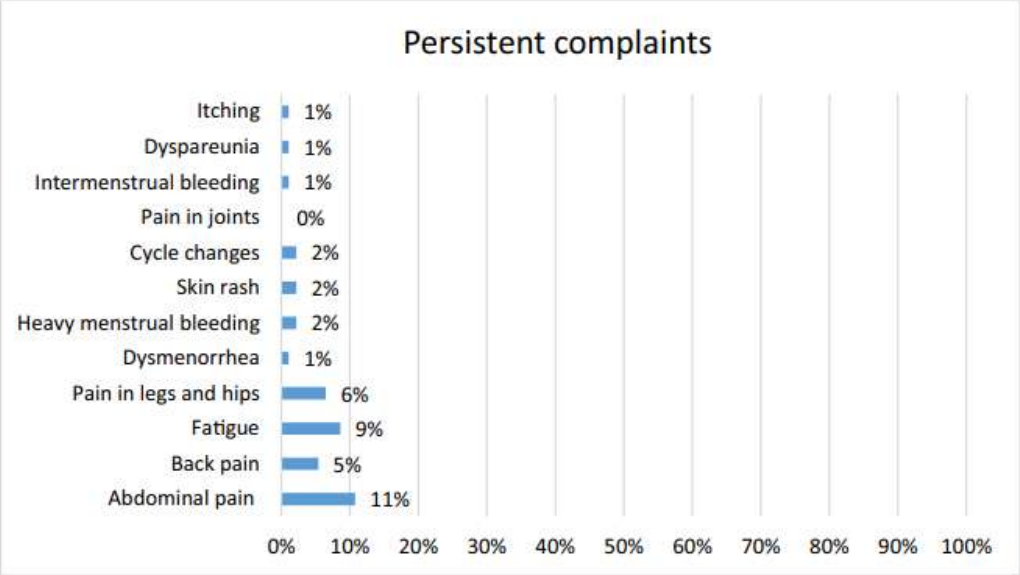


657 The authors followed up 73 patients after their removal surgery. The median time between removal and the post-procedure visit was 45 days. Fifty-seven of these patients (61.3%) reported high satisfaction following Essure removal, and 39.8% reported the complete resolution of their symptoms. Eleven patients (15.1%) did not notice any relief in symptoms. Persistent complaints after surgical removal were recorded in the following figure:[701]

[701] Ibid at 4.

Fig. 3

Persistent complaints. Ongoing symptoms reported by patients after removal surgery. Only the most frequently mentioned symptoms are displayed, as a percentage of the total patients (N = 73).



658 The authors collated data of the pathological assessments of fallopian tube tissue following explantation in the 93 patient records included in the study. Their findings were as follows:[702]

Table 3

Pathological Assessment (N = 93)

Assessment Findings	n
Normal findings	55
Reactive tissue changes	13
Chronic inflammatory infiltrate	6
Paratubal cyst	19

Findings from the pathological assessment are displayed as numbers.

There is no further explanation in the study of what is meant by 'Normal findings', 'Reactive tissue changes' or 'Chronic inflammatory infiltrate'.

659 The study findings were compared to those in Valle 2001 as follows:

> The [PET] fibers used in Essure® are known for causing tissue in-growth into medical devices. Within 12 weeks after placement, the tissue in-growth causes complete tubal occlusion. In pathological assessment of removed tissue in 6 cases a form of chronic inflammation of the resected tissue was seen. Other samples showed reactive tissue changes, normal histology or benign findings

[702] Ibid at 5.

> like Para tubal cysts. In 2001 a study consisting of 27 women who were hysteroscopically sterilized using the STOP device, a previous version of Essure, received a hysterectomy. The removed parts were investigated in order to see histological changes. Results showed a strong tissue response with fibrosis and chronic inflammation. These findings differ from our cohort since only in 6 patients these reactions were found. This could be explained by the duration of the material present in the tube. In our study the mean duration of sterilization was 43 months, in [Valle 2001] the STOP device was in situ for 30 weeks maximal.[703]

660 The authors expressed the following conclusion:

> Complaints after Essure sterilization are a much-discussed topic. In this retrospective cohort, patients reported a wide variety of symptoms. Only 39.8% reported complete resolution of symptoms at the postprocedure visit. Given the previously mentioned limitations of this study, further research of the reported symptoms after Essure sterilization and symptom resolution after the removal surgery is necessary. A larger prospective cohort with a longer period of follow-up is needed in order to inform patients about the expected symptom resolution after removal. The knowledge of the decrease in symptoms is necessary for both patients and gynecologists in order to make a well-considered decision about taking the risks of surgery compared with the expected benefits.[704]

661 No information was included in Maassen 2018 to enable a comparison between the histological findings and the time between sterilisation and removal. It is not known how long the six women whose pathological assessments showed chronic inflammatory infiltrate wore the inserts.

662 The authors also noted that the results may be biased due to incomplete follow-up and documentation; the possibility of pre-existing chronic pain syndromes; the relatively short follow-up period; and a possible placebo effect.[705]

663 Robertson agreed that it was possible but unlikely that the six patients in Maassen 2018 who were identified as having a chronic inflammatory infiltrate were the same six patients who had Essure in place for less than three months. She agreed that the six might also include patients who had Essure in for a little longer than three

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703 Ibid at 8.
704 Ibid at 6.
705 Ibid.

months.[706]

664 Robertson did not agree with the authors that the reduced number of patients with chronic inflammation compared to the pre-hysterectomy study was likely explained by the increase in wear time. She said that the more likely explanation was that the pathology results considered in Maassen 2018 were for tissue which was further away from the insert.[707] Robertson reasoned that it is 'impossible to take sections from the area of [the fallopian tube near the insert] unless specialist approaches are used' or to section the tube when the insert is in situ. In her view, this meant that the tissue samples were likely from another part of the tube which was unlikely to have been impacted by the device to the same degree.[708]

665 Murdock agreed that the authors of Maassen 2018 had observed chronic inflammation in six patient cases. However, she said it was not known whether the authors had simply identified immune cells in normal healthy tissue, given that the level of chronic inflammation was not quantified nor was it clear where the tissue samples came from.[709] She added that the timeframe was unknown as the authors did not identify, in terms of duration of wearing, which cases exhibited the chronic inflammatory infiltrate.[710]

666 Murdock agreed that the authors identified the six cases with chronic inflammatory infiltrate as being different from 'normal'.[711] Murdock added:

> But if you have one or a couple of inflammatory cells in a normal anatomy and you have, let's say five, they could be different than normal, than doesn't necessarily [sic] a pathologic process.
>
> …
>
> Well have [the authors] or have they not identified in this article that these six cases were not the normal anatomy?---I think you're trying to get me to say that this is not a normal response, but this, to me, is a normal

706 T2935 (TRA.500.031.0001_2 at 0009).
707 T2935 (TRA.500.031.0001_2 at 0010).
708 T2937 (TRA.500.031.0001_2 at 0011).
709 T2962 (TRA.500.031.0001_2 at 0036).
710 T2964 (TRA.500.031.0001_2 at 0038).
711 Ibid.

response to a device if the tissue was taken directly adjacent to it and there's chronic inflammation there, like that's a - -

I'm not asking for your opinion about it, I'm asking you whether the people who wrote this article have come to the conclusion when reporting this what they were reporting was not a normal response?---That is incorrect. I think this is a normal response and they're saying that this is different. That's how they define it as different. They don't term it abnormal.

They say normal findings - let's look at table 3, which is on the next page?---Correct, but they're not defining chronic inflammation as abnormal either, they're saying it's different, it's there.[712]

Murdock said the identification of chronic inflammatory infiltrate was consistent with what would be expected around an insert.[713]

667 Finally it was put to Murdock:

I'm putting to you that there is an identification here of an elevated chronic inflammatory response in those six cases beyond the other 55, would you agree with that?---Yes, but we don't know again how much.

I'm suggesting to you that it's an elevated response beyond what you would find in normal tissue, isn't that right?---Yes.[714]

668 Badylak was asked about the finding of chronic inflammatory infiltrate in six cases:

Yes, and my question to you is you'd have to accept here, wouldn't you, that the persons involved in this study drew a distinction between normal anatomy in 55 cases and chronic inflammatory infiltrate which was, by definition, not normal in their view?---Right. A chronic inflammatory infiltrate would be consistent with the finding of mononuclear cells at the site.

So not a normal process, but likely suggestive of an active inflammatory response?---Well, we talked about what active means and we also talked about what a chronic inflammatory cell is and the significance and relevance of those types of cells in the foreign body response. I'm not saying anything that's inconsistent with what we've talked about already.

HIS HONOUR: Do I understand that to mean that your expectation is adjacent to the device you would expect to see the continued presence of mononuclear cells in the steady state?---Yes, Your Honour. That's definitely the case. In fact those cells will be present there for as long the

712 T2964-5 (TRA.500.031.0001_2 at 0038–39).
713 T2965 (TRA.500.031.0001_2 at 0039).
714 T2967 (TRA.500.031.0001_2 at 0041).

> device is present in the patient, which in most cases is going to be for the life of the patient. They will be there. They're in the response to any permanent implant. What we do know also is that those few cells that are there are very - I don't want to use the term dormant too loosely, but they're not acting in a way like we talked about a couple of weeks ago with the secretion of things that cause inflammation. You'll note in the wording here is a chronic inflammatory infiltrate, they're describing the cells. The process of inflammation, as we said, is much more involved than simply the presence of cells. But the short answer - I guess it's not so short any more, sorry - to your question, there will be mononuclear cells present for as long as the device is present in the patient, for the life of the patient.
>
> If that's the explanation for the six cases, what's the explanation for that finding not being made in the 55 cases?---I guess the - I'm just - I'm assuming now from a pathologist's standpoint that the number of cells were so small that they weren't even worth mentioning. That is indeed what happens with these cases. Those cells become so infrequent that they're not worth knowing in a conclusion.[715]

669 Sokol was also asked about the six cases of chronic inflammatory infiltrate:

> What I'm asking you or suggesting to you is that's indicating a state which the author has determined to be not normal?---Well, we do not know whether or not there is active inflammation. So chronic inflammatory infiltrate we do not know if those are active cells, so I would want to know, like we've talked about and like I've mentioned, whether or not there are neutrophils in the site, whether there's evidence of activation there.
>
> She's certainly identified it as not being normal, hasn't she?---She has identified it as such. Or she has identified a pathological assessment of chronic inflammatory infiltrate there. My problem, though, is that chronic inflammatory infiltrate means a lot of different things to a lot of different pathologists.[716]

Submissions

Turner

670 Maassen 2018 is limited as it lacks detail of the location of tissue examined histologically, and of the meaning of 'chronic inflammatory infiltrate'. However, the authors' identification of tissue reacting in a way that was other than normal suggests an active inflammatory state, or certainly one that is unresolved. The study is therefore additional evidence of an ongoing active chronic inflammatory response to

715 T4304-5 (TRA.500.043.0001_2 at 0022_17-0023_27).
716 T4113-4 (TRA.500.041.0001_2 at 0031-2).

Essure for a period longer than three months.[717]

Defendants

671 Maassen 2018 does not provide information about the location of fallopian tube sections submitted for histologic assessment, or whether the assessed tissue was only from the fallopian tube or from both the tube and uterus. Accordingly, the study results must be approached with caution.[718]

672 The authors of the study do not define the terms 'chronic inflammatory infiltrate' or 'reactive tissue changes'. Without this information, it is impossible to conclude with any certainty that an active inflammatory process was in fact occurring in some cases.[719]

673 There is no evidence in the study that the chronic inflammatory cells detected were present in any abnormally increased amount to warrant a diagnosis of a pathologic process.[720]

674 'Chronic inflammatory infiltrate' was observed in only six cases. That is the same number of participants who had Essure inserts in place for fewer than three months. In these circumstances, if 'chronic inflammatory infiltrate' is accepted as identification of an active inflammatory process occurring, there is no evidence that the inflammatory process would not have ultimately resolved according to the normal kinetics of a foreign body response to a medical device.[721]

Analysis

675 I accept the defendants' submissions in relation to Maassen 2018. The lack of detail in the study about the location of fallopian tube sections analysed, what is meant by the terms 'chronic inflammatory infiltrate' and 'reactive tissue changes', and the wear time of participants in which those changes were observed means that the study is of

717 SBM.001.001.0004 at 73 [201].
718 SBM.500.001.0003_2 at 552.
719 Ibid.
720 Ibid at 553.
721 Ibid.

very limited utility.

676 Robertson's reasoning about the location of fallopian tube tissue sections being the likely explanation for the reduced number of patients with chronic inflammation is no more than speculation. There is simply no way to tell where the tissue sections were taken by reference to the presence of the device.

Rubin 2020

677 Rubin 2020 compared histological features of six hysterectomy specimens removed for a primary diagnosis of chronic pain.[722] Three of the specimens were from women who had Essure and three were from women who did not. The wear time for the three women with Essure ranged from six to 10 years.

678 The pathologic findings for two of the three women with Essure were reported as follows:

> *Patient 1:* On gross examination, both tubes contained metal coils without protrusion into the endometrial cavity. Tissue from the coil site demonstrated a few macrophages containing debris and a rare giant cell in the left tube … and mild fibrosis of the right tube … No evidence of acute inflammation at the coil sites was seen. The isthmic sections of the tubes demonstrated dilation with loss of the normal folded epithelial configuration.
>
> *Patient 2:* Grossly, metal coils were present in both tubes with the left coil protruding into the endometrial cavity. Microscopic analysis of the interstitial left coil site demonstrated fibrosis with near-total occlusion of the tube … The right interstitial tube showed phagocytic uptake of foreign debris with one associated giant cell at the isthmus ... There was bilateral dilation of the isthmus and ampulla with obliteration of folds.[723]

No evidence of acute or chronic inflammation was observed in the third Essure patient.[724]

679 The pathology for the remaining three non-Essure patients was reported as follows:

> *Patients 4–6:* Six tubes from three control patients were examined histologically. The interstitial segment of these tubes did not show epithelial denudation, mural fibrosis, muscular hypertrophy, or giant cell reaction. One tube showed

722 Rubin 2020 (PUB.500.001.0247).
723 Ibid at 3.
724 Ibid.

> clinically unsuspected acute salpingitis, i.e., neutrophils subjacent to the epithelium. Another tube showed serosal adhesions to the ovary.[725]

680 The authors said in their discussion:

> Our major finding is that changes in the tubes of Essure patients were bland and showed only minimal chronic inflammation, in the form of foreign-body reaction, and no acute inflammation, suggesting that pain is unlikely to be due to an ongoing localized inflammatory process. Chronic inflammation was not seen in the tubes of control patients and is therefore likely to be due to the device, but does not appear to be a compelling correlate of pelvic pain.[726]

681 The authors noted that their findings related to a small number of cases and may not be generalisable for this reason.[727]

682 Robertson said that the specimens from the first two women with Essure devices showed 'quite good' evidence of chronic inflammation and phagocytosis of material likely to be shed from Essure.[728] Robertson agreed that macrophages may be present at very low levels after resolution of a foreign body response.[729]

Submissions

Turner

683 Viewed objectively, Rubin 2020 represents an additional piece of evidence of ongoing chronic inflammation in women with Essure long after one would expect such a reaction to cease.[730]

Defendants

684 The only sensible construction of the use of 'inflammation' in Rubin 2020 is that it refers to the mere presence of particular types of inflammatory cells, and not to any form of active inflammatory process. The authors characterise 'minimal chronic inflammation' as being the 'foreign body reaction' with no suggestion that any

725 Ibid at 4.
726 Ibid.
727 Ibid.
728 T2945 (TRA.500.031.0001_2 at 0019_1).
729 T2945 (TRA.500.031.0001_2 at 0019_29).
730 SBM.001.001.0004 at 74 [202]–[205].

abnormal or pathologic process was observed.[731]

685 The results of the study are consistent with the expected, normal response to implantation of Essure. The study is not evidence of an association between Essure and the formation of a 'chronic wound'. Identification of 'one rare giant cell' and 'one associated giant cell' is not synonymous with active inflammation, but indicates that a foreign body response is occurring or has occurred at the site of the insert.[732] Further, all of the Essure patient samples showed at least loose (and in most cases dense) fibrosis and obliteration of the fallopian tube lumen.

Analysis

686 I accept the defendants' submissions. Rubin 2020 described the histologic changes in the tubes of Essure patients as 'bland'. Acute inflammation was not found. Robertson agreed that macrophages may be present after resolution of a foreign body response. The finding in Rubin 2020 of 'minimal chronic inflammation' does not suggest the presence of an active inflammatory process.

Banet 2020

687 Banet 2020 is a retrospective study of the histological findings of explanted fallopian tube tissue of Essure wearers following surgery.[733] The stated aim of the study is to further characterise these findings. Of the 137 women included in the study, 121 had submitted fallopian tube tissue for histological analysis. The average duration of Essure implantation was 48 months, with a range of zero up to 166 months. The chief complaints by women in the study were pelvic pain (72) and AUB (54).

688 Microscopic findings included inflammation in 59 cases, with 31 of these showing some component of giant cells, 37 showing chronic inflammation in the form of lymphocytes and plasma cells, and 19 showing acute inflammation, most of which included at least focal eosinophils. The trend was towards acute inflammation for shorter duration implantation, and chronic inflammation for longer implantation. The

731 SBM.500.001.0003_2 at 542.
732 Ibid.
733 Banet 2020 (PUB.001.001.3744).

type and duration of inflammation is plotted as follows:[734]

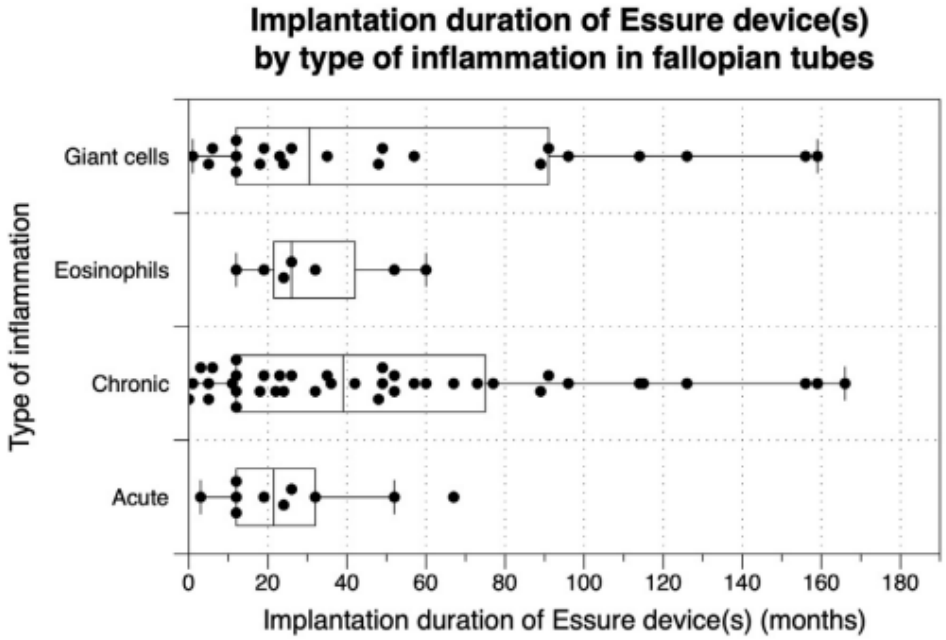

Fig. 3. Data distribution for inflammation type noted in fallopian tube by duration of implantation of the Essure device by months. Categories of inflammation are giant cells, eosinophils, chronic (plasma cells and lymphocytes), and acute (neutrophils). The vertical line in the middle of each box indicates the median, the left and right edges of the box mark the 25th and 75th percentiles, the whiskers to the left and right of the box represent the 10th and 90th percentiles, and the point beyond the whisker is an outlier beyond the 90th percentiles.

689 Banet 2020 set out some relevant findings as follows:

> In the patients who presented with a clinical symptom of pelvic pain who had tissue submitted, (n = 71), 30 had inflammation in associated tubal specimens, the most common being chronic inflammation (18), with giant cells noted in 15, and acute inflammation noted in 5, and eosinophils in 3.[735]

690 The description of histological images included:

> Chronic inflammation of lymphocytes and plasma cells was marked in some cases (F, 40×), while in others (G), eosinophilic inflammation was prominent (200×). Changes reminiscent of salpingitis isthmica nodosa (H) were noted in selected cases (20×).[736]

691 Discussion of the study outcomes included:

---

734 Ibid at 3.
735 Ibid.
736 Ibid at 4.

> Polyethylene terephthalate (PET) fibers were chosen for the device, as they are known to cause tissue ingrowth of medical devices. The accompanying inflammatory infiltrate caused by the fibers has been described as a mix of macrophages, foreign-body giant cells, and plasma cells,[737] and has been characterized as peaking at 2–3 weeks post-implantation, with resolution by 10 weeks. Though the mix of inflammatory infiltrate is similar in the current study, the duration of inflammation in this study ranged to 156 months for foreign-body type giants cells, and 166 months for lymphocytic inflammation, which exceeds this characterized limit.
>
> Clinical parameters in this patient population must be approached with caution, as this cohort is not representative of the general population, those with Essure coil devices, nor is there a control population available for comparison. Nonetheless, in a population of patients who presented for removal of their devices for assorted symptoms,[738] similar common symptoms of pain and increased or abnormal uterine bleeding were noted. However, this was conducted by clinicians with access to patients with the specific aim of symptom characterization, which was outside the scope of the current study. Of note, the duration of coil implantation for these two studies are similar, 0–125 months, compared to 0–166 (current study). Though the current study cannot be faithfully extrapolated to reflect the general public, the overall pattern of complaints with the device registered with the FDA are similar to those noted in patients in this study [Table 1]. Of note, an increase in patients presenting with self-reported pelvic pain was noted in the same time period of 2015–2016 [Fig. 1] in which the FDA lodged a citizen petition and subsequently issued labeling changes to the device.[739]

692 Robertson was asked in cross-examination about Banet 2020:

> Then you'll see, 'Chronic inflammation in the form of lymphocytes and plasma cells', so it's saying nothing other than the presence of lymphocytes and plasma cells?---Yes, sufficient to attribute chronic inflammation, which is the critical issue that the authors were evaluating.
>
> …
>
> MR COLLINS: That's your reading of it but all it says is in the form of lymphocytes and plasma cells consistent with the definition in figure 3 of being a definition of cell types observed?---Sufficient numbers and organisation and, to a degree, a distribution with other features that the pathologist has noted chronic inflammation.
>
> Nowhere in the article does it say that, does it?---No, but that is the basic fundamental tenet of what pathology and the definition of inflammation is. It's not necessary to say that in every article.[740]

Robertson said that Image F (referred to in [690] above) showed very obvious

737 The authors cited Valle 2001 (PUB.500.001.0100).
738 The authors cited Maassen 2018 (PUB.500.001.0066).
739 Banet 2020 at 5 (PUB.001.001.3744).
740 T2943 (TRA.500.031.0001_2 at 0017).

inflammatory infiltrate.[741] She said that Image G showed an accumulation of cells, indicating inflammation, with the presence of eosinophils, indicating an allergic response to the device.

693 Murdock said that Banet 2020 is limited by its retrospective design and because the tissue section locations in the tubes are unknown.[742] Murdock did not agree that the reason the study author recorded chronic inflammation in 37 cases was because it was 'histologically significant'. She said that without quantification, it may be the case that the presence of 'one plasma cell or one lymphocyte is still going to be termed chronic inflammation.'[743]

694 Murdock agreed that the example in Image F showed marked inflammation that went beyond the presence of one or two immune cells.[744]

695 It was put to Murdock that the author of Banet 2020 noted that the chronic inflammation they found exceeded the characterised inflammation resolution limit in response to PET fibres of 10 weeks, to which she said:

> So the way I interpret it is that the characterised limit has been previously been set at X, Y or Z and that this paper has more information to add to that. If somebody was writing a review afterwards they would say since we take Banet's information into account, and we can take the first study into account, then we can come up with a new characterised limit.[745]

It was put to Murdock:

> But what they're saying here is it's being characterised as peaking at two to three weeks with a resolution by ten weeks. That's what it says there, isn't it?---But this is not related to the Essure Device in particular.
>
> I'm asking you what it says here?---You're asking me about the Essure Device and here they're referring to another device.
>
> They are, but what they're talking about is whether the PET fibres usually - what this article is saying is that usually and previously it was thought that the inflammatory reaction to the PET fibres would peak at two to

741 T2955 (TRA.500.031.0001_2 at 0029).
742 T2968 (TRA.500.031.0001_2 at 0042).
743 T2969 (TRA.500.031.0001_2 at 0043).
744 T2970 (TRA.500.031.0001_2 at 0044).
745 T2973 (TRA.500.031.0001_2 at 0047_23-30).

three weeks and resolve by ten weeks, isn't that what that's saying?---That's what she is summarising. I don't know, I haven't read that paper.

You agree that's what she's summarising?---Yes.

Now what she's saying is even though the mix is similar in the current study, what we've found is that the inflammatory response is not resolving by ten weeks because of what we found in the study, isn't that what she's saying?---Correct.

So the inflammatory response is not resolving, but continuing on, and here it was showing that it was still continuing on at 166 months; isn't that what she's saying?---That is correct.

So it's showing that this study shows that in a proportion of women, for at least 166 months, that inflammatory reaction is not resolving and it's continuing, isn't that right?---That is correct, but we don't have any quantified information on that.[746]

696 Badylak said that Banet 2020 was very consistent with the way that tissues in patients respond to the presence of a non-degradable foreign material.[747] He said that the study was a retrospective analysis and that the author did not have access to all of the records; that it was a good example of a pathologists' process where tissues and cell types are discussed in certain numbers; and that the publication did not describe whether or not this was consistent with a foreign body response. He said that the study identified the presence of cell types, rather than an inflammatory reaction.[748]

697 Badylak was questioned about the discussion of PET fibres and inflammation in the study (see [691] above). He said that PET fibres were chosen because they had been used safely for decades in many medical devices, and because they would elicit an inflammatory response. He said that he did not agree with 'resolution by 10 weeks' because PET is designed to elicit inflammatory infiltrate (meaning there would always be inflammatory cells present), but agreed that there would be a resolution of active inflammation by 10 weeks. I asked Badylak what cells would be present if there was active inflammation years after device implantation. He said:

You'd have a prominent number of neutrophils and the chronic inflammatory cells as well because the process had been going on for, you know, whatever,

746 T2974-5 (TRA.500.031.0001_2 at 0048_31-0049_27).
747 T4308 (TRA.500.043.0001_2 at 0026).
748 T4309 (TRA.500.043.0001_2 at 0027).

> months or years. That would always be the case with a chronic active inflammatory response.[749]

698 Sokol said that she could not trust Banet 2020 because of what she said was an 'inconsistency' in the numbers. The author noted chronic inflammation in 37 out of 59 cases, but Figure 3 in the study plotted 40 cases of chronic inflammation.[750] She agreed that if patients had chronic inflammation, acute inflammation and/or giant cells they could fall into a number of categories, but questioned how three extra cases of chronic inflammation in the figure were found. She said that it was either 'incredibly sloppy' or was on purpose.[751]

699 Sokol agreed that Image F showed marked inflammation, and that Image G showed eosinophils and neutrophils. She said that the presence of eosinophils indicated active inflammation, and that this may be due to a delayed-type hypersensitivity reaction ('DTHR').[752] I will return to DTHR later in these reasons. She agreed that the presence of neutrophils beyond six weeks was an indication of ongoing inflammation.[753]

700 Sokol said that the discussion in Banet 2020 about inflammatory response peaking at two to three weeks post-implantation and resolving by 10 weeks was in reference to PET fibres generally, and not in particular reference to Essure.[754]

Submissions

Turner

701 Banet 2020 has some limitations because there is no control group and the inflammation is not quantified. However, the author, who is a pathologist, has clearly designated cases where chronic inflammation was notable. If there was a low level chronic inflammatory response as part of a steady state, it would be expected in all cases. The author's chosen example images show significant inflammation, including

749 T4314 (TRA.500.043.0001_2 at 0032_11-16).
750 T4108 (TRA.500.041.0001_2 at 0026); Banet 2020 (PUB.500.001.0264).
751 T4109 (TRA.500.041.0001_2 at 0027_14-5).
752 T4110 (TRA.500.041.0001_2 at 0028).
753 T4111 (TRA.500.041.0001_2 at 0029).
754 Ibid.

the presence of neutrophils well beyond six weeks. The discussion of PET fibres causing persisting chronic inflammation beyond the 10-week characterised limit indicates that the author was reporting an active, ongoing, and unresolved inflammatory state.[755]

Defendants

702 Banet 2020 should be treated with some caution because of the numerical inconsistency identified by Sokol.

703 The author does not specify the definition of 'inflammation' being used, or the criteria by which it is assessed. As Murdock said, the author's reference to 'chronic inflammation' could indicate 'just one cell'. Sokol's evidence was consistent with Murdock's, in that she did not consider that Banet 2020 provides evidence of persistent or chronic inflammation.

704 The study did not compare the Essure samples with any control tissue. Relevantly, Sokol said that '[s]ince the fallopian tubes normally contain immune cells, it is essential to not only quantify the number of immune cells seen in these pathological samples, but to compare them to normal control tissue'.[756] Further, Sokol said that the investigator needed to clearly identify the numbers of immune cells to conclude whether there is an abnormal presence which correlates with inflammation. In the absence of such information, it is not possible for the Court to properly conclude that the author of Banet 2020 used 'inflammation' in the manner contended by Robertson. Properly construed, Banet 2020 should be understood as using the terms 'acute inflammation' and 'chronic inflammation' to refer to the presence of particular cell types, rather than to persistent, pathologic inflammation.

705 The trend towards acute inflammation for shorter wear time and chronic inflammation for longer wear time is consistent with the expected or normal response to Essure. There is no indication that the author identified any kind of abnormal or

755 SBM.001.001.0004 at 72.
756 SBM.500.001.0003_2 at 535.

pathologic inflammatory process, and there are no recorded features of a chronic wound in any of the study subjects.

706 At its highest, Banet 2020 is evidence that certain inflammatory cells were present in tissue samples at a particular point in time following device implantation. Even if it is accepted that there was evidence of an active inflammatory process occurring, there is no evidence that it would not have ultimately resolved according to the altered, but still normal, kinetics of a foreign body response to a medical device.

707 There was considerable variation in the tissue types submitted for histologic review. The study recorded that 'five fallopian tubes had peri-coil only soft tissue submitted, 118 had representative sections, and in three cases the entire fallopian tube was submitted for histologic review'. Comparison of different tissue types from different positions in the fallopian tube, in circumstances where there was no control tissue, necessarily limits the weight that can be placed on the study.

Analysis

708 There were other discrepancies in the inflammation case numbers in addition to those identified by Sokol (outlined at [698] above). Acute inflammation was noted in 19 out of 59 cases, but only 10 dots appear on the graph. There are similar discrepancies for giant cells and eosinophils. Further, the total number of dots on the graph is 79, but inflammation was only found in 59 cases. The whiskers for each type of inflammation to the left and right of the box represent the 10th and 90th percentiles. A further 20% of cases must have been distal to the whiskers. On the graph in Figure 3, only one dot is shown outside the whiskers.

709 The explanation for these discrepancies is that Figure 3 plots individual fallopian tubes, whereas the narrative discussion in the study relates to identification of cases in which relevant findings were made. It is clear from earlier discussion in the study that a 'case' refers to an individual patient. Tissue was submitted for 126 of the 137 cases (patients) included in the study. Inflammation was noted in the tissue of 59 of those 126 cases (patients). Fallopian tube tissue was submitted in 121 cases.

710 The inflammation findings come from all of the 126 cases in which tissue was submitted. However, the wear duration was not available for all of those patients. The study said 'the duration of the coils being in place was available for 104/137 patients, with an average of 48 months and a median of 43 months (range 0–166 months)'.[757]

711 The Figure 3 graph is plainly limited to those patients where the implantation duration was known. It is likely therefore that only a proportion of the 59 cases (and up to 118 fallopian tubes) in which inflammation was found were available to be plotted in Figure 3.

712 It is clear from the heading and notation accompanying Figure 3 that it plotted findings of inflammation in individual fallopian tubes, not cases.

713 Robertson, Murdock and Sokol agreed that Image F showed active chronic inflammation. However, there is no way of knowing whether each of the 37 cases in which chronic inflammation was found were consistent with what is seen in the image. Reference in the description of the images to chronic inflammation being 'marked in some cases' suggests, as Murdock said, that there was a range in the findings of inflammation. Further, I note that the study does not give the wear time relevant to the image. It is possible the image comes from a case where the wear time is only a few weeks or months.

714 The trend observed in Banet 2020 was for acute inflammation to be present for a shorter wear time, and chronic inflammation for a longer wear time. It appears from Figure 3 that chronic inflammation reduced over time.

715 There is no evidence in Banet 2020 of the clinical features said by the experts to be consistent with or indicative of pathologic chronic inflammation to which I have previously referred. There was no apparent correlation between complaints of pelvic

757 Banet 2020 at 2 (PUB.001.001.3744).

pain and the findings of chronic or acute inflammation.

716 Banet 2020 is evidence that in some cases, chronic inflammation is present in fallopian tubes with Essure beyond the timeframe for the expected resolution of the foreign body response. Sufficient cells were present to warrant designating chronic inflammation in 59 cases, but not in the remaining 62. The presence of acute inflammation is an indication that in some cases inflammation may have been active. However, the study does not define what is meant by 'inflammation' or set out the criteria by which it is assessed. I do not accept Robertson's evidence that a designation of chronic inflammation necessarily involved the assessing pathologist concluding that immune cells were present in sufficient numbers, organisation and distribution to justify the finding. Further, the study does not include analysis of control tissue against which the histological findings can be compared, and the precise location of the histologic sections that were analysed was not specified. In light of these limitations, it is not possible to say what proportion of the cases in which inflammation was noted were related to the Essure inserts and involved active inflammation.

717 Where the inflammation was caused by the Essure devices, it may reflect a foreign body response that was resolved or was on the path to resolution. In other words, the study may reflect the varied kinetics of a normal foreign body response to Essure. There were no features of pathologic ongoing chronic inflammation reported in the study.

Hoogendam 2020

718 Hoogendam 2020 is a short case study of a woman who had Essure removed by salpingectomy surgery.[758] The authors recorded the patient's history as follows:

> A 43-year-old woman visited our outpatient clinic with a complaint of abdominal pain, most pronounced at the left lower quadrant and radiating to the left hip, existing continuously for 2 years. Uncomplicated hysteroscopic bilateral Essure microinsert (Bayer AG, Leverkusen, Germany) placement for permanent contraception had been performed 9 years prior.[759]

[758] Hoogendam 2020 (PUB.001.002.0123).
[759] Ibid at 2.

The result of histological assessment was described by the authors as follows:

> At laparoscopy, both fallopian tubes were clearly enlarged at the isthmus (Fig. 1B). These 3-cm tubal masses contained a white, soft solid content (Fig. 1C) that surrounded each microinsert. Bilateral salpingectomy and microinsert removal were performed, including complete resection of these—clinically suspected—granulomas (Fig. 1D). The histology showed that the tubal masses contained almost exclusively neutrophilic granulocytes and granuloma, confirming the clinical diagnosis (Fig. 1E).[760]

The tests administered to exclude bacterial infection were described as follows:

> Additional Gram and periodic acid–Schiff diastase staining identified no underlying infection by a microorganism.[761]

719 The authors concluded:

> This is the first report in the literature on a foreign body (i.e., noninfectious) granuloma after Essure microinsert placement. It re-emphasizes the range of possible long-term complications that could occur after this permanent contraception method.[762]

720 Robertson said that Hoogendam 2020 was a case showing a serious bilateral inflammatory response to Essure.

721 Robertson disagreed with Murdock that the tests conducted in Hoogendam 2020 were insufficient to exclude chlamydia or gonorrhoea as possible causes of granulomas (outlined at [724] below). She said that both conditions can be readily detected by Gram stain, especially in a purulent infection like this case. She said that the Gram stain and PAS-Schiff stain are the traditional investigations for the presence of bacteria and microbial infection, and that neither stain used in Hoogendam 2020 showed any evidence of bacteria. Robertson said that while DNA testing is the current 'state of the art' method in addition to the stain tests, the stains had been relied on and proven very informative in identifying infection for many decades. She added:

> But it's almost impossible to, as I've said, expect that bacteria are causing this if you couldn't find bacteria in such a huge mass of an inflammatory infiltrate. A DNA test, like a PCR test, will find one bacteria, you know, in a gram of tissue. Sorry, it will find that one bug. But you don't need to look for one bug

760 Ibid.
761 Ibid.
762 Ibid.

> when you have something like this. There would have been billions of bugs and they would be very evident by these more traditional approaches.[763]

She concluded that chlamydia and gonorrhoea were highly unlikely given the presentation of this case.[764]

722 Robertson said that the images in Hoogendam 2020 showed that the granuloma consisted largely of neutrophils, with some macrophages.[765] In terms of causation, she said it was critical that the granuloma was found in the immediate vicinity of the Essure insert in both fallopian tubes. She said that if the granuloma was caused by a bacterial infection, bacteria would likely have spread to other tissue.

723 Robertson said there were three possible explanations for the delay between implantation of Essure and the patient's symptoms commencing. First, she proposed that the damage to the epithelial layer and other fallopian tube tissues caused by insertion of the device interfered with the 'housekeeping' and management of the microbiome and immune response, allowing a pathogen to access the fallopian tubes at some later time. Second, she said that the pathogen was present the whole time and slowly began to win out against the immune system. Third, she proposed that neuropathic pain resulting from an ongoing inflammatory response to the Essure devices took a long period of time to build. She said that 'the inflammatory response slowly changes pain sensation and training for perception of pain and that will also change over time'.[766] It is not clear to me how the first two explanations, which contemplate the development of a bacterial infection, fit with the case brought by Turner.

724 In the pathology JER, Murdock said that Hoogendam 2020 '[described] an acute salpingitis, which is the histologic manifestation of pelvic inflammatory disease (PID)'. Murdock said that the most common causes of PID include chlamydia trachiomatis and neisseria gonorrhoea. She said that the tests used in Hoogendam

763 T2949 (TRA.500.031.0001_2 0023_5-13).
764 T2948 (TRA.500.031.0001_2 at 0022_27).
765 T2947 (TRA.500.031.0001_2 at 0021_22).
766 T2951 (TRA.500.031.0001_2 at 0025_26).

2020 were not standard care and were insufficient to exclude these conditions.[767] Murdock said that other possible causes of granuloma included sarcoidosis, Crohn's disease, parasitic infections and long-term bacterial infections. She concluded that Hoogendam 2020 was a case of PID bacterial infection until proven otherwise,[768] which the authors had failed to do.

725 Murdock noted that the patient in Hoogendam 2020 had Essure for nine years, was asymptomatic for seven years, and then presented with two years of abdominal pain.

726 Badylak agreed that Hoogendam 2020 showed an inflammatory response which was 'clearly a problem'. Badylak said:

> I think this speaks to something that we talked about right from the very beginning, you know, there's no perfect medical device for any clinical application. There's going to be cases like this in any medical device. I don't know what was going on with this patient but there's clearly an active inflammatory response in this particular case, yes.[769]

727 Sokol agreed that Hoogendam 2020 was an example of an active inflammatory state well beyond the expected resolution time in a patient who had the device for nine years.[770]

Submissions

Turner

728 It should be accepted that Hoogendam 2020 is an example of an active inflammatory response to Essure, as was ultimately conceded by Sokol and Badylak.[771]

Defendants

729 The correct construction of Hoogendam 2020 is that the authors reported an acute salpingitis, being a histologic manifestation of PID. The most common causes of this condition are chlamydia and gonorrhoea, which are both sexually transmitted

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767 Revised Pathology JER at 30 [121] (EXP.500.001.0007_2).
768 T2959 (TRA.500.031.0001_2 0033).
769 T4306 (TRA.500.043.0001_2 at 0024_26).
770 T4117 (TRA.500.041.0001_2 at 0035).
771 SBM.001.001.0004 at 75.

infections. No specific test was done for either disease.[772]

730 The following indicia point to a sexually transmitted infection being the most likely cause of the acute salpingitis observed. First, the patient had Essure implanted for seven years without complaint before her abdominal pain commenced. This suggests that she was exposed to the bacteria causing sexually transmitted infections around that time, which produced the infection and the ensuing symptoms.

731 Second, the authors reported that the tubal masses found 'contained almost exclusively neutrophilic granulocytes and granuloma'. Robertson's suggestion that Essure alone caused the masses seven years after implantation is implausible. For this to be true, it would mean either that:

(a) acute inflammation was occurring 'silently' at the site of the device for seven years before any symptoms of abdominal pain manifested in the patient, or

(b) acute inflammation only started (or started up 'again') seven years after the device had first been implanted.

Neither hypothesis is credible, particularly in circumstances where the most likely cause of the acute inflammation – bacterial infection – was not excluded by the study authors for the reasons identified by Murdock.

732 Hoogendam 2020 does not contain the data or detail required to properly attribute causation of the inflammatory process described by the authors to Essure. Robertson herself accepted that the tubal masses may have been caused by an infection occurring at the site of the inserts.[773]

733 Robertson's failure to critically review Hoogendam 2020 and identify the authors' failure to test for the most common causes of PID is an example of the difference between her expertise as a scientist and, for example, Murdock's expertise as a clinical

[772] SBM.500.001.0003_2 at 555.
[773] SBM.500.001.0003_2 at 557.

pathologist. Robertson's evidence that 'until the last 10 years or so for many, many decades we have relied on Gram stain and PAS stains' seemingly ignores the fact that the study was published in late 2020.[774] To the extent that there is disagreement between the experts about this study and the tests that should have been conducted, Murdock's evidence ought to be preferred given her capacity as a practising pathologist and clinician.

734 Badylak's evidence is not inconsistent with a conclusion that it is far more likely that Essure was not the cause of the active inflammatory response recorded in Hoogendam 2020.

Analysis

735 There are three reasons to doubt the causal connection between the granulomas and the Essure devices in the Hoogendam 2020 case study.

736 First, the patient history suggests that abdominal pain commenced two years before surgical explantation of the devices. The authors do not consider the relevance of the first seven years following device implantation. I do not accept Robertson's explanation about the possible delay in development of neuropathic pain. As-Sanie explained the three mechanisms of pain as follows:

> Nociceptive pain is pain that arises through the activation of peripheral nociceptors because of actual or threatened tissue damage such as inflammation. Neuropathic pain is defined as pain caused by a lesion or disease of the peripheral nervous system. Nociplastic pain, often termed "centralized pain" or "central sensitization," is defined as pain due to central nervous system alterations in pain processing.[775]

It seems likely that Robertson's reference to neuropathic pain should have been to nociplastic pain. As-Sanie's evidence, which I accept, is consistent with the evidence of other experts including Badylak that pain is a feature of pathologic chronic inflammation. The history of pain weighs against there being a causal connection between the Essure devices and the granulomas.

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774 T2948 (TRA.500.031.0001_2 at 0022_19-21).
775 As-Sanie at 38 [122] (EXP.001.002.0005).

737 Second, while the Gram and acid-Schiff tests were administered, there is no indication that the authors specifically turned their minds to the alternative diagnoses identified by Murdock. For example, there is nothing to suggest that the authors enquired about the history of exposure to transmissible infections or other matters relevant to the alternative diagnoses.

738 Third, relatedly, the definitive tests identified by Murdock were not administered. There was a direct conflict between Murdock and Robertson about whether the Gram and acid-Schiff tests were sufficient to exclude other possible causes of the granulomas. I accept the defendants' submission that Murdock's evidence on this point should be preferred given that she is a practising pathologist and clinician.

739 Badylak, and possibly Sokol, accepted that the granulomas in Hoogendam 2020 were causally related to the Essure devices. However, their consideration of the study was superficial.

740 I am not satisfied that a causal connection has been established between the Essure devices and the granulomas identified in Hoogendam 2020.

741 If I am wrong, then the causal connection between Essure and the granulomas may have been, as Robertson said, because of bacterial infection. The case brought by Turner is not based upon a mechanism where ongoing chronic inflammation is caused by bacterial infection. There is no evidentiary basis to conclude that the possibility of bacterial infection is a less likely cause of the granulomas than a failed foreign body response to Essure.

Catinon 2022

742 Catinon 2022 is a retrospective study which examines associations between local and systemic symptoms and wear of the tin weld of Essure inserts.[776] The study involved 18 women who had an Essure wear time of between 44 and 178 months (the average being 94 months), who requested removal and underwent salpingectomy and

[776] Catinon 2022 (PUB.001.001.3758).

hysterectomy between September 2019 and July 2020.[777]

743 The pathological analysis was reported in the study as follows:

> The pathological study by optical microscopy (Table 1) shows that all women presented some granulomas (17/18 patients) or fibrosis (1/18) identified in the fallopian tube (9/18), uterine horn (6/18) or both (3/18). We also observed uterine adenomyosis (14/18), nonspecific inflammatory signs (10/18) and foreign bodies (7/18 patients).[778]

744 The authors said that 17 participants responded to a post-surgery questionnaire as follows:

> The most frequent local symptoms before explantation, irrespective of perceived intensity, were: pelvic pains (13/17 patients), urinary sphincter disorder (12/17), bleeding (11/17), pains during intercourse and genital prurit (9/18), and symptoms linked to microbian urinary infection (8/18). For 17 patients there was a global improvement in the intensity of symptoms after explantation (Fig. 2).[779]

745 The authors considered it was:

> … plausible that the tin weld corrosion inducing inflammatory granulomatosis could also be responsible on a non-exclusive basis, along with adenomyosis, for the pelvic and intercourse pains and bleeding.[780]

746 The study included the following declaration of competing interest:

> All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; *Michel Vincent is Chief Executive Officer of Minapath Développement. Mickaël Catinon and Elisabeth Roux are employees of Minapath Développement*; no other relationships or activities that could appear to have influenced the submitted work.[781]

747 Some months after publication of the study, and two years after publishing an earlier study that I will consider in Chapter XIII, the authors published a corrigendum with the following declaration of interest:

> Michel Vincent is Chief Executive Office of Minapath [Développement]. Minapath [Développement] has been involved in 154 mineralogic analysis for

777 Ibid.
778 Ibid at 3.
779 Ibid.
780 Ibid at 6 (footnotes omitted).
781 Ibid at 8.

> 96 Essure victims. For lawsuit it was paid by eight patients and only one victim is concerned by the JETMB's article.
>
> Dr Sournies, co-[author] of the article, acted as a private expert of two cases.
>
> Mickaël Catinon and Elisabeth Roux are employees for Minapath [Développement]. No other relationships nor paid activity can be subject of conflicts of interest for the submitted work.[782]

748 Robertson said that granulomatous tissue usually includes neutrophils and macrophages in varying proportions, but usually a predominance of neutrophils.[783] She said that the authors described the presence of non-specific inflammation which could be acute or chronic inflammation, and agreed that they had not specifically defined the individual cell types. However, she said it was not necessary to describe the specific cell types to know what the authors meant by terms like 'granuloma'.[784]

749 Robertson said that there was a good suggestion of a chronic wound in Figure 1 in the study. She said the figure showed phagocytosis of metallic material, likely to be tin, and very good evidence of an inflammatory response. She said that the disorganisation of the tissue, complete absence of the epithelium and underlying stroma, accumulation of foreign material, and localisation of that accumulation indicating phagocytic uptake (which can only be done by macrophages) are hallmark indications of a chronic wound.[785]

750 Robertson did not accept that the authors' failure to disclose conflicts of interest when they published the study cast doubt on their independence. She said:

> It certainly does not because if they are found to exhibit any bias or to have any question mark whatsoever in their technical capability or their interpretation of their data, especially when it's published in the scientific literature where they are held to account by their scientific peers and the editors and readers of this journal, then their company is in deep trouble. So, if anything, their integrity is improved by publishing and engaging with the scientific community more broadly.[786]

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782 PUB.500.003.0049.
783 T2952 (TRA.500.031.0001_2 at 0026).
784 T2952 (TRA.500.031.0001_2 at 0026).
785 T2954 (TRA.500.031.0001_2 at 0028).
786 T3395 (TRA.500.034.0001_2 at 0109_23).

751 Murdock responded to Robertson's evidence about what was shown in Figure 1 of Catinon 2022:

> In figure 1A I don't see a chronic wound. To me this is fibrosis. The epithelium, I agree, has been denuded or is completely gone, which is consistent with a device. I don't see at this magnification a phagocytotic process. I don't see - you can't tell what is there, what cell types are around the material in question out into the fallopian tube wall. You can't tell at this cell magnification if those are macrophages or not. All you see is fibrosis, which is the dense scar. So to me this is not a chronic wound, this is a healed scar process.[787]

752 Sokol said that one of her concerns was that the description of inflammation in Catinon 2022 was non-specific, and that she did not know what the authors meant by 'granulomas' or 'non specific inflammatory signs'.[788] She agreed that granuloma was indicative of a history of an active inflammatory state.[789]

Submissions

Turner

753 Catinon 2022 is further evidence of chronic inflammation in both the fallopian tubes and uterine horn caused by Essure, long after one would expect such a reaction to cease. It is also evidence of that inflammation extending into the uterine area.[790]

Defendants

754 Robertson's evidence fails to address the real issue that the corrigendum presents — that there was an obvious, unavoidable and material conflict of interest that the authors of Catinon 2022 did not disclose at first instance. The Court ought to have regard to why that conflict was not disclosed when the study was published. Viewing the study through this prism means that a substantial degree of caution should be exercised before relying on the evidence it contains.[791]

755 For the following reasons, little weight should be placed on Catinon 2022. First, as the study does not define 'non-specific inflammatory signs', it is not possible to conclude

787 T2961 (TRA.500.031.0001_2 at 0035_22).
788 T4114 (TRA.500.041.0001_2 at 0032_13-4).
789 T4114 (TRA.500.041.0001_2 at 0032_17-9).
790 SBM.001.001.0004 at 74.
791 SBM.500.001.0003_2 at 547.

with any certainty that inflammation was in fact occurring.[792]

756 Second, deficiencies in the study methodology include self-evaluation of symptoms by patients, not systemically performing blood metal measures (meaning there was no proper comparison within the cohort of patients involved in the study) and the absence of a control population.[793]

757 Third, Murdock's evidence about what is seen in Figure 1 in the study should be preferred over Robertson's evidence, due to Murdock's training and clinical practice.[794]

Analysis

758 I accept the defendants' criticisms of Catinon 2022. For the following reasons I conclude that little weight should be attached to the study.

759 First, Catinon 2022 does not explain what is meant by 'non specific inflammatory signs' or 'granulomas'. The term 'non specific inflammation' is so general and undefined that it is not possible to say what it means, or that it describes the presence of a current active inflammatory process. I accept Sokol's evidence that 'granuloma' may indicate a current inflammatory process or a history of active inflammation.

760 Second, beyond what was said by the authors, it is not possible to reach any firm conclusion about what is shown in the three images in Figure 1 from the study. The authors simply reported those images as showing 'mineral particles', often in clusters, present in the fallopian tube. Robertson and Murdock had only the small copy images available for their consideration. I found Robertson's evidence surprising in two respects: first, because of the level of detail in what she said could be seen in the image; and second, because it was not until cross-examination that she identified what she said were hallmark indications of a chronic wound. I conclude that given her training and clinical practice, Murdock's evidence about what was seen in Figure 1 should be

792 Ibid at 549.
793 Ibid at 550.
794 Ibid at 549–550.

preferred.

761 Third, the authors' failure to disclose conflicts of interest in the published study further undermines my confidence in the evidence it contains.

Further expert evidence

762 Robertson reiterated that the six histological studies, each from different research groups across the globe, all concluded that Essure caused persistent chronic inflammation and/or acute inflammation in some women. She said that more than 50% of the women in the histological studies had acute or chronic inflammation which lasted longer than three months, and that in a substantial proportion of women this inflammation was found to persist for years.[795]

763 Murdock said that the studies showed that there was a normal inflammatory response to Essure. She said the device resulted in the development of fibrosis that would not be found if there was a problem with the inflammatory response.[796] She agreed that the Essure histological studies showed that a localised chronic inflammatory response to the device can persist at a moderate level for months or years.[797] Murdock was asked:

> That moderate level is more than what you just expect in just normal quiescent tissue, that's true?---Well I mean what are they comparing to normal? Are they comparing it to the fibrotic tissue of the fallopian tube around the device when you might get one? Are they comparing it to the normal tissue, that there's ten cells in this one millimetre square? If we go back to the (indistinct) paper, they have quantified per millimetre square. So if you're comparing it to the normal fallopian tube or you're comparing it to the fallopian tube that has no cells in it and it's fibrotic, so if you compare it to that then it's increase to the fallopian tube fibrotic scar. If you compare it to the normal fallopian tube, it might be less.
>
> We certainly know that in some of the material that we looked at on Friday there was a degree of quantification, wasn't there, you described this morning that fact that - - - ?---Mild, moderate, severe I think it was, yes.
>
> That's right. We know, we've been through the evidence that the inflammatory process that was being looked in at least in those cases was more than

795 T2986 (TRA.500.031.0001_2 at 0059).
796 T2986 (TRA.500.031.0001_2 at 0059_18-21).
797 T3002 (TRA.500.031.0001_2 at 0076).

> just a few cells in a surveillance role, you accepted that, didn't you?---Right, I agree.
>
> And the annual reports showed that, that after a significant amount of time the acute and chronic inflammation in some of the slides was at (indistinct) level 2, wasn't it?---Yes.
>
> That was a level of inflammation which was beyond that normal level, would you agree with that?---Again, normal for what, but yes.[798]

764 Sokol said that there was a lack of criteria to define the inflammatory state, and a lack of quantitative data. She said some of the studies used the term 'chronic inflammation' to simply refer to the presence of types of immune cells.[799] She said that both the Rubin 2020 and Banet 2020 studies had issues because there was no control population to provide a basis for assessing what represented elevated numbers of inflammatory cells.[800] Sokol said that these studies did not provide evidence of persistent or chronic inflammation.[801]

765 Sokol agreed that some of the studies showed evidence of inflammation that persisted six or more weeks after Essure placement.[802] She said that in the context of Essure, such a period of inflammation was not abnormal.

766 Sokol was asked about the agreed definition of chronic inflammation set out at [471] above. She said:

> Well that's the definition of chronic inflammation, the presence of cells for more than six weeks, or the presence of inflammation for more than six weeks, or inflammatory cells. The question is whether or not that chronic inflammation is expected and part of the normal response, because chronic inflammation can be part of a normal foreign body response.[803]

The further part of the definition, referring to inconsistency with optimal health, was put to Sokol:

> That's what you agreed with, didn't you, that when it was present in the body

798 T3002-3 (TRA.500.031.0001_2, at 0076_5-0077_9).
799 T4088 (TRA.500.041.0001_2 at 0006).
800 T4086 (TRA.500.041.0001_2 at 0004_27-39).
801 T4088 (TRA.500.041.0001_2 at 0006).
802 T4115 (TRA.500.041.0001_2 at 0033).
803 T4117-8 [TRA.500.041.0001_2 at 0035_27–0036_2).

for six weeks or longer since the initiating insult, it was inconsistent with optimal health, it wasn't part of a resolved foreign body response; that's right, isn't it?---No, because I specifically made sure that we wrote, 'We agree that the term chronic inflammation generally implies a pathological state of abnormal immune activation'. That is, it's a general statement.

What, for this case?---Well, no, any foreign body response. If you didn't have inflammation past six weeks in a foreign body response then that would be pathologic.

You're stepping back from what you've stated here to say that in the case of an Essure Device there is an unknown length of time that it can sit in the body and it will never be a problem, is that what you're telling His Honour?---No, I think I've been clear, and I think I've clearly mentioned that if this is going on for years on years then, yes, this is not a good thing.

There are examples of it going on for years and years and years?---There are several examples. I think we've agreed upon six to eight examples.[804]

Submissions on Essure histological evidence

Turner

767 The following table summarises the histologic data from studies in which fallopian tubes were examined and inflammation recorded:[805]

Study	Number of patients or tubes	Chronic Inflammation	Acute Inflammation (neutrophils present)
Valle	47 tubes (0 to 29 weeks)	42	26
	29 (> 12 weeks)	26	17
Pre-hysterectomy Data BU sections	94 tubes (0 to 29 weeks)	91 (any level)	78 (any level)
	94 tubes (0 to 29 weeks)	64 (level 2 or 3)	45 (level 2 or 3)
	52 (> 12 weeks)	49 (any level)	40 (any level)
	52 (> 12 weeks)	32 (level 2 or 3)	25 (level 2 or 3)
Banet (Chronic	126 cases	37	19

804 T4118 (TRA.500.041.0001_2 at 0036_10-31).
805 SBM.001.001.0004 at 77 [221].

inflammation 0 to 166 months) (acute inflammation 3 to 65 months)			
505 Study (90 days)	9 cases (location 1)	7	3
	9 cases (location 2&3 mean)	9	5
Annual Report (20 to 39 months)	4 cases	3	2
Hoogendam (9 years)	1 case	1	1
Maassen (mean 43 months)	93 cases	6	
Catinon (44 to 127 months)	18 cases	10 (non-specific) 17 (granuloma)	

It is acknowledged that there is overlap between Valle 2001 and the pre-hysterectomy study.

768 This is not a biostatistical analysis and there are limitations in the studies. However, on any reading of the above table and even accepting limitations on comparisons, control groups and generalisability, the following is evident from the available data:

(a) where there have been hysterectomies performed on Essure patients after more than 12 weeks (and even longer), a significant proportion of them still show 'chronic inflammation' on a pathological assessment;

(b) where more granular data is available, a significant proportion of patients also still show chronic inflammation to a moderate level;

(c) even if the Court were to accept that 'active' chronic inflammation only occurs in cases where there are neutrophils present, in studies where both acute and chronic inflammation were specifically recorded there are still a significant

proportion of cases in which both were present more than 12 weeks after device insertion (and even longer);

(d) where more granular data is available, a significant proportion of these cases also show acute and chronic inflammation to a moderate level.

Defendants

769 When properly construed, the histological studies do not support Robertson's central thesis that Essure causes persistent, pathologic chronic inflammation.

770 First, the simple presence of immune cells in tissue does not, without more, mean an active inflammatory response is occurring. The number and type of cells present in tissue will inform, but will not necessarily determine, an assessment of whether active inflammation is occurring at a particular time.[806] Other factors to be considered in this context include:

(a) clinical information about the patient, including age, medical history, surgical history, medication use, family medical history, imaging and lab results;

(b) a gross (macroscopic) examination of the tissue in question, which involves looking for visible pathologies such as tumours;

(c) the location of cells within tissue, and the relationships with other cells and other tissue structures. Relevant features include evidence of phagocytic activity, the presence of a pro-inflammatory stimulus and the spatial proximity of immune cells to the stimulus;

(d) whether test data is available indicating the presence of inflammatory markers.

For these reasons, it is important to have regard to control tissue when undertaking an analysis of immune cells to ascertain whether inflammatory processes are occurring in a sample, in order to determine whether there is a substantial excess of

806 SBM.500.001.0003_2 at 516.

cells above the numbers usually present. The presence of inflammatory cells at the site of an implanted medical device is part of the body's recognition that foreign material is present. Further, there are no criteria that can be rigidly applied to differentiate 'normal' from 'abnormal' in histopathology.

771 Second, 'inflammatory cells', 'acute inflammatory cells', and 'chronic inflammatory cells' are scientific terms that are frequently used in pathology (and other scientific) literature to describe particular kinds of immune cells. The evidence establishes that the use of these terms does not necessarily, without more, mean that the cells described are participating in an active inflammatory response.[807]

772 Third, the ways in which different study authors or scientists use these terms and the term 'inflammation', may vary. Murdock, Badylak and Sokol gave evidence that depending on the context, 'inflammation' may be used to describe either:

(a) the presence of particular cell types in tissue; or

(b) the presence of an active inflammatory response (but not necessarily an abnormal or pathologic one).

It is critical, when interpreting histopathological data, to understand the way in which the authors or investigators have used these terms. When authors and investigators fail to define the terms they use, it can be impossible to say with the requisite level of certainty whether the reported data in a study supports Turner's theories of causation.

773 The foreign body response to a biomaterial includes an inflammatory response that activates local fibroblasts which, together with accompanying fibrotic tissue, creates a barrier around the foreign body to prevent it further provoking the body's immune response.[808] The presence of foreign body giant cells and macrophages at the implantation site for the lifetime of the implanted device is consistent with a normal, resolved foreign body response. In this capacity, the cells are quiescent and their

807 Ibid at 518.
808 Ibid at 522.

presence is not evidence of ongoing or active inflammation.

774 There is no universally accepted or precise timeframe for wound healing. There are numerous factors that can affect the kinetics of a foreign body response to a biomaterial. These include host factors, such as the tissue site where the device is implanted, host immune status, health, age and comorbidities; and features of the device such as size, surface area, material and composition.[809]

Analysis

775 The Essure histological studies are evidence that immune cells are commonly present in the fallopian tubes adjacent to or in the vicinity of the Essure device more than three months after implantation. The pre-hysterectomy study shows that the presence of immune cells was relatively common at 12 to 16 weeks. Studies such as Maassen 2018 and Banet 2020 suggest that immune cells are less commonly found in the vicinity of the device as more time passes. In combination, the studies show that acute inflammation reduces more quickly than chronic inflammation.

776 There are a number of difficulties faced when attempting to draw further conclusions from the results of the Essure histological studies and other histological data.

777 First, the studies do not define the terms used to describe inflammation. On at least some occasions, terms such as 'acute inflammation' and 'chronic inflammation' appear to do no more than denote the presence of certain types of immune cells. The studies do not specify the number of cells in tissue required to meet the definition of 'inflammation', or to determine whether inflammation should be graded as 'mild', 'moderate' or 'severe'. Further, with the exception of the Essure 505 study, there is nothing in the studies to indicate whether matters such as the location, distribution and organisation of immune cells were relevant to whether the definition of 'inflammation' was met or to the grade attributed to it. In the pre-hysterectomy study, chronic inflammation was graphed at a mean of 2 for moderate (see [564]) but was

809 Ibid at 523.

described in the conclusion as a 'low level chronic inflammatory response'. Further, with the exception of the pre-hysterectomy study and the data from the PMA reports, there was no consistency in the description of inflammation between the studies. The difficulty in understanding what is meant by the terms used to describe inflammation in the studies is compounded by the different ways in which those terms can be used by immunologists and pathologists, depending on context.

778 Second, macrophages and infrequently neutrophils may be present in normal fallopian tube tissue. Further, macrophages and neutrophils are expected to be present in increased numbers as part of the foreign body response to implantation of biomedical devices such as Essure. It is important to keep in mind that in their evidence, the experts used 'chronic inflammation' to mean different things. Murdock, Sokol and Badylak said, in effect, that immune cells in tissue proximate to a device were part of the normal foreign body response, and may remain in the tissue long after the active inflammatory stage of the response had resolved. Those experts referred to the continued presence of increased numbers of macrophages close to a biomedical device as being part of the 'chronic inflammatory response' to the device.

779 I have accepted the evidence of Murdock, Sokol and Badylak that active, ongoing chronic inflammation cannot be diagnosed merely by the presence of certain immune cells. As Badylak said, there is no cut-off in the number of immune cells present in tissue between what is normal and what represents pathology, or a chronic wound. Murdock described diagnosis of pathologic chronic inflammation as a 'gestalt'.[810]

780 Third, studies such as Maassen 2018 and Banet 2020 did not include, as a control, histologic assessment of fallopian tube tissue from non-wearers of Essure. The failure to include assessment of control tissue made it more difficult to determine the significance of finding macrophages or neutrophils in tissue adjacent to the Essure device. It cannot be assumed that in every case where neutrophils and macrophages

[810] T3014 (TRA.500.031.0001_2 at 0088).

were found, their presence was related to the device.

781 Fourth is the question of the normal kinetics of the foreign body response to implantation of Essure. Robertson agreed that the kinetics of the foreign body response to implantation of a biomedical device can be affected by subjective factors including tissue site, immune status, age and comorbidities; and device features including size, surface area, material and composition. However, she rigidly maintained that the active inflammatory stage of the foreign body response to an implantable biomedical device should normally resolve by six weeks, and by a maximum of three months.

782 Sokol said 'that host and device factors can lead to widely disparate "normal" kinetics for wound healing that should be considered before speculating whether a foreign body response has failed or become stalled'.[811] Badylak agreed.

783 Turner relied on the agreement by Sokol and Badylak in the biomaterials and immunology conclaves and JERs concerning chronic wounds, chronic inflammation, and time for resolution of the foreign body response to Essure. That reliance was misplaced. On a fair reading of their evidence, Sokol and Badylak did not agree to an absolute time for resolution of a foreign body response to an implanted biomedical device beyond which active inflammation in the vicinity of the device would be considered pathologic and harmful to health. Murdock gave evidence to a similar effect.

784 A possibility that arises from the histological studies and expert evidence is that at least in some women, the kinetics of the foreign body response to Essure mean that it will take longer than three months to resolve. The discussions in Maassen 2018 and Banet 2020 may support this possibility. I accept Sokol's evidence about the disparate 'normal' kinetics or the foreign body response to biomedical devices. This means that it cannot be assumed that where an active inflammatory response is present more than

811 Immunology JER at 3 (EXP.500.001.0004).

three months after implantation of Essure, it reflects a failed or stalled foreign body response to the device and is therefore pathologic chronic inflammation.

785 Fifth, there are no features or hallmarks identified in the pre-hysterectomy study, annual PMA reports or Essure 505 study that point strongly towards the presence of pathologic ongoing chronic inflammation. Turner has not established that the granulomas found in Hoogendam 2020 were causally related to Essure, or that the granulomas reported in Catinon 2022 were associated with current active inflammation. None of the features of pathologic chronic inflammation or a chronic wound referred to by the experts were reported in the studies. A history of pain is recorded in the case of some study participants. However, the evidence does not establish a relationship between the history of pain and an identified presence of inflammation. The routine laboratory tests that Sokol said could be used to assess even low levels of chronic inflammation were not performed.

786 Neutrophils are a surrogate for the presence of active inflammation. Neutrophils were identified as being present more than three months after Essure implantation in a number of cases from the pre-hysterectomy study, for the first patient in the annual PMA report, and in some of the cases reported in Banet 2020. In some of these cases the presence of neutrophils may have been causally related to the Essure devices. The studies show a trend of reducing acute inflammation over time. There is very little information in the studies about the number, location, distribution or organisation of cells where the presence of neutrophils was identified. In the circumstances, it is not possible to conclude that in every case where residual neutrophils were identified as being present there was an ongoing active inflammatory response to Essure. Further, the presence of neutrophils or macrophages in tissue adjacent to Essure devices months, and in some cases years, after implantation does not, without more, establish an ongoing pathologic chronic inflammatory response to Essure.

XIII. CORROSION

787 It was not disputed that implanted Essure devices corroded and leached metal ions and particles. The degree to which the different constituent metals of the device corroded, and whether the corrosion caused any of the pleaded inherent defects, failure defects and adverse events, was in issue.

788 Turner alleged first that corrosion of metals from implanted devices was a cause of ongoing chronic inflammation experienced by some women and that this resulted in adverse events, in particular CPP and AUB.

789 Second, Turner alleged that metal corrosion, either alone or together with movement and fatigue, increased the risk of breakage and fragmentation of the device. Turner alleged that if the device broke or fragmented, there was a risk it would cause adverse events including damage to internal organs, CPP and AUB, directly or via ongoing chronic inflammation.

790 Third, Turner alleged that the component metals of the device (nickel in particular) caused an allergic reaction in some women. The defendants accepted that some women implanted with Essure suffered a DTHR to nickel from the nitinol outer coil. The defendants submitted that the proportion of women who suffered DTHR as a result of Essure was 'vanishingly small', that the condition was amenable to treatment and that they had given a reasonable and appropriate warning of the potential occurrence of this adverse outcome.

791 The defendants submitted that, apart from rare cases of DTHR, Turner had not established that corrosion occurred at a harmful level, or that it caused ongoing chronic inflammation, pelvic pain or AUB.

792 The defendants argued that there was no evidence that corrosion, movement or fatigue caused devices to break or fragment in vivo.[812]

793 I will deal with the issue of corrosion as follows. First, I will set out some definitions

812 SBM.500.001.0003_2 at 767 [4.66].

and other matters that the experts largely agreed on.

794 Second, I will describe the tests used to assess biomedical device corrosion, those being the immersion bench test and the potentiodynamic cyclic polarisation test. I will also say something about testing standards for biomedical device corrosion and safety levels for relevant metals.

795 Third, I will deal with the corrosion bench test conducted by Conceptus ('corrosion bench test') and potentiodynamic testing performed by an organisation engaged by Conceptus in 2012 ('potentiodynamic test'). Turner alleged that the corrosion bench test was inadequate but still demonstrated significant corrosion, and that Essure did not meet acceptance criteria in the potentiodynamic test. The defendants argued that the corrosion bench test was the 'gold standard' test for biomedical devices, and that Essure satisfied reasonable and appropriate acceptance criteria for subsequent approval by the FDA. The defendants submitted that, having regard to the more rigorous corrosion bench test and FDA guidance at the time of the PMA application, it was unnecessary for Conceptus to undertake potentiodynamic testing at that time, and that the results of the potentiodynamic test raised no concerns about the clinical performance of the device.[813]

796 Fourth, I will consider five studies conducted since 2020 that involve assessment of fallopian tube tissue and, in two of the studies, peritoneal fluid, in order to investigate corrosion; and a sixth study that involved in vitro corrosion assessment of Essure:

(a) 'Potential release of toxic metal elements from Essure device in symptomatic patients: First results of the French Ablimco cohort' by François Parant et al ('Parant 2020');[814]

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813 Ibid at 731, 273.

814 François Parant et al, 'Potential release of toxic metal elements from Essure device in symptomatic patients: First results of the French Ablimco cohort' (2020) 252 (September) *European Journal of Obstetrics & Gynecology and Reproductive Biology* 434 (PUB.001.001.3197) ('Parant 2020').

(b) 'Release of metal elements from the Essure implant: A prospective cohort study' by François Parant et al ('Parant 2022');[815]

(c) 'Identification of inorganic particles resulting from degradation of ESSURE implants: Study of 10 cases' by Mickaël Catinon et al ('Catinon 2020');[816]

(d) Catinon 2022, discussed in the previous Chapter of these reasons;

(e) 'In Vitro Corrosion Assessment of the Essure® Medical Device in Saline, Simulated Inflammatory Solution and Neutral Buffered Formalin' by Can Aslan and Jeremy L Gilbert ('Aslan 2022');[817] and

(f) 'Retrieval Analysis of the Essure® Micro Insert Female Sterilisation Implant: Methods for Metal Ion and Microscopic Analysis' by Charley Goodwin et al ('Goodwin 2023').[818]

797 Fifth, I will analyse the evidence and set out relevant conclusions.

Essure composition

798 The metal components of Essure comprise different alloys set out at [35] above. An alloy is a mixture of component metallic elements. For example, stainless steel is comprised of iron (Fe), chromium (Cr), and nickel (Ni). Nitinol ('NiTi') is comprised of nickel and titanium (Ti). The material composition of Essure components are set out in more detail in the following table:[819]

Table 2. Material composition of components in the Essure ESS205 and ESS305 micro-

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815 François Parant et al, 'Release of metal elements from the Essure implant: A prospective cohort study' (2022) 273 (June) *European Journal of Obstetrics & Gynecology and Reproductive Biology* 20 (PUB.500.001.0362) ('Parant 2022').

816 Mickaël Catinon et al, 'Identification of inorganic particles resulting from degradation of ESSURE implants: Study of 10 cases' (2020) 250 (July) *European Journal of Obstetrics & Gynecology and Reproductive Biology* 162 (CB) (PUB.001.001.3757) ('Catinon 2020').

817 Can Aslan and Jeremy L Gilbert, 'In Vitro Corrosion Assessment of the Essure® Medical Device in Saline, Simulated Inflammatory Solution and Neutral Buffered Formalin' (2022) 147 (July) *Acta Biomaterialia* 414 (PUB.500.001.0506) ('Aslan 2022').

818 Charley Goodwin, Can Aslan and Jeremy L Gilbert, 'Retrieval Analysis of the Essure® Micro Insert Female Sterilisation Implant: Methods for Metal Ion and Microscopic Analysis' (2023) 162 (May) *Acta Biomaterialia* 312 (MSC.001.002.0013) ('Goodwin 2023').

819 Eiselstein at 28 (EXP.001.002.0004).

insert (Conceptus 2007c).

Component	Specification No.		Raw Material	Composition (in wt% where applicable)	Current Design	Proposed Design
	Current (ESS205)	Proposed (ESS305)				
Micro-Insert Subassembly						
	101029-01	101454-01				
Inner Coil	100734	100734	Stainless steel round wire	Type 316LVM	Yes	Same
Outer Coil	100776	100776	Nickel-Titanium Ribbon	Ni: 55.3-56.3 / Cr: 0.25 / Ti: Balance	Yes	Same
Platinum Band	100769	100769	Platinum/Iridium	Pt: 90 / Ir: 10, 0.0256" OD	Yes	Same
Platinum Band	100777	100777	Platinum/Iridium	Pt: 90 / Ir: 10, 0.026" OD	Yes	Same
Platinum Band	100814	n/a	Platinum/Iridium	Pt: 90 / Ir: 10, 0.031" OD	Yes	n/a
Platinum Band	n/a	101408	Platinum/Iridium	Pt: 90 / Ir: 10, 0.027" OD	n/a	Yes
Pt/Ir Ribbon	100967	n/a	Platinum/Iridium	Pt: 90 / Ir: 10	Yes	n/a
Thread Coil	100781	n/a	Stainless Steel	Type 316L Medical Grade	Yes	n/a
Ball Tip	101029-02	n/a	Stainless Steel	Type 316LVM	Yes	n/a
	Alt.100713	100713	Tin/ Silver Solder	Sn: 95 / Ag: 5	Alternate	Same
Solder, Neutralizer, Flux	100713, 100763, E2114	100713, 100763, E2114	Tin/ Silver Solder	Sn: 95 / Ag: 5	Yes	Same
Fiber	100913	100913	PET	Polyethylene Terephthalate (PET)	Yes	Same
Sulphamic Acid, Hydrogen peroxide, Neutralizer	100809, 100810, 100932	100809, 100810, 100932	Acid, H_20_2, detergent, $NaHCO_3$	Sulphamic acid (pickling solution Ti-121 or ETSER-07), hydrogen peroxide 30%, powdered detergent, sodium bicarbonate	Yes	Same

Eiselstein said that approximately 94% of the metallic surface area of the device is made up of stainless steel and nitinol, with the remaining 6% made up of platinum/iridium and tin/silver solder.

799 The following table sets out the mass and surface area of the device components:[820]

Table 3. Surface area and volume of metallic materials in the ESS305 micro-insert for one Essure Device.

Component	Material	Mass (mg)	Surface Area (cm^2)	Percentage of Total Surface Area (%)
Outer Coil	Nitinol (NiTi)	8.7	1.14	45.8
Inner Coil	Stainless Steel	31.3	1.20	48.2
Solder Bond	Tin-Silver (Sn-Ag)	1.9	0.038	1.5
Positioning Marker (Inner Coil Proximal Band)	Platinum / Iridium (Pt-Ir)	8.6 (total)	0.045	1.8
Half Band	Platinum / Iridium		0.067	2.7
		50.5	**2.49**	**100.0**

820 Ibid at 29.

316LVM stainless steel

800 Eiselstein said that 316L remains the most widely used stainless steel for implantable biomedical devices. He said that the spontaneous formation of a passive, chromium-rich oxide surface film protects against corrosion and gives the steel its 'stainless' characteristic. He said that 316LVM stainless steel has been vacuum arc re-melted to maximise its corrosion resistance. Biomedical device applications for stainless steel include bone screws and pins, cardiovascular stents, neurosurgical aneurysm and microvascular clips, and IUDs. Chrzanowski agreed that 316L stainless steel demonstrates good corrosion resistance and is regularly used in biomedical applications.

Nitinol

801 Nickel titanium alloys have had medical application since the 1980s. Nitinol has been used in the manufacture of cardiovascular stents and endodontic wires and drills because of its super elasticity and shape memory. Chrzanowski said that nitinol has good corrosion resistance which is comparable with stainless steel. Eiselstein agreed that nitinol exhibits good biocompatibility and corrosion resistance in vivo. He said that like stainless steel, nitinol owes its biocompatibility and corrosion performance to the spontaneous formation of a passive titanium-rich oxide layer.[821]

802 Chrzanowski put the following caveat on the biocompatibility of nitinol:

> … [I]ts corrosion resistance is highly sensitive to material impurities and to the nature and integrity of the oxide that is created by surface processing. NiTi characterises with good fatigue behaviours, however it is highly complex process with performance influenced by a wide range of material and test variables. Fatigue behaviour of NiTi has become even more important in recent years, given the increased occurrence of peripheral cardiovascular stent fractures. This subject is particularly important in the field of implants, where the influence of multiaxial loading is present.[822]

Chrzanowski said that multiaxial loading occurs when forces are applied to a material in the directions of the three coordinate axes. He said that in the human body, those forces could stem from movements, muscle tension, gravitational forces, and the

821 Ibid at 34 [5.3.7].
822 Chrzanowski at 11 (EXP.001.001.0082).

pulsative flow of blood and body fluids.[823]

803 Eiselstein did not agree with Chrzanowski's opinion about the susceptibility of nitinol to material impurities and fatigue.

Tin-Silver solder

804 The experts agreed that tin is considered non-toxic.[824]

Key definitions

Leach

805 The biomaterial experts agreed that leaching occurs when, by way of solvent, a molecule becomes detached or extracted from its carrier substance.[825] In the context of implanted biomaterials such as Essure, the solvent is interstitial fluid within the local environment. Leaching is dependent on factors including fluid movement, porosity of the implant/device, pH level, temperature and chemical composition. Leaching from a metal medical device involves metal ion release.

Corrosion

806 Chrzanowski and Eiselstein agreed that in the areas of corrosion science, electrochemistry and medical devices, corrosion may be defined as 'the chemical or electrochemical reaction between a material, usually a metal, and its environment that produces a deterioration of the material and its properties'.[826] The experts agreed that corrosion occurs to some extent in all medical devices 'but the extent of the corrosion depends on the materials used (and their combination) and their surface preparation'.

807 Eiselstein said that corrosion refers to the release of an atom from a metallic state into an ionic state. However, the atom may stay on the oxide surface of the material. Leaching refers to release of the atom from the oxide surface into solution.[827]

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823 Ibid.
824 Biomaterials JER at 14 (EXP.500.001.0006).
825 Ibid at 7.
826 Ibid at 6.
827 T3277 (TRA.500.033.0001_2 at 0120).

808 Chrzanowski said that the resulting final biological effects of corrosion depend on factors including its extent, tissue injury, inflammation and mechanical loads. He said that in contrast to Essure, 'the majority (if not all) long-term metal implants have surfaces modified to minimise corrosion and modulate tissue responses'.[828] Eiselstein agreed that surface modifications and treatments can potentially provide more corrosion resistance and minimise metal ion release rates.[829] He said that while the specific details of Essure are not available, it appeared to him that the surface of each of the alloys used in the device was treated.

Galvanic corrosion

809 Eiselstein and Chrzanowski agreed on the following definition of galvanic corrosion:

> [G]alvanic corrosion occurs when a metal or alloy is electrically coupled to another metal in the same electrolyte. The galvanic series is an arrangement of alloys according to their potentials measured in a specific electrolyte. The galvanic series allows one to determine which alloy in a galvanic couple is more "active" and likely to undergo an increase in corrosion rate. Examples of active alloys are carbon steel, magnesium, and zinc and examples whereas alloys such as stainless steel, nitinol, titanium, silver, gold and platinum are considered least active or more "noble".[830]

Metal release

810 Chrzanowski and Eiselstein agreed that metal release can refer to the release of metal particles by, for instance, wear or fretting, or to the release of metal ions by leaching or corrosion.

Local toxicity

811 Robertson, Chrzanowski and Badylak agreed that local toxicity describes the adverse effects of a medical device on a range of cells or tissues within its immediate vicinity. They agreed that this may be caused by a bacterial infection, toxic chemical, or the release of metal particles, metal ions, polymers or other non-metal components from the device.[831] They agreed that:

> These components can result in cell death or damage, and/or activation and

828 Biomaterials JER at 6 (EXP.500.001.0006).
829 T4359 (TRA.500.043.0001_2 at 0077).
830 Biomaterials JER at 6-7 (EXP.500.001.0006).
831 Ibid at 7.

> perpetuation of inflammatory responses in the vicinity of a device. The term contrasts with 'systemic' toxicity, which describes the effects of materials released from a device on organs and tissues at distant sites in the body from the device.[832]

Delayed-type hypersensitivity reaction

812 In the biomaterials JER, Robertson, Badylak and Chrzanowski agreed:

> … that a hypersensitivity reaction is a harmful immune response against a foreign entity (antigen) that is encountered in the body by skin contact, ingestion, by implantation of a medical device, or by other methods of exposure.[833]

They agreed that:

> Hypersensitivity involves cells of the adaptive immune response (specifically T cells and B cells) that must be 'primed' by pro-inflammatory macrophages and/or dendritic cells to become activated and proliferate. In the context of a medical device, a hypersensitivity reaction can be generated against metal ions such as nickel, chromium or tin that are leached from the device. The ions form haptens with tissue proteins in the vicinity of the device, that then are recognised by previously primed T cells and 330 antibodies. This recurrent exposure results in activation of mast cells that release histamine to elicit local inflammation at the site of antigen reencounter (causing swelling, redness, pain and itching). A hypersensitivity reaction can be 'delayed-type' or 'immediate-type'. The reaction may occur in the same site of antigen priming, or in a different tissue site (eg. skin) depending on where antigen reencounter occurs.[834]

813 In the immunology JER, Robertson and Sokol agreed that a hypersensitivity reaction to Essure and/or its components, for example nickel, could cause chronic or persistent chronic inflammation.[835] They agreed:

> We agree that nickel hypersensitivity is a delayed type hypersensitivity reaction mediated by T cells that are specific and respond to nickel ions bound to a variety of proteins (haptens). This commonly manifests as contact dermatitis, which presents several hours to days after exposure to a chemical or metal that is applied to the skin. As well as contact dermatitis, we agree that nickel hypersensitivity can manifest in other tissues of the body including mucosal surfaces. This reaction can also be induced by exposure to nickel ions in sites other than the skin, including for example joints and other mucosal surfaces.[836]

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832 Ibid.
833 Ibid.
834 Ibid (citations omitted).
835 Immunology JER at 16 (EXP.500.001.0004).
836 Ibid at 23.

814 Robertson and Sokol differentiated between sensitisation and a DTHR:

> We agree that sensitization and delayed type hypersensitivity, or hypersensitivity, responses are different. Nickel sensitization is marked by the presence of immune cells specific to nickel (as noted by positive patch testing or lymphocyte transformation test) in the absence of clinical reactivity (e.g., absence of nickel related rashes after exposure). Nickel allergy describes the delayed type hypersensitivity reaction to nickel and is marked by evidence of that reaction in response to nickel exposure.[837]

Robertson and Sokol differed about whether systemic contact dermatitis was a central clinical manifestation of delayed type hypersensitivity.

Corrosion tests

Immersion bench test

815 An immersion bench test is an in vitro test to determine the leaching/corrosion rate of a metallic object. The object is placed in a solution designed to replicate its intended in vivo environment. At intervals throughout the test period, the solution is examined to determine the leaching/corrosion rate. The object may also be examined for signs of corrosion after the test concludes.

Potentiodynamic cyclic polarisation test

816 A potentiodynamic cyclic polarisation test is an accelerated in vitro test of the susceptibility of a metallic object to corrosion. The test involves rapidly increasing the electrical potential of a solution within which the object is placed to stimulate corrosion, and then reducing the electrical potential to observe how the object re-passivates. Relevant parameters include the 'rest potential' of the object in solution before increasing the electrical potential ('E_r'); the corrosion commencement point, known as the 'breakdown' or 'pitting potential' ('E_b'); and the point at which corrosion ceases and active corrosion pits re-passivate, known as the 're-passivation' or 'protection potential' ('E_p').[838] The following schematic shows some possible test outcomes:[839]

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837 Ibid at 24.
838 Eiselstein at 10 (EXP.001.002.0004).
839 Ibid at 41.

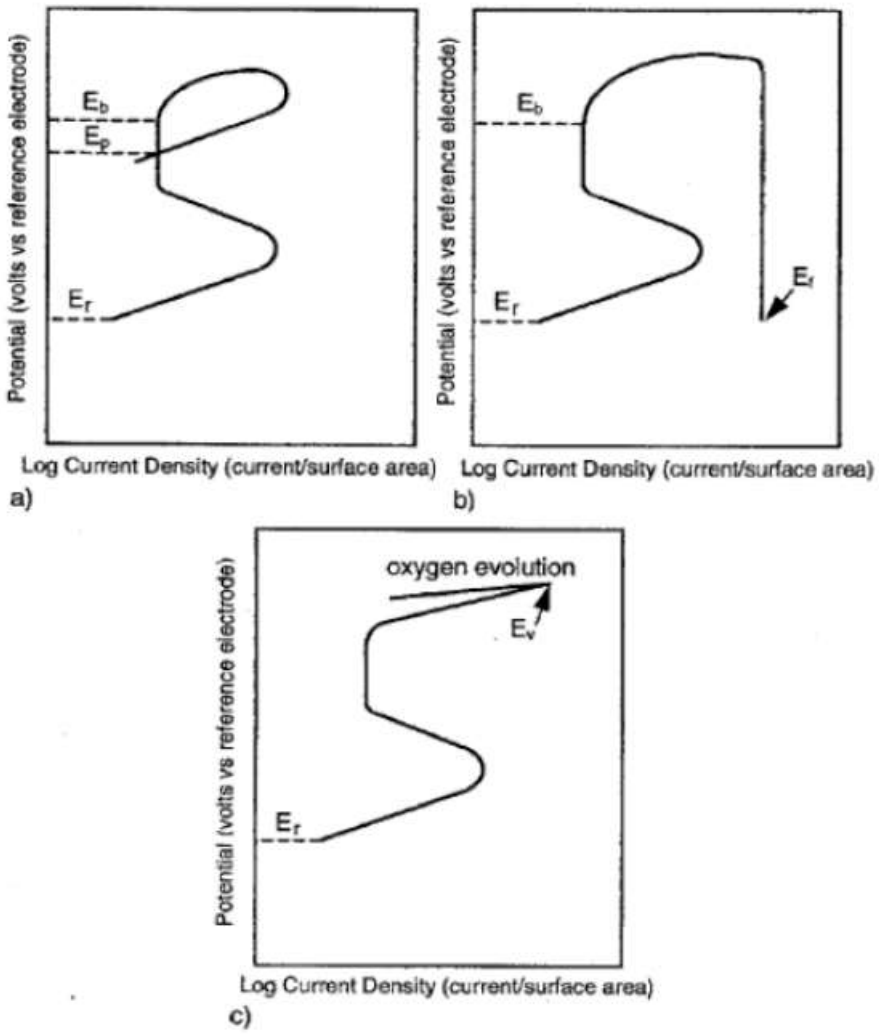

Figure 8. Schematic of cyclic potentiodynamic curves illustrating corrosion parameters: (a) material that exhibits a protection potential (E_b and E_p), (b) material that does not exhibit a protection potential (E_p), and (c) material that exhibits oxygen evolution at its surface but no breakdown or pitting (ASTM 2019A).

The hysteresis curve between E_b and E_p shown in Figure 8(a) above provides information about corrosion degree and susceptibility. A device is very susceptible to corrosion if, when the electrical potential is reversed, a re-passivation potential is not shown before reaching E_r (Figure 8(b)).

Relevant standards for implantable devices

817 ASTM develops standards for characteristics and performance of materials, products, systems and services in the US.

818 'ISO standards' are international standards for implant materials and devices developed by the International Standards Organisation.

ASTM F2129

819 ATSM F2129 is a standard method for conducting potentiodynamic testing to determine the corrosion susceptibility of small implantable devices. The standard was first released in 2001 and was preceded by standard ASTM F746.

820 Potentiodynamic testing is commonly performed in phosphate-buffered saline ('PBS'). The standard mandates that potentiodynamic curves be maintained in de-aeriated solution.[840]

821 The standard does not provide acceptance criteria. Eiselstein said that there are three general acceptance criteria methodologies:

(a) corrosion resistance of the device being tested should be similar to, or better than, approved devices with no known corrosion problems currently on the market;

(b) the E_b of the device should be greater than some threshold value, independent of the material used for the implant; or

(c) evaluating the margin for safety against corrosion as the difference between E_b and E_r.

Eiselstein said he favoured the approach in (c) above. He said that there is a large margin of safety against pitting if, in vivo, E_r is much lower than the pitting potential (E_b) of the device. However, if E_b minus E_r is nearly zero or negative, then the device will most likely pit when exposed to that in vivo environment.[841]

822 Eiselstein noted research which indicated that long-term exposure to oxygenated blood in vivo can increase the rest potential of nitinol by as much as 150 millivolts (mV), but that its E_b appears to be relatively unaffected. He said that for this reason, he adopts a safety margin of $E_b - E_r$ being greater than 200 mV.[842]

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840 Ibid at 44 [6.20].
841 Ibid at 45 [6.25].
842 Ibid at 47 [6.28.2].

ASTM F3306

823 ASTM F3306, first published in 2019, is a standard method for conducting an immersion bench test by exposing a device to solutions which stimulate the in vivo environment and temperature in a container for a predetermined timeframe, with regular sampling at various intervals.[843] There was no equivalent standard before 2019. There is no settled acceptance criteria or test duration, although the standard notes the FDA recommendation that testing be conducted for at least 60 days for devices containing nickel-rich alloys.

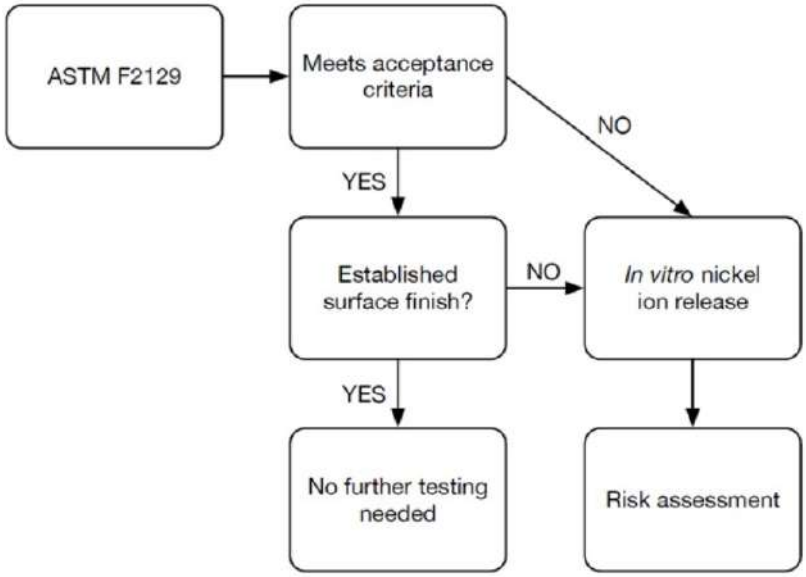
ISO-10993

824 ISO-10993 is a standard to identify and quantify degradation products from metals and alloys in medical devices. Providing it can be justified by the function of the medical device, the standard allows for either electrochemical polarisation testing or immersion testing.

FDA 2015a and 2019e

825 Released by the FDA in 2015 and 2019 respectively, FDA standards 2015a and 2019e address corrosion testing for implanted devices with nickel-rich alloy components, including nitinol and stainless steel. The following flowchart documents the 2019e testing approach:[844]

843 Ibid at 47 [6.29].
844 Ibid at 52 [6.47].



FDA 2015a provided a similar flowchart. 'In vitro nickel ion release' is a reference to immersion bench testing.

Acceptable metal ion release rates

826 Eiselstein said that there were no FDA guidelines in the early 2000s for the acceptable nickel release rate from a biomedical device. He said that the current FDA guidance recommends comparing the amount of nickel released from a device with a tolerable intake ('TI') value. This is defined as an 'estimate of the average daily intake of a substance over a specified time period, on the basis of body mass, that is considered to be without appreciable harm to health'.[845] He said:

> CDRH recommends a TI value for parenteral (non-oral) exposure to nickel of 0.5 µg/kg/day (e.g., 35 µg/day for a 70 kg adult) to minimize adverse systemic effects (excluding hypersensitivity) that may occur following prolonged or permanent patient exposure to nickel released from a nickel-containing device. … CDRH also notes that it is important to understand that the TI values are not intended to be protective for local effects (e.g., necrosis, inflammation, irritation) that may result from nickel release from an implant into tissues surrounding the implant.[846]

827 Eiselstein said, in relation to the issue of nickel hypersensitivity:

> Since there is no known lower limit on the amount of nickel that can elicit allergic reactions in some patients, it is not possible to derive a hypersensitivity-based TI for nickel released from Nitinol (FDA 2020e). The

845 Ibid at 63 [6.86].
846 Ibid at 63 [6.87].

> FDA recommends that the risk of potential allergic reaction to nickel be mitigated through labeling for Nitinol-containing devices. Specifically, the FDA recommends that the labeling include a warning for prolonged and permanent contacting devices.[847]

828 Eiselstein said the acceptable parenteral exposure to tin advised by the FDA is 640 µg per day.[848]

Expert evidence on corrosion testing

Acceptance criteria

829 Acceptance criteria are pre-determined criteria used to assess whether a corrosion test outcome meets an acceptable level. Chrzanowski and Eiselstein did not agree on the appropriate acceptance criteria for either the corrosion bench test or the potentiodynamic test for Essure.

Chrzanowski

830 Chrzanowski said that potentiodynamic testing allows evaluation of susceptibility to pitting corrosion, crevice corrosion, fretting corrosion or stress corrosion of a device. It provides an understanding of whether the device has a tendency to corrode in a specific environment and what that corrosion process is, thus informing design. He said that the hysteresis curve provides some information about the level of corrosion.[849]

831 Chrzanowski said that he usually uses potentiodynamic and immersion bench tests complementarily. He said that the immersion bench test provides information about the degree to which metal ions were actually eluted into the test solution, and that the potentiodynamic test provides information about what kind of corrosion may occur for a particular device.[850] He said:

> They should be around at the same time because one measures the amount of metal ions and the second one tells you what processes are happening and it is [an] accelerated test which tells you whether your material is prone to a specific type of corrosion and what the process

847 Ibid at 63 [6.89].
848 Ibid at 63 [7.2].
849 T3219 (TRA.500.033.0001_2 at 0062).
850 T3226 (TRA.500.033.0001_2 at 0069).

looks like.[851]

Chrzanowski did not agree that the immersion test was more useful. It was put to him:

> And the potentiodynamic testing does not relate to the in vivo performance, it provides the reaction to increased voltages that are applied to the solution?---These voltages are existing in our body, that's why it's of relevance. … But it's [an] accelerated test and this is a test which allows us to understand the physical chemical behaviours of the material in the environment, in this particular case the environment which is electropositive.[852]

832 Chrzanowski agreed that the standards provided for a range of different tests for metal ion release, but said it was a manufacturer's responsibility to select appropriate tests and make informed decisions to mitigate risks associated with devices.[853]

833 It was put to Chrzanowski that the FDA guidance was that an immersion bench test should be performed on a medical device if it does not meet the acceptance criteria for potentiodynamic testing. He said that he did not understand why progression to immersion bench testing would be allowed if those criteria were not met.

834 Chrzanowski said that for the immersion bench test, it is important to simulate the biological system, meaning that the test solution is critical. He said that in his practice, both inorganic and biological components are used to mimic the environment in vivo because of their potential impact on corrosion.[854] He said that other important factors are the length of the study and whether oxygen and/or nitrogen are included in the solution. He said that it is necessary to consider whether the solution should replicate the changed pH of a diseased or pathological state.[855]

Eiselstein

835 Eiselstein agreed that potentiodynamic testing is directed towards corrosion

851 T3258 (TRA.500.033.0001_2 at 0101_23-28).
852 T3271 (TRA.500.033.0001_2 at 0114_20-31).
853 T3256 (TRA.500.033.0001_2 at 0099).
854 T3224 (TRA.500.033.0001_2 at 0067).
855 T3225 (TRA.500.033.0001_2 at 0068).

susceptibility,[856] while immersion bench testing quantitatively measures the amount of corrosion in particular circumstances and more closely mimics reality. He said that while potentiodynamic testing tests a device to failure, this does not mean the device will fail in reality.

836 Eiselstein estimated that he had performed over 1000 potentiodynamic tests. He said that the test assists comparison of new and current devices. He said that device manufacturers find the tests helpful in choosing manufacturing processes, particularly when considering alternate manufacturing steps, surface conditions or treatments, but that the guidance provided by the test is limited to this.

837 Eiselstein said that the re-passivation potential of a metal device was very difficult to determine using the ASTM F2129 test. He said this was because in that test, the electrical current is reversed at a potential extreme enough to create a hole in the passive layer of the device. This means that once the material returns to E_p, the corrosion 'will have eaten halfway through' it, making it very difficult to re-passivate. He agreed that review of potentiodynamic test results required expertise. He said that the key question was the difference between E_b and E_r. If they were too close, the investigator might want to adjust the process with methods including surface modification.

838 Eiselstein agreed that an immersion test does not determine the re-passivation potential of a metal device.[857] He said, however, that a device will not pit in vivo if there is no pitting during an immersion test, such that the re-passivation potential is not a concern.

839 Eiselstein agreed that ASTM F746[858] preceded ASTM F2129, and was in place from 1999. He agreed that ASTM F746 stated that '[m]ost candidate materials for modern implants cannot be differentiated or screened for corrosion by simple conventional

856 T3294 (TRA.500.034_0001_2 at 0008).
857 T3315 (TRA.500.034_0001_2 at 0029).
858 PUB.001.001.4099.

immersion testing', and that this recognised that immersion testing alone may not be sufficient.[859] He agreed that ASTM F746 stated:

> 'For instance, if candidate alloy is placed in a relevant solution such as blood, salt water, saliva or mild acid for ten years, less than 0.1 per cent weight change would occur during that entire period. Therefore to screen candidate materials in a reasonable period, corrosion processes must be promoted or accelerated in some way. …'[860]

It was put to him:

> You accept, don't you, that this paragraph is saying that … when concerned with the long-term it may be preferable or it should be preferable to use accelerated testing, correct?---To me the key point is to screen candidate materials but it's saying that this is a quick and easy way to screen materials with respect to accelerated corrosion and I certainly agree with that. …
>
> It's also saying, in effect, that an immersion test may not capture the long-term corrosion behaviour of a particular metal alloy if, for instance, placed somewhere in the body for 10 years?---I think that's a fair reading of it. I'm not sure I necessarily agree with it.[861]

840 He agreed that ASTM F746 was concerned with capturing long-term change, and in this context stated that electrochemical stimulation may be used to accelerate the corrosion process.[862] He said that an issue with potentiodynamic testing is whether acceleration is appropriately performed with respect to the relevant device. He said that '[y]ou can always break things with accelerated tests', and that the question was whether you were accelerating corrosion beyond the service conditions that will apply.[863]

Conceptus corrosion tests

841 Conceptus conducted an immersion bench test of Essure in 2001 (the corrosion bench test) and a potentiodynamic test in 2012.

842 Chrzanowski argued that the corrosion bench test was insufficient, and that

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859 T3340 (TRA.500.034_0001_2 at 0054_20-24).
860 T3340-1 (TRA.500.034_0001_2 at 0054_31-0055_4).
861 T3342-3 (TRA.500.034.0001_2 at 0056_24-0057-16).
862 T3342 (TRA.500.034.0001_2 at 0056).
863 Ibid.

potentiodynamic testing should have been performed before Essure was made commercially available. He said that the potentiodynamic test outcomes were unsatisfactory and demonstrated that Essure was susceptible to harmful corrosion levels.

843 Eiselstein said that the tests conducted by Conceptus were amazingly similar to the ASTM F3306 standard, even though they were conducted 15 years before that standard came into effect. He said that metal release testing (being the corrosion bench test) provides much more sensitive information than potentiodynamic testing, meaning that release rates for incredibly low metal concentrations can be calculated to a very fine level. [864]

844 Eiselstein said that Conceptus did more testing than was normally required at the time. He did not agree with Chrzanowski that potentiodynamic testing should have been done before Essure was commercially supplied.[865] He said that the ASTM F2129 is the low bar, and that long-term metal release rate testing is the gold standard.[866] He said that potentiodynamic testing of Essure would probably not provide any information other than the fact that there is dissolving tin.

Corrosion bench test

845 As outlined in Chapter X of these reasons, Conceptus conducted the corrosion bench test of Essure as part of its FDA PMA application. The corrosion bench test involved placing 48 Essure devices in vials of a physiological saline solution at 37°C for three months. Two inserts were placed in each vial. The pH of the solution was buffered to a level between 6.0 and 7.0.[867]

846 At each of five time points — one week, two weeks, one month, two months and three months — the samples in three vials were removed from the study for destructive analysis. The solution in each vial was analysed for levels of chromium, tin and nickel.

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864 T3282 (TRA.500.033.0001_2 at 0125).
865 T3310 (TRA.500.034.0001_2 at 0024).
866 T3313 (TRA.500.034.0001_2 at 0027).
867 BAY-JCCP-0616252 at 40.

The devices were cleaned and examined using scanning electron microscope ('SEM') imaging.

847 At the same time points, the solution in a further six vials was removed for analysis, after which the devices were cleaned and new solution was added to the vials.

848 The remaining six samples were placed in three vials without solution as controls.

849 Conceptus recorded the results of the corrosion bench test as follows:

> Results: The levels of Nickel, Chromium, and Tin ions released into the solution were found to be at least 2000x below the EPA average levels of human intake of these ions from diet and the environment. No Micro-inserts showed loss of mechanical integrity. As expected, the solder showed signs of corrosion resulting in surface pitting and increasing porosity. All the other components appeared unaffected by corrosion.[868]

The authors concluded that the potentially harmful metal ions released from the device posed 'no more danger to the woman than everyday intake of food and water and exposure to the environment'.[869] The authors described some 'minor pitting and porosity' of the solder that did not affect mechanical integrity and hence was not of concern. The authors noted that the test solution was potentially more corrosive than the in vivo environment.

850 The corrosion bench test outcomes were summarised as follows:

> • The Essure Micro-insert passes the corrosion susceptibility bench test.
>
> • 54 Essure Micro-inserts were tested for up to six months in a worst-case bench environment.
>
> • The daily leaching rate of nickel and tin ions released are at least 2000 times less than everyday intake of food and water and exposure to environment.
>
> • The daily leaching rate of chromium is below the detection limit.
>
> • The Essure Micro-insert maintained mechanical integrity during the six months of exposure to a corrosive saline environment.[870]

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868 Ibid at 116.
869 Ibid.
870 Ibid at 218.

851 On examination for signs of corrosion, the study reported:

> As expected, the solder showed signs of corrosion resulting in pitting and increasing porosity with the worst corrosion damage on the ball tip. At the three-month time point, approximately 25-50% of the solder had corroded. At the six-month time point, the ball tips of some of the samples were almost completely corroded, but all of the solder bonds continued to hold together. In all cases, the outer coil remained attached to the fibered inner coil. This is an acceptable level of solder corrosion, because it did not result in the loss of mechanical integrity. No other components showed signs of corrosion.[871]

852 The acceptance criteria for the test were set as follows:

> **8.1 Leaching Rate of Nickel**
>
> The leaching rate of nickel ions from the samples must be lower than the average levels of human intake of nickel from diet and the environment.
>
> **8.2 Mechanical Integrity**
>
> The Micro-inserts must maintain mechanical integrity for at least three months. That is, each Micro-insert must still be in one piece after exposure to a corrosive saline environment for three months. In particular, the fibered inner coil must remain attached to the outer coil.[872]

853 The leaching rates were tabulated as follows (citations omitted):[873]

Metal	Normal Human Daily Intake	Highest Measured Leaching Rates
Nickel	300 µg/day	0.14 µg/day
Tin	100,000 µg/day	27 µg/day
Chromium	no published data is available	less than 0.03 µg/day (below detection limit)

854 An example of a more granular analysis of leaching rates over time was set out in Table 3 of the study:[874]

Table 3: Cumulative Simulated Environment (A Samples)

Sample #	Time in Saline (days)	Nickel (µg/day)	Chromium (µg/day	Tin (µg/day)

871 Ibid at 228-9.
872 Ibid at 224.
873 Ibid at 225.
874 Ibid at 232.

A-1-a	7	0.03	<0.03	4.2
A-1-b	7	0.13	<0.03	23
A-1-c	7	0.057	<0.03	6.9
Average per vial		*0.07*	*0.03*	*11*
A-2-a	14	0.066	<0.01	11
A-2-b	14	0.046	<0.01	17
A-2-c	14	0.063	<0.01	14
Average per vial		*0.058*	*0.01*	*14*
A-3-a	30	0.007	<0.007	0.37
A-3-b	30	0.047	<0.007	8.9
A-3-c	30	0.016	<0.007	2.5
Average per vial		*0.023*	*0.007*	*3.9*
A-4-a	60	0.005	<0.003	1.09
A-4-b	60	<0.003	<0.003	0.720
A-4-c	60	<0.003	<0.003	0.28
Average per vial		*0.004*	*0.003*	*0.70*
A-5-a	90	<0.002	<0.002	0.098
A-5-b	90	<0.002	<0.002	0.20
A-5-c	90	<0.002	<0.002	0.20
Average per vial		*0.002*	*0.002*	*0.17*
A-6-a	120	0.0033	<0.002	0.587
A-6-b	120	0.002	<0.002	0.23
A-6-c	120	0.002	<0.002	0.21
Average per vial		*0.002*	*0.002*	*0.34*
A-7-a	180	0.0009	<0.001	0.12
A-7-b	180	0.0031	<0.001	0.13
A-7-c	180	0.0089	<0.001	0.258
Average per vial		*0.0043*	*0.001*	*0.17*

855 The test was eventually extended to six months.[875] The results were reported as follows:

> The test passed both acceptance criteria. The leaching rate of nickel and tin ions released due to corrosion were at least 2000 times lower than the daily human intake of these metal ions from the diet and environment. The leaching rate of chromium was below the detection limit. All of the samples tested maintained mechanical integrity, not just for three months, but for all six months of the study.[876]

856 The examination results for signs of corrosion were reported as follows:

> At the six-month time point, the ball tips of some of the samples were almost completely corroded, but all of the solder bonds continued to hold together. In all cases, the outer coil remained attached to the fibered inner coil. This is an acceptable level of solder corrosion, because it did not result in the loss of

875 Ibid at 218.
876 Ibid at 224 [9.0].

mechanical integrity. No other components showed signs of corrosion.[877]

It was concluded that 'besides the solder, no other signs of corrosion were visible in the SEM images'.[878]

857 Conceptus also evaluated existing clinical data from the pre-hysterectomy study, Phase II study and Pivotal trial as part of the corrosion bench test as follows:

(a) retrospective evaluation of histological data from the pre-hysterectomy study for evidence of corrosion;

(b) retrospective evaluation of x-ray data from the Phase II study and Pivotal trial for evidence of loss of mechanical integrity; and

(c) retrospective evaluation of adverse event data from the Phase II study and Pivotal trial for evidence indicative of an allergic reaction to nickel ions.[879]

858 The retrospective evaluation of histological data from the pre-hysterectomy study involved review of 17 sample slides under an optical microscope. The samples were chosen on the basis of the potential for investigators to view the inner coil, outer coil and solder joint of devices.[880] The insert wear time ranged from four to 103 weeks. The study reported that increased porosity on the solder joint surface was the only evidence of corrosion.

859 The retrospective evaluation of x-ray data from the Phase II study and Pivotal trial involved examination of x-rays from 30 women taken at zero days, three months and approximately 12 to 15 months post-placement of Essure. The study noted that the x-ray equipment, settings and location were not consistent between women. The study found no evidence of fracture, breakage or other gross loss of mechanical integrity of the device, no loss of solder, and no visual signs of widespread corrosion such as missing components. The study concluded that corrosion resulting in the loss of

877 Ibid at 229 [9.3].
878 Ibid at 230.
879 BAY-ESSURE-0006158 at 38.
880 BAY-JCCP-0616252 at 117.

mechanical and structural integrity of the device did not occur.[881]

860 The retrospective evaluation of adverse event data from the Phase II study and Pivotal trial involved review of the records of over 650 women for adverse events potentially related to nickel allergy.[882] The women were followed up with for a period of three to 27 months post device implantation. The study found no reports of chronic skin rash or itching, and only two reports of skin rashes on one occasion for a few days. The evaluation concluded there was no evidence of nickel allergy, which indicated that 'the Essure Micro-insert was not going through corrosive processes resulting in the harmful release of Nickel ions'.[883]

Expert evidence

Chrzanowski

861 Chrzanowski criticised the methodology of the corrosion bench test for a number of reasons. First, he said that it did not test the release rate of all metals. He said that this was a significant omission, given that each element will interact with cells and influence the biological response. He said that the different elements together may have a synergistic effect on cells,[884] and that it was essential to evaluate the cumulative effect of ion release.

862 Second, Chrzanowski said that the test used sodium chloride, which is the most 'primitive' solution and not representative of the biological system. He said that there was a plethora of literature and relevant ISO standards on how to develop physiological solutions which would have been known to Conceptus at the time. He said that the chemical composition of the solution may impact how the material reacts, and potentially the corrosion rate of the device.

863 Chrzanowski said that when metal is exposed to a biological solution, electrons on its surface easily bind with proteins in that solution. A strong bind prevents surface re-

881 Ibid at 119.
882 Ibid.
883 Ibid at 120.
884 T3228 (TRA.500.033.0001_2 at 0071).

passivation/re-oxidisation and contributes to an increase in the corrosion rate. He said that he would have supplemented the solution in the corrosion bench test with albumin, a protein which can interfere with the re-passivation process if injury occurs to the surface of the metals used in a device.

864 Third, Chrzanowski said that, given the potential for multiaxial loading on devices in vivo, dynamic deformation should have been applied to the device using a rig to more accurately simulate the natural environment of the body. He said it was not unusual to test materials under distress.[885]

865 Fourth, Chrzanowski said that dietary intake was not the appropriate safety measure for metal ion release in the fallopian tubes. He said that the dietary absorption of metals is very low, being a maximum of 1% for nickel and 0.4% for chromium. Primary organs such as the liver, kidneys and lungs would absorb most of this. He said that leaching and corrosion from Essure would result in the accumulation of metal ions and particles in the tissues and cells in the vicinity of the device. Unlike in the case of dietary intake, those ions and particles would not be purged from the body.[886]

866 Fifth, Chrzanowski said that the retrospective evaluation of histological data in the PMA application was relatively limited, especially because the magnification of the optical microscope used was insufficient to pick up corrosion. He said that more sophisticated techniques and higher magnification were necessary to evaluate the device surface and tissue chemistry.[887]

867 Chrzanowski concluded that the corrosion bench test clearly showed that Essure corroded and released metal ions. He said that there had been no effort to evaluate the concentration of metal ions in surrounding tissues and its potential contribution to the ongoing inflammatory process. He said that the test showed relatively severe

885 T3237 (TRA.500.033.0001_2 at 0080).
886 T3238 (TRA.500.033.0001_2 at 0081).
887 T3241 (TRA.500.033.0001_2 at 0084).

ongoing corrosion in some sections of the devices.[888] He said this was relevant because it meant that some parts were corroding extremely quickly, and that there was a continuous corrosion process releasing metal ions into the surrounding environment.

868 Chrzanowski said that the continuous release of metal elements from the device and accumulation in surrounding tissue concerned him, as it would promote certain changes in cellular function.[889] He said that device fragmentation as a result of corrosion was likely the next phase, and that the SEM examination clearly showed disruption of the connection between the inner and outer coil. However, he agreed that he had not seen any evidence that the outer coil did, in fact, detach from the inner coil.[890]

869 Chrzanowski explained that each Essure device has a very thin oxide layer on its surface which spontaneously forms when implanted. He said that when the device expanded, the surface would stretch and the layer would crack, exposing the material underneath. Because the layer has no treatment to allow rapid and effective re-passivation, this would result in two materials of different electrochemical potential, creating a microscale galvanic surface and causing pitting corrosion. He said that the same process occurs with body movements. He said that the purpose of surface modification is to aid immediate re-passivation.[891] Chrzanowski noted that tests or cross-section reviews looking for evidence of pitting corrosion were not performed on explanted Essure devices.

Eiselstein

870 Eiselstein said that at the time Conceptus performed the corrosion bench test, the medical device community was most concerned about the potential release of metals such as chromium, nickel and cobalt. He said that there was less concern about

888 T3245 (TRA.500.033.0001_2 at 0088).
889 T3269 (TRA.500.033.0001_2 at 0112).
890 Ibid.
891 T4366 (TRA.500.043.0001_2 at 0083).

titanium, which was considered a fairly non-toxic metal.[892]

871 Eiselstein summarised the results for nickel release as follows:

> As noted above, the FDA has recommended that Nitinol devices demonstrate a nickel release rate below the tolerable intake value for parenteral exposure (excluding hypersensitivity) of 0.5 µg/kg/day (which is 35 µg/day for a 70 kg adult) (FDA 2019e). Thus, the Conceptus device test results (0.14 µg/day) show that the nickel release rate of two devices is at least 250 times lower than the current FDA-cited daily tolerable intake for a 70 kg adult. Based on FDA "worst case" estimates, the Conceptus device testing indicates two-device daily nickel-release rates over 40 times less than tolerable intake levels for a 70 kg adult. Further, even assuming an absolute worst-case condition in which all the nickel leached in the 180-day test occurred in a single day, the maximum amount of leached nickel in a Conceptus 180-day test is still roughly 15 times less than the daily nickel tolerable intake level for a 70 kg adult.[893]

872 Eiselstein said that the standard testing solution at the time was a 0.9% saline solution buffered to a pH of 7.4, to align with the pH of the body. He said the corrosion bench test went beyond this standard and tested at a lower pH. He said that tests of the effect of albumin found it to be less corrosive than simple buffered saline solutions.[894] He said that the solution used in the corrosion bench test was potentially more aggressive than what would be expected in the fallopian tube.

873 He did not accept Chrzanowski's concern that parts of the oxide protective passive layer of the Essure device may crack when the outer coil expands. He said that physical examination of explanted devices showed no significant corrosion, including pitting. He said that this would not have been the case if the re-passivation potential of the device components was poor.

874 Eiselstein said that the corrosion bench test showed no pitting corrosion on the stainless steel or nitinol, and showed corrosion only on the tin solder. He said that the review of pre-hysterectomy study samples gave a measure of confidence that there was no pitting corrosion apart from that of the weak part of the device (the tin), which

892 T3315 (TRA.500.034.0001_2 at 0029).
893 Eiselstein at 68 [8.9] (EXP.001.002.0004).
894 T3317 (TRA.500.034.0001_2 at 0031).

was known and reported and would not cause the device to come apart.[895] Eiselstein said that while evaluation for signs of corrosion using SEM imaging would be preferable, such evaluation was typically done using optical microscopy. He said that if either the nitinol or the stainless steel from the pre-hysterectomy study samples had suffered pitting corrosion, it would have been clearly visible using optical microscopy.[896]

875 Eiselstein said that periodic mechanical loading was not at play in the case of Essure.[897] He said that the corrosion studies of Essure devices (which I will address later in these reasons) showed no indication of fatigue, cracking or pitting corrosion. He said that he was unaware of any metal release rate testing conducted under fatigue loading conditions at the time Conceptus conducted the bench corrosion test.[898]

Potentiodynamic test

876 The potentiodynamic test was conducted by Corrosion Testing Laboratories, Inc ('CTL') in 2012 in accordance with the ATSM F2129 standard. The ESS505 model was tested against the then-commercially available ESS305 model, which acted as a control. Seven ESS505 devices and three ESS305 devices were tested.[899] The test results were tabulated as follows:[900]

Table 2. Key-Point Electrochemical Data *

Scan	E_r	E_b	E_v	E_p	Hysteresis	Pitting
Sample 1	+42	+514	N/A	N/A	Yes	Yes
Sample 2	+35	+501	N/A	+185	Yes	Yes
Sample 3	+9	+560	N/A	N/A	Yes	Yes
Sample 4	-68	+572	N/A	N/A	Yes	Yes
Sample 5	-192	+468	N/A	+36	Yes	Yes
Sample 6	-156	+556	N/A	-112	Yes	Yes
Sample 7	+24	+476	N/A	N/A	Yes	Yes
Control Sample 1	-452	-28	N/A	-228	Yes	Yes

895 T3308 (TRA.500.034.0001_2 at 0022).
896 Eiselstein at 71 [8.24] (EXP.001.002.0004).
897 T3321 (TRA.500.034.0001_2 at 0035).
898 T3323 (TRA.500.034.0001_2 at 0037).
899 Ibid at 2.
900 Ibid at 7.

Control Sample 2	-428	-140	N/A	N/A	Yes	Yes
Control Sample 3	-496	-12	N/A	-396	Yes	Yes

*E-values are milliVolts vs. SCE

877 A post-test examination of each sample, which appears to have been performed at 40x magnification, revealed pitting and localised corrosion.[901]

878 CTL described the results for the control samples as follows:

> The "control" samples had much lower breakdown potentials (~-140 to -10 mV (vs. SCE) and lower rest potentials (~-430 to -500 mV (vs. SCE)) than the "new design" samples. On these samples, all experienced corrosion of the weld where the outer coil is welded to the inner coil. In addition, Control Sample #2 had corrosion of the nitinol outer coil.[902]

879 CTL referred to the 'somewhat odd shape on the reverse polarization', and said:

> On the "control" samples, this effect may have been due to the extremely low potentials (and current densities) at which "breakdown" occurred. In the case of these samples, breakdown was actually corrosion of the weld, which was probably better characterized by active corrosion than true pitting. For Control Sample #2, this may also have been caused by a piece of the outer nitinol coil detaching (due to pitting), similar to that of the "new design" samples.[903]

880 CTL concluded that any sample with an E_b of less than 300 mV had unacceptable corrosion resistance, and concluded:

> Projecting real-world corrosion behavior from such laboratory test results is not reliable. Our results show that a significant improvement in corrosion resistance is present in the "new design" devices as compared with the "control" devices submitted by Conceptus. Per our internal criterion, we would conclude that the "control" devices have *unacceptable* corrosion resistance per ASTM F 2129.[904]

881 Conceptus reported the results of the potentiodynamic test to the FDA in 2013. Conceptus reported that, in summary:

> The testing performed by CTL is aggressive and accelerated and is only intended to identify how corrosion resistant a device is to instantaneous pitting. CTL also acknowledges that projecting real-world corrosion behavior from these types of lab results is not reliable, and that additional data from predicate devices/studies should be used to better clarify the device

901 Ibid at 9.
902 Ibid at 10.
903 Ibid at 10-1.
904 Ibid at 12.

> performance. An analysis of potential failure modes and past clinical performance demonstrated continued successful use of the Essure device in vivo. Therefore, given the extensive successful clinical use, the corrosion resistance data provided by CTL, as interpreted by Conceptus, does not indicate any problem or concern in product performance.
>
> ASTM F2129 is an aggressive test for demonstrating where pitting corrosion potentially begins and shows the locations where a break in the protective oxide layer could occur. It is an investigative test intended to take a sample to failure in order to provide general information on corrosion properties.[905]

882 Conceptus said that there were several factors in the potentiodynamic test that could affect the interpretation and relevance of CTL's conclusion that Essure was outside of acceptable ranges in terms of the breakdown potential:

> CTL's acceptance criteria for Breakdown Potential are based primarily on *in-vitro* or bench-top test results for other blood-contacting devices. The upper "acceptable" criterion is set in a range in which a human body would not allow for potentials at or above that level. The lower bound of 300 mV was selected as "unacceptable" because CTL's literature suggests that this condition has a reasonable chance of being seen *in-vivo*. The range in between the limits was designated as "marginally acceptable" as a safety factor for CTL's testing limits, based on lab testing in animal tissue. The physical structure of the original electric potential tests does not exactly match the structure inside the fallopian tube or uterus. It is unknown what electric potentials (if any) are actually encountered at the implant site. Additionally, none of the test conditions or outputs used in this study can be correlated to an amount of time in the body. Therefore, CTL's acceptance criteria for this test are unrelated to the application of the Essure device.[906]

883 Conceptus discussed the relevance of historical and commercial data to CTL's conclusions:

> The results found in this corrosion study indicate that some parts of the insert could break-off due to pitting corrosion or breakdown of the metal. If these results were applicable to the clinical use of the Essure device, then we would expect to see more adverse events such as perforations, devices breaking in half, and nickel allergies.
>
> In the 10 years of distributing the Essure device and tracking adverse events in our complaint handling system, no complaints of corroded or broken devices have been reported. In addition, a study of x-ray data on 30 patients from early clinical studies who wore the device for up to 15 months indicated no evidence of corrosion, and in all 30 cases, the mechanical and structural integrity of the device was maintained… This evidence demonstrates how durable the device is and that the types of failures seen in this corrosion testing do not typically

905 BAY-ESSURE-0060827 at 1162.
906 Ibid at 1163–4 [6.1.1].

occur after long term use of the device.

> A small number of complaints for rash or suspected nickel reactions have been reported in the complaint handling system. Analysis of these adverse events is, documented in the publication *Adverse Events Due to Suspected Nickel Hypersensitivity in Patients with Essure Micro-Inserts*, Zurawin RK, Zurawin JL, J Minim Invasive Gynecol, 2011 Jul-Aug, 18(4): 475-82. The publication stated that the incidence of adverse events suspected to be related to nickel hypersensitivity is 0.01%. Nitinol is commonly used in surgical implants that are in direct blood contact, and have been implanted in thousands of patients without issue. Therefore, the chance of the corrosion seen in this testing resulting in an adverse nickel reaction in the patient is extremely low.[907]

Expert evidence

Chrzanowski

884 Chrzanowski said that the potentiodynamic test was a conventional approach involving two classes of the device, the then current design (ESS305) and the new design (ESS505). He said the ESS305 model, tested as the control, did not pass the acceptance criteria for the test. The breakdown potential for all samples was negative, and re-passivation either did not occur or was low. He said that the test result showed an anotic node, which indicated a level of continuous corrosion. He said that '[b]earing in mind that our body environment has the endogenous electrical potential [and] is electro positive, this material will corrode inside the body.'[908] He said that in vivo rest potential was typically around the level of a few tenths of a millivolt.

885 Chrzanowski said that there was a lack of consistency between the devices that were tested, which indicated non-uniformity between the surface preparation for individual devices.[909] He said that the very erratic behaviour of one of the hysteresis curves was consistent with the extremely complex architecture of the device.

886 Chrzanowski said that the post-test examination using 40x magnification would not identify all corrosion, and that the visible corrosion of the nitinol outer coil at that magnification indicated that it was substantial.[910]

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907 Ibid at 1164 [7.1.1]–[7.1.3].
908 T3247 (TRA.500.033.0001_2 at 0090_20).
909 T3252 (TRA.500.033.0001_2 at 0095_23–27).
910 T3273 (TRA.500.033.0001_2 at 0116).

887 Chrzanowski agreed with CTL's conclusion that the observed corrosion rate in the potentiodynamic test was unacceptable. He said that there was no consensus in the scientific community about Eiselstein's acceptance criteria focusing on the difference between E_b and E_r. He said that potentiodynamic testing is the only test which sweeps across all the electrical potentials in the body and provides an indication about whether the material will corrode in a specific environment. He said that the re-passivation potential and the hysteresis curve allow for determination of the existence and extent of corrosion. He said that the results of the study showed evidence of pitting corrosion on alloys other than tin.

Eiselstein

888 Eiselstein said that the difference between E_b and E_r in the potentiodynamic test was about 400 mV, which was a substantial margin of safety. On this basis, he considered that the test results did not indicate pitting corrosion in vivo.[911] He said the CTL acceptance criteria was overly conservative.[912]

889 Eiselstein said that each metal element of the device contributes to its resting potential.[913] He said that articles cited in the FDA guidance document for nitinol gave resting potentials in the body of around -200 mV.[914]

890 Eiselstein said that the 'real question' was which of the components of the Essure device had corroded.[915] He said that the potentiodynamic test confirmed his hypothesis that tin was actively corroding 'from the get go'.[916] He said that there appeared to be some passivation of tin occurring, which was consistent with the metal release rate testing showing a decrease in the rate of tin release with time. He said that this may explain why no mechanical fractures of the solder joint were seen in

911 T3334 (TRA.500.034.0001_2 at 0048).
912 T3369 (TRA.500.034.0001_2 at 0083).
913 T3336 (TRA.500.034.0001_2 at 0050).
914 T3335 (TRA.500.034.0001_2 at 0049).
915 T3331 (TRA.500.034.0001_2 at 0041).
916 T3368 (TRA.500.034.0001_2 at 0082).

explanted devices.[917]

Essure corrosion studies

Parant 2020

891 The purpose of Parant 2020 was to test the concentrations of nickel and chromium in peritoneal fluid and fallopian tube tissue following laparoscopic removal of Essure.[918] The prospective cohort study was conducted from August 2018 to February 2020 and included 37 patients with adverse effects possibly related to Essure. The median time between Essure placement and removal was 6.4 years.[919]

892 The concentrations of metal elements was reported in the study as follows:

> For Ni and Cr, a gradient of concentrations was observed with declining levels from tissues surrounding the implants to the distal parts of the fallopian tube. Concentrations in the tissues surrounding the Essure® were 4.12 (IQR: 0.52–6.68) and 12.72 µg/g of dry tissue (4.09–17.53) for Ni and Cr, respectively. In the distal parts of the fallopian tube tissue, concentrations were 0.35 (0.24–0.56) and 1.35 µg/g of dry tissue (1.00–2.23) for Ni and Cr, respectively (Fig. 2). All comparisons were significant at $p < 0.05$. A significant correlation was also observed between Ni and Cr concentrations (rho = 0.792, $p < 0.0001$) (Fig. 3).[920]

The authors noted that the concentration of metal elements in fallopian tube tissues were characterised by high interpatient variability, particularly for the tissue around the Essure inserts.

893 Concentration in peritoneal fluid was reported as follows:

> In peritoneal fluid, Ni and Cr concentrations were 2.24 µg/L (IQR: 0.32–3.67) and 5.39 µg/L (2.22–8.68 µg/L), respectively. As observed in the fallopian tube tissue, there were (i) a significant correlation between Ni and Cr levels (rho = 0.756, $p < 0.0001$) (Fig. 3) and (ii) a high interpatient variability.[921]

894 Parant 2020 found a significant correlation between nickel and chromium concentrations in the fallopian tube tissue and peritoneal fluid, which the authors

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917 T3333 (TRA.500.034.0001_2 at 0047).
918 Parant 2020 (PUB.001.001.3197).
919 Ibid at 2.
920 Ibid.
921 Ibid at 3.

concluded suggested a 'complex exchange between these two compartments'.[922]

895 Parant 2020 found no clear relationship between the three main reported symptoms of fatigue, psychological disorders and joint pain, and the concentrations of metal elements found on analysis. The authors concluded that the study lacked statistical power, making it difficult to draw definitive conclusions. The authors concluded that:

> … all of these results should be interpreted with caution. We have not proven the causal relationship but simply highlighted the presence of Ni and Cr. It is not certain that these potential toxic metals are necessarily responsible for the adverse effects.[923]

Parant 2022

896 Parant 2022 again evaluated concentrations of nickel, chromium and tin in peritoneal fluid and fallopian tube tissue during laparoscopic Essure removal. On this occasion, the study results were compared to a control group. The study involved 131 symptomatic women undergoing laparoscopic Essure insert removal (group A), and 92 patients undergoing benign laparoscopic surgery (group B).

897 The median length of time between Essure placement and removal for group A patients was seven years. Group A was divided into four categories according to the time wearing the inserts: zero to 3.5 years; 3.5 to seven years; seven to 10.5 years; and beyond 10.5 years.[924]

898 Parant 2022 found significantly higher concentrations of nickel, chromium and tin in the fallopian tube tissue from group A compared to control group B. The study also found significantly higher levels of nickel and chromium in the peritoneal fluid of patients in group A than in the control group, but no difference in tin concentrations between the groups.

899 Parant 2022 summarised the metal concentrations for patients in group A as follows:

> Globally, the concentrations of Cr, Ni and Sn in the distal part of the fallopian tube tissue trended to decrease with the length of time between Essure®

922 Ibid at 4.
923 Ibid.
924 Parant 2022 at 3 (PUB.500.001.0362).

> placement and removal (Cr: from 1.55 µg/g to 0.73 µg/g, p = 0,002, Ni: from 0.36 µg/g to 0.24 µg/g, p = 0,023, Sn: from 8.11 µg/g to 0.86 µg/g, p < 0,001, Kruskal–Wallis test) (Fig. 2). In the proximal part, the concentrations remained quite stable except for Sn where there was a decrease with time (Cr: from 1.95 µg/g to 1.79 µg/g, Ni: from 0.35 µg/g to 0.43 µg/g, Sn: from 7.87 µg/g to 1.51 µg/g) (See Fig. 2).[925]

Assessment of the concentration of metals in peritoneal fluid is reported in the study as follows:

> Results showed that Cr and Ni concentrations were highest between 3.5 and 7 years post-placement of the Essure® implants (respectively 6.58 µg/L and 3.06 µg/L), and significantly decreased thereafter to 2.91 µg/L for Cr and 1.26 µg/L for Ni (P < 0.001) (see Fig. 3).[926]

900 The authors said that the data raised the question of whether the metallic elements of Essure were responsible for the symptoms experienced by women.[927] However, the authors noted that they had only focused on symptomatic patients which '[suggested] that [they did] not know whether there is the same metal element release in non-symptomatic patients'.[928]

901 Parant 2022 concluded:

> Our study highlighted the potential role of metallic elements in the occurrence of side effects. The fact that there is a release of some metals from Essure® device could be enough to explain some adverse effects even if there is no correlation between symptoms and concentration of either metals. It is very difficult to determine whether a metal particle or the combination of several metals can cause the adverse events. Further long-term epidemiological studies in symptomatic patients with Essure® and non-clinical animal models are needed to answer this question.[929]

902 Eiselstein highlighted two limitations of Parant 2022. First, the study did not include women undergoing laparoscopic removal of Essure without symptoms as an additional control group. Second, the study did not explain why the patients in group B were undergoing benign laparoscopic surgery, what symptoms they were

925 Ibid.
926 Ibid.
927 Ibid at 5.
928 Ibid.
929 Ibid at 6.

experiencing if any, and how those symptoms compared to the patients in group A.[930]

Catinon 2020

903 Catinon 2020 involved SEM analysis of fallopian tube, uterine horn tissues and explanted Essure inserts from 10 patients after hysterectomy or salpingectomy. The mean time from implantation to hysterectomy or salpingectomy was 85.5 months. Mineralogical analysis was performed on 13 tissue biopsies and four implants by SEM, coupled with energy dispersive x-ray spectrometry ('EDS').

904 The study detected tin-based particles in five patients, and found other metallic particles in smaller proportions. A cluster of particles greater than one millimetre in diameter were observed in one patient. Analysis showed that the particles were mainly composed of tin. The pathology report for this patient mentioned macrophagic granuloma and multinucleated giant cells associated with the particles.[931]

905 The possible degradation of the device solder joint was identified in seven of the 10 cases, along with local dissemination of tin in the fallopian tube or uterine horn. This was sometimes accompanied by an inflammatory reaction and/or encystment of particles.[932] Catinon 2020 continued:

> All analyses of used implants showed an important level of degradation, with a destructive appearance of the tin weld and the presence of organic tissue around the damaged weld, as well as tin particle dissemination inside the organic tissue. In two cases, implant analysis showed abnormal deterioration of the weld without evidence of tin particles in the tissue. It is possible that these specimens came from tissue distant from the tin solder. Future prospective studies should focus on tissue closer to the tin solder.
>
> Local inflammatory lesions associated with the presence of tin particles may explain the pelvic pain and dyspareunia reported by patients.[933]

The authors concluded that their analysis supported the hypothesis of a causal relationship between abnormal degradation of Essure inserts and locoregional

930 Eiselstein at 81 [9.23] (EXP.001.002.0004).
931 Catinon 2020 at 4 (PUB.001.001.3757).
932 Ibid at 7.
933 Ibid.

symptoms.[934]

906 Eiselstein said that the findings in Catinon 2020 of certain extraneous metals, which he said were not in the Essure inserts, indicated that the samples were contaminated.[935] He said that the authors may have misinterpreted some of the findings and/or wrongly reported that certain analysis was performed.[936]

907 Under 'Discussion', the study authors state:

> This analysis of implants and uterine biopsies shows that tin particles were found most frequently in the samples. However, other element constituents of the implant were also identified (silver, nickel, gold, chromium, platinum and titanium). It is therefore possible that supplementary toxicity could be added to tin toxicity.[937]

This suggests that the authors had already reached a conclusion as to toxicity. The authors then state:

> In seven of the 10 cases in this study, possible degradation of the weld was identified, with local dissemination of tin in the fallopian tube or uterine horn, sometimes accompanied by an inflammatory reaction and/or encystment of particles. …
>
> Local inflammatory lesions associated with the presence of tin particles may explain the pelvic pain and dyspareunia reported by patients.[938]

No further detail is given of the 'inflammatory reaction' or 'local inflammatory lesions'. The investigation that led to those findings is not described, and there is no detail of precisely what was found. The authors then discuss the relevance of tin release from the Essure device in the following terms:

> Organotin bioproduction after leaching and tin corrosion, similar to the processes observed for mercury, could explain some systemic symptoms. Although most mineral tin salts are considered to have low toxicity for mammals, the issue is less clear for organic compounds that could potentially interfere with many biochemical intracellular mechanisms. Indeed, organotin compounds are considered very toxic, with headaches, depression, asthenias and visual disturbances among the symptoms frequently observed among

934 Ibid at 10.
935 Eiselstein at 101 [11.8.2] (EXP.001.002.0004).
936 Ibid.
937 Ibid at 6.
938 Ibid at 7.

ESSURE cases.[939]

There is no factual basis set out for the hypotheses proposed by the authors, which appear to be no more than speculation directed to impugning Essure. Catinon 2020 lacks detail and precision. A proper foundation for the commentary adverse to Essure is not apparent. These matters add to my concern about the failure to disclose a conflict of interest. I conclude little weight should be placed on the study.

Catinon 2022

908 As explained earlier in these reasons, Catinon 2022 examined associations between local and systemic symptoms and the wear of the tin solder of Essure devices.[940] The study involved 18 women implanted with Essure for a period of time (the mean period being 94 months) who had their devices removed by salpingectomy or hysterectomy.

909 Pathological study of specimens by optical microscopy showed that 17 patients presented with granulomas and one with fibrosis. Uterine adenomyosis was observed in 14 patients, non-specific inflammatory signs observed in 10, and foreign bodies observed in seven. Tin-based particles were observed in all samples along with some titanium, platinum, silver and steel particles. The authors said that the sampling of specimens at the solder joint explained why tin particles were found in all cases, compared to a previous study where specimens were taken far from the solder joint and where tin was only detected in half of the specimens. This also explained the findings of granulomatous inflammation, or in one instance fibrosis lesions.

910 The authors concluded that the risk of toxicity related to corrosion of the solder joint had previously been underestimated. They said that:

> The presence of foreign body granulomas in contact with the weld zone is, in our opinion, related to wear of the implant weld. This wear phenomenon could explain the high frequency of adenomyosis in the patients we followed (77.8%), but also some local signs of pain and bleeding.[941]

939 Ibid.
940 Catinon 2022 (PUB.001.001.3758).
941 Ibid at 8.

Aslan 2022

911 Aslan 2022 investigated the electrochemical properties and ion release profile of Essure during storage in PBS, a simulated inflammatory solution, and 10% neutral buffered formalin.[942] The study goals were to evaluate galvanic interactions between different alloys in the device in different solutions; measure the release of metal ions over a period of 107 days; and document the corrosive damage to the inserts.

912 The authors identified significant galvanic coupling between the tin solder/stainless steel portion and the nitinol/platinum iridium portion of the Essure inserts, with the tin solder acting as an anode and the nitinol/platinum iridium acting as a cathode. The authors concluded that:

> The Essure® implant has four different alloys, two of which are passive alloys (316L SS, NiTi), one is a noble alloy (PtIr) and one is an active alloy (SnAg). Typically, galvanic effects are most pronounced on active alloys that are serving as the anode in the cell as is the case with the SnAg solder which demonstrated clear evidence of corrosion degradation. The passive alloys (NiTi and 316L SS), because their oxide films, act as kinetic barriers to corrosion and play a more limited role in developing galvanic interactions or serving as the anode.[943]

913 Under 'Discussion', the authors noted:

> To our knowledge there are no other biomaterials examples of the use of SnAg solder used in permanent implants in direct contact with the living system. Indeed, there is almost no published literature of the use of metallic Sn in the body as a biomaterial. While Ag and Sn have comprised alloying elements in dental amalgams (alloys of Ag, Sn, Cu, and Hg), there is no other indication of the use of SnAg alloy in direct contact with the body for a sustained period.[944]

The authors found evidence of tin corrosion similar to that in Catinon 2020 and Catinon 2022. They concluded that corrosion seen after 107 days of immersion may raise the risk of loss of connectivity between the nitinol outer coil and stainless steel inner coil of the insert.

914 The authors observed:

> It should be kept in mind that the Essure® implant was designed to promote

942 Aslan 2022 (PUB.500.001.0506).
943 Ibid at 11.
944 Ibid.

> inflammation in the surrounding tissue with the use of PET fibers. These fibers are known to promote inflammation locally and are a part of the implant designed to promote scarring and occlusion of the fallopian tubes. Interestingly, it may be possible that the high rate of corrosion of the SnAg solder and its degradation products may also be a promoter of an inflammatory response that would alter the local solution chemistry in vivo potentially altering the corrosion interactions present and affecting the fibrotic tissue formation process.[945]

915 The authors referred to limitations of the study including that:

> … no mechanical tests were performed in this work. The flexibility of the micro-insert and the fallopian tubes should not be disregarded when considering modes of damage and degradation of the device. Future work should focus on the effects of mechanical movement of the device, such as the 316L stainless steel coil wearing/fretting with each movement, as well as more detailed observations focused on the nickel-titanium coil, particularly the growth and damage of its oxide layer under different conditions and mechanical loading.[946]

916 They concluded:

> This study demonstrated the electrochemical properties and ion release profile of the Essure® implant in three different solutions: phosphate buffered saline, a simulated inflammatory solution (10 mM H_2O_2/PBS), and neutral buffered formalin solutions. Galvanic corrosion processes were documented between the SnAg solder and the NiTi/PtIr portions of the implant. This investigation demonstrated that the tin-silver solder, holding the inner and outer coils together, actively corrodes when exposed to physiologically representative solutions. The presence of hydrogen peroxide, simulating a more inflammatory condition, led to the increased release of nickel and titanium ions from the nickel-titanium outer coil.[947]

917 The data in Aslan 2022 for release of nickel and tin was very similar to the results of the corrosion bench test. Eiselstein said that '[the] findings in [Aslan 2022] do not indicate any corrosion or metal release rate concerns regarding the Essure device because the levels of metal release reported are significantly below the limits [which the] FDA follows when evaluating the safety of metals used in medical devices.'[948] Eiselstein tabulated a comparison of nickel release rates as follows:[949]

Table 7. Comparison of Conceptus nickel release rate data to that of Aslan and Gilbert.

945 Ibid at 12.
946 Ibid at 13.
947 Ibid.
948 Eiselstein at 71 [9.2] (EXP.001.002.0004).
949 Ibid at 77.

FDA Limit[1]	Conceptus PMA Data[2] (Percentage of FDA Limit)	2015 FDA Calculation of Conceptus's Data[3] (Percentage of FDA Limit)	2022 Aslan & Gilbert (H_2O_2/PBS)[4] (Percentage of FDA Limit)	2022 Aslan & Gilbert (PBS)[5] (Percentage of FDA Limit)
35 µg/day	0.14 µg/day (0.4%)	<0.77 µg/day (2.2%)	2.5 µg/day (7.1%)	0.053 µg/day (0.15%)

1 Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol – Guidance for Industry and Food and Drug Administration Staff, in section: "D. Biocompatibility" issued on October 15, 2020 (FDA 2020b).

2 Conceptus Corrosion Test – Six Month Report. Conceptus (Table 2) found 0.14 µg/day over seven days for one individual test point (two devices) in the Group B disruptive tests. The cumulative series tests (Group A) had a similar highest value of 0.13 µg/day at seven days for two devices (Conceptus 2001 to 2016).

3 FDA Review Document: Review of the Essure System for Hysteroscopic Sterilization, September 24, 2015, meeting of the Obstetrics and Gynecology Devices Advisory Panel, Table 19 (FDA 2015b).

4 Aslan and Gilbert report 30 ppb (µg/l) released in six days in H_2O_2/PBS; therefore, the rate is (30/6) µg/L/day x .250 liter = 1.25 µg/day for one device, or 2.5 µg/day for two devices (Aslan and Gilbert 2022).

5 Aslan and Gilbert report 0.88 ppb (0.63 ppb after considering the initial concentration) released in PBS after six days: therefore, the rate is (0.63/6) µg/L/day x .250 liter = .026 µg/day per device, or 0.053 µg/day for two devices (Aslan and Gilbert 2022).

918 Eiselstein tabulated a comparison of tin release rates as follows:[950]

Table 8. Comparison of tin release data from Conceptus and Aslan and Gilbert's data.

FDA Limit[1]	Conceptus PMA Data[2] (Percentage of FDA Limit)	2022 Aslan & Gilbert (PBS and H_2O_2)[3] (Percentage of FDA Limit)	2022 Aslan & Gilbert (PBS)[4] (Percentage of FDA Limit)
640 µg/day	18 µg/day (2.8%)	1.7 µg/day (0.3%)	18.1 µg/day (2.8%)

1 Q3D(R1) Elemental Impurities Guidance for Industry (FDA 2020f). These permitted daily exposure (PDE) rates assume body mass of 50 kg. According to FDA, "[t]his relatively low mass provides an additional safety factor against the standard masses of 60 kg or 70 kg that are often used in this type of calculation."

2 Conceptus Corrosion Test – Six Month Report. Conceptus found 18 µg/day over seven days for two devices in the disruptive tests. The cumulative series tests gave 11 µg/day over seven days for two devices (Conceptus 2001 to 2016).

3 Figure 6c (Aslan and Gilbert 2022): 20.7 ppb (20.6 ppb after considering the initial concentration) Sn concentration in 250 ml solution for six days; therefore, 20.6 µg/l x (0.25 liter)/6 days = 0.86 µg/day/device x 2 for a pair = 1.72 µg/day/pair.

4 Figure 6c (Aslan and Gilbert 2022): 217 ppb Sn concentration in 250 ml solution for six days; therefore, 217 µg/l x (0.25 liter)/6 days = 9.04 µg Sn/day/device or 18.1 µg Sn/day/pair.

919 Eiselstein said that, in relation to the test in Aslan 2022 for galvanic corrosion, the tin-silver solder acted as a 'sacrificial anode' that in effect sacrificed itself to protect the other alloys in the device.[951]

950 Ibid at 79.

951 T3371 (TRA.500.034.0001 at 0085_29).

Goodwin 2023

920 Goodwin 2023 is part of the 522 study.[952] Its goals were to develop retrieval methods to measure local tissue metal levels and their spatial distribution proximal to Essure inserts, and to assess and document degradation of retrieved inserts.

921 The fallopian tubes and Essure inserts were removed from four patients and sectioned at three locations: 'S1' was the most proximal containing platinum iridium, nitinol and stainless steel; 'S4' was the region containing the PET fibres, the solder, stainless steel and nitinol; and 'S6' was the region distal to the insert. The following table shows the average and standard deviation of metal ion concentrations in dry fallopian tube tissue in each location:[953]

	Ti	Cr	Fe	Ni	Mo	Ag	Sn
S1	1.93 ± 0.7	0.58 ± 0.6	27.25 ± 6.0	0.97 ± 0.3	1.77 ± 2.0	4.32 ± 6.0	9.46 ± 8.0
S4	1.58 ± 0.5	1.08 ± 2.0	27.88 ± 15.0	1.13 ± 2.0	0.76 ± 0.6	5.35 ± 6.0	57.92 ± 54.0
S6	1.37 ± 0.8	0.33 ± 0.4	26.57 ± 17.0	0.87 ± 1.0	0.84 ± 1.0	0.51 ± 0.8	4.05 ± 5.0
Used NBF[954]	5.13 ± 2.0	0.10 ± 0.0	0.83 ± 0.9	0.02 ± 0.1	0.03 ± 0.0	0.00 ± 0.0	0.26 ± 0.3
Unused NBF	3.30 ± 0.6	0.13 ± 0.0	0.03 ± 0.0	0.00 ± 0.0	0.01 ± 0.0	0.00 ± 0.0	0.00 ± 0.0

Table 1: Average and standard deviation of metal ion concentration in dried fallopian tube tissue of sections S1 (n=3), S4 (n=7) and S6 (n=7) in µg ions/ g dried tissue as well as NBF used for fixation (n=7) and fresh lots of NBF (n=4) in µg ions/ ml of NBF.

922 The authors observed and assessed the state of retrieved Essure device components. They recorded the following observations in relation to stainless steel:

> After the cleaning of the devices, SS coils were reinspected … The cleaned coil surfaces appear similar to that of an as-manufactured coil, with linear marks on the inner coil and an "orange peel" surface on the exposed surface. In the implants where the coil had been pulled apart, the inside coil could be analyzed as well with no differences from an as manufactured device identified.[955]

923 The authors noted that the results they obtained were preliminary and part of the ongoing 522 study. They concluded:

> The most significant observation of the present study relates to the corrosion

952 Goodwin 2023 (MSC.001.002.0013).
953 Ibid at 10.
954 Neutral buffered formalin.
955 Goodwin 2023 at 19 (MSC.001.002.0013).

> of the Sn-Ag solder. This includes high concentrations of Sn ions found in the surrounding tissue and the corroded appearance of the Sn-Ag solder on the retrieved devices. This was observed in all retrieved implants analyzed. Evidence of 316L SS corrosion, causing an accumulation of Mo and development of Fe-P-O adsorbed [sic] deposits are unique to this report. Additionally, increased Fe, Mo and Ni ion levels in tissue further indicate corrosion. In addition, the Ni-Ti and Pt-Ir surfaces did not appear to undergo major degradation with implantation.[956]

The study noted that the S4 sections contained significantly higher concentrations of tin, consistent with tin products not dispersing through tissue easily and likely being more solid corrosion products than ionic.[957]

924 Goodwin 2023 further concluded:

> Early results have shown significant degradation of the Sn-Ag solder as well as cluster of particles of Sn, several dozen microns in diameter, embedded into the fallopian tube or horns of the uterine wall. Around the particles, exist Ca as calcium phosphate or calcium oxalate, leading investigators to believe Sn is causing endogenous calcification of uterine horns and the fallopian tubes. In case studies, the presence of calcium carbonate, $CaCO_3$, have been observed as bilateral white deposits on an Essure® device. The tissue surrounding the device has appeared as granulomas or fibrotic with some signs of uterine adenomyosis and other nonspecific inflammatory reaction. Additionally, our results showing Ca/Fe/P/O deposits on the device are similar to several groups' observations of calcification of tissue surrounding the device. This Ca appears to be a form of Calcium Phosphate (e.g., $Ca_3(PO_4)_2$) and suggests that the tissue surrounding the device is experiencing possible calcification. Sn has not been thoroughly studied as a biomaterial and thus, the inflammatory process associated with Sn is unknown.[958]

925 In relation to stainless steel, Goodwin 2023 found:

> 316L SS has been studied as a biomaterial in other applications and is generally accepted to be resistant to corrosion in vivo though can be subject to pitting corrosion attack under some conditions. When galvanically coupled to other alloys, cobalt and titanium based, it is known to be more susceptible to corrosion. Our ion results show relatively high levels of Fe dispersed though the tissue, however, Fe is also found biologically. It is difficult to determine if or how much Fe ion concentration the SS coil contributed to the total amount. The other alloying elements, Cr, Ni and Mo are all lower and evenly dispersed across the tissue sections. The surface analysis, however, shows signs of corrosion produced from likely fretting between coils and likely produced

956 Ibid at 24.
957 Ibid at 25.
958 Ibid at 26–27 (citations omitted).

from biological interaction.[959]

926 Commenting on tissue reaction to Essure, the authors said:

> Proof of the PET reaction is indicated in more dense soft tissue on the inside and in between the SS coils, however, more soft tissue appears to be tightly connected to the Sn-Ag solder and not the PET fibers. It may be possible that the corrosion of the solder itself is the main driving force in the tissue reaction of the device.[960]

927 Goodwin 2023 concluded:

> We demonstrated that the Sn-Ag solder region which connects the SS and Ni-Ti alloys together corroded in all retrieved implants. In addition, the highest ion levels measured in tissue were Sn and these tissue ion levels were a function of the location relative to the implant with the highest Sn ion levels immediately adjacent to the solder location. Increased in Mo and decreased Cr concentrations that appear to interact with biological environment, provide evidence of 316L SS corrosion present within this device. The Ni-Ti, Pt-Ir and PET fibers do appear predominately unaffected by implantation but have evidence of biological attachment and, for the Ni-Ti surfaces, adsorption of Fe-Ca-P-O layers that may be associated with possible calcification.[961]

928 Chrzanowski said that Goodwin 2023 confirmed corrosion of Essure, including by galvanic and fretting corrosion, and associated elevated levels of tin, iron, titanium, nickel and chromium.[962] He said that the largest effect of corrosion was observed around the solder joint with significantly elevated tin levels. He said that the analysis in Goodwin 2023 showed that metal elements accumulate in the tissue surrounding the insert which leads to localised biological effects,[963] and that the detection of tin some distance from the solder joint suggested translocation of metal elements and debris.

929 Chrzanowski said that the findings of metal particles and debris suggested the likely disintegration of the device, and that observations by microscopy showed substantial corrosion of the solder which would have increased the risk of loss of integrity.

930 Eiselstein criticised the findings and methods in Goodwin 2023 for the following

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959 Ibid at 27 (citations omitted).
960 Ibid at 28.
961 Ibid at 30–1.
962 Chrzanowski at 2 (EXP.001.002.0019).
963 Ibid at 3.

reasons. First, as non-exposed tissue was not measured as a test control, he said that the metal ions detected in the tissue could not be credited entirely to the implanted device.[964] Eiselstein said that there was no statistically significant difference between the concentration of metals found at the three locations analysed apart from the concentration of tin, which was found in higher relative quantities at the location of the solder joint in S4.

931 Second, the drying of tissue before testing resulted in higher reported metal concentrations than would have been the case in vivo.[965]

932 Third, Eiselstein raised concerns about the use of EDS to analyse the chemistry of various surfaces on the retrieved inserts. He said that EDS is only semiquantitative even when performed on flat surfaces, and may become less accurate when performed on small curved surfaces. Further, because the EDS spectra are formed from a mixture of the composition of the substrate alloy and the organic deposits on the surface, metals commonly in the body and in the substrate alloy make it difficult to determine whether any concentration change is associated with the substrate, surface deposits or corrosion products.[966]

933 Eiselstein said, in summary, that the Goodwin 2023 examination of retrieved Essure inserts showed:

- There was no pitting or fracture on the stainless steel coils even though some coils were deformed and stretched during retrieval.
- There was no pitting or fracture on nitinol coils.
- There was no difference in condition between before and after retrieval on the Pt-Ir markers.
- Corrosion of the solder joint was noted, but solder joint failure was not seen for any of the four cases examined in the article.[967]

964 Eiselstein at 11 (EXP.500.500.0008).
965 Ibid at 10.
966 Ibid at 12.
967 Ibid at 14.

Further expert evidence on Essure corrosion studies

934 Robertson said that metals released into tissues as ions or metal particles in sufficient concentrations can exert toxic effects on cells in the tissue and interfere with the biochemical function of the cells.[968] She said that immune cells can be activated into a pro-inflammatory state by metal ions and by particles that are phagocytosed. The net effect is to induce cell death and promote inflammation.[969] She said that macrophages are highly responsive to metals leached from biomedical devices. The cellular uptake of metal particles by macrophages can lead to further release of metal ions, which propagates as a positive feedback loop. Metal ions can cause cell death, which further amplifies and perpetuates the inflammatory response.[970]

935 Robertson concluded that the amount of metal ions released from Essure was sufficient to cause the toxic effects explained above. She said this opinion was based on her understanding of evidence of metals added to cells in vitro causing changes to biochemistry, exerting cell stress and inducing inflammation. She also drew inferences from the corrosion studies which showed the levels of metal ions that actually exist in tissues proximate to Essure inserts.[971] She said that the effect of very high concentrations of metal ions in one place, as opposed to being diluted in a big area, was important context to consider.

936 Robertson said that the particles of tin and other metals were detected 'in the same vicinity as the immune cell infiltrates associated with chronic inflammation in the site of the Essure devices, indicating that local immune cells are likely to be directly impacted by levels of metals that are much higher than background physiological levels.'[972]

937 Robertson said that there is a distinction in the levels of exposure to metals such as nickel, chromium and tin that are required to elicit inflammation versus general

968 T3375 (TRA.500.034.0001_2 at 0089).
969 T3376 (TRA.500.034.0001_2 at 0090).
970 Robertson at 159-63 (EXP.001.001.0127_2).
971 T3377 (TRA.500.034.0001_2 at 0091).
972 Robertson at 159 [444] (EXP.001.002.0015_2).

toxicity. She said:

> In physiology, an inflammatory response is not equivalent to toxicity response. It is well known that immune cells engaged in an inflammatory response can be stimulated by entities at concentrations that are well below the threshold concentrations that induce toxicity due to acute or chronic exposure. For example, in the case of nickel, the amounts required to induce hypersensitivity are well below the amounts required to cause general toxicity, which is commonly understood to arise through pathophysiological effects on organs and systems other than the immune response.
>
> This distinction in levels required to elicit inflammation versus toxicity is important for metals such as nickel and chromium found in the Essure Device and shown to be leached from it as metal ions. …These metals are found in the Essure Device and can be leached from it as metal ions or particles. When present in the body in their ionic form these metals (especially nickel) can form haptens that are immunogenic. When sufficient hapten levels form in sites that are effective for priming immune responses, they stimulate adaptive immune responses that cause hypersensitivity reactions, and in turn promote chronic inflammation. Epithelial and mucosal surfaces are effective sites for generation of anti-hapten immune responses. Hapten formation in sufficient levels to prime an immune response can occur at levels below the thresholds for ingestion or environmental exposure that are based on general toxicity.[973]

938 Robertson said:

> When you see a level of a material that's 10 to 20, or even 5 times, higher than the background tissue levels, you start to be concerned as a biochemist and a cell biologist that that's impacting the biochemistry and the physiology of the tissue.[974]

She said that there was no doubt that the metals aggregated in the vicinity of the inflammatory response to the Essure insert would substantially and adversely impact the behaviour of cells in that tissue. She said that while she was unaware of any relevant standards regarding the lowest threshold of metal concentrations in the vicinity of medical devices, the findings in the corrosion studies were a 'red flag'.[975]

939 During the immunology concurrent evidence Robertson identified what she said was the main point of the Parant studies:

> They clearly show — I've just indicated a piece of data in [Parant 2020] that shows a relationship to the proximity to the device in the fallopian tube tissue,

973 SBM.001.001.0004 at 46-7; Robertson at 160 (EXP.001.002.0015_2).
974 T3392 (TRA.500.034.0001_2 at 0106_16-20).
975 T3394 (TRA.500.034.0001_2 at 0108).

> and then in [Parant 2022] where they evaluate the concentrations of various metals in the peritoneal fluid and the blood. They show that women with devices have high concentrations of these metal ions, higher than people with other kinds of metal devices, like joint replacements, and certainly higher than the allowable limits for the European standards. That was the point of the paper. The paper was not to evaluate relationships with severity of symptoms, and the studies were not empowered to do that. So it's not unexpected that those relationships were not evident, and certainly doesn't detract from the main finding of the papers.[976]

940 Sokol challenged this evidence on two bases: first, that neither Parant study examined blood concentrations of metal ions; and second, that the Parant studies did not find that women with Essure had higher concentrations of metal ions than people with other kinds of metallic devices, such as joint replacements.[977] Sokol said:

> However, in the Parant studies they specifically did not examine patients with other metallic implants, specifically excluding patients from the control group that had Essure Devices and were asymptomatic, that had orthopaedic implants and cardiovascular metal implants from the control group … there was no connection with orthopaedic implants and there [were] no blood levels tested.[978]

941 Robertson responded by acknowledging that it was Catinon 2022 that examined the blood concentrations of metal ions. She then said:

> But I don't pull back from my comments regarding the comparison with blood concentrations in women, or in people with other kinds of metal devices because [Catinon 2022] did, at length, go into a comparison and made that point quite clearly[.][979]

942 Catinon 2022 describes the results of metal blood concentration measurements as follows:

> Before explantation, the plasmatic nickel levels were above the superior limit (SL) in 11/17 patients, and so were the plasmatic tin level in 1/9 patient and the total blood chromium level for 2/17 patients. After explantation the total blood tin level was still higher than SL in 3/ 11 patients, and in three cases we observed a higher total blood tin level after explantation compared to the plasma level before explantation.[980]

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976 T4189 (TRA.500.041.0001_2 at 0107_5).
977 T4236 (TRA.500.042.0001_2 at 0014).
978 T4236 (TRA.500.042.0001_2 at 0014_31).
979 T4237 (TRA.500.042.0001_2 at 0015_19).
980 Catinon 2022 at 3 (PUB.001.001.3758).

The authors noted as a relevant limitation of the study:

> The results of blood tests are incomplete due to the retrospective nature of our study. In fact, the patients did not systematically carry out this type of examination.[981]

There is no explanation in Catinon 2022 of what is meant by 'superior limit'.

943 The results of blood analysis were tabulated in Catinon 2022 as follows:[982]

Table 5
Nickel, tin and chromium concentrations (µg/L) in plasma (p) and whole blood (wb) of patients before and after explantation of their ESSURE implants. Plasma nickel < 1.3 µg/L (95th percentile) (Cesbron A, 2013); Whole blood tin < 0.6 µg/L (95th percentile) (Cesbron A, 2013); Whole blood chromium < 0.87 µg/L (95th percentile) (Cesbron A, 2013).

	nickel		tin		chromium	
	Before (p)	After (p)	Before (p)	After (wb)	Before (wb)	After (wb)
1	4.8	<0.5	<0.7	0.23	<0.87	
2	2		<0.1	0.31	0.74	
3	2.6		0.1		0.5	
4	1.2			0.34	1.36	
5	1.4				0.65	
6	1.2			0.25	0.68	
7	1		0.17	0.23	0.5	
8	1.4				<0.5	
9	1.2			0.35	<0.5	
10	0.6				2.65	
11	2.3				<0.5	
12	1.8				0.88	
13	0.3		<0.5	0.85	3.2	
14	1.2			0.66	<0.5	
15	3.5		0.32		<0.5	
16		1.4		0.37		<0.5
17	2.3		1.34	0.73	<0.5	
18	1.6			0.33	0.69	

The study compares the results of plasma and whole blood analysis against the 95th percentile level found in 'Cesbron A, 2013' ('Cesbron 2013'). The title of Cesbron 2013 is 'Metallic profile of whole blood and plasma in a series of 106 healthy volunteers'.

944 Catinon 2022 does refer to two studies of blood analysis in patients with long-term hip

981 Ibid at 3.
982 Ibid at 6.

prostheses, the first with 13 patients and the second with 20 patients. Catinon 2022 said:

> The frequent occurrence of high levels of nickel in the blood for Essure implants, compared to their very rare occurrence for hip prostheses, is probably linked to the high vascularization of the uterine horn tissue, in sharp contrast with the bone support of hip prostheses.[983]

No comparative analysis was undertaken by the authors in respect of other metals. There was no further analysis of this comparative finding in Catinon 2022, and the authors did not seek to draw any conclusions from it. Contrary to Robertson's evidence, Catinon 2022 did not deal 'at length' with the comparison of blood concentrations of metals between Essure and other biomedical devices.

945 Catinon 2022 reported that granulomas were found in 17 of the 18 study patients. The study said:

> The sampling made in the present study, at the implant weld level, explains the systematic observation of (most often) granulomatous inflammation or (in one instance) fibrosis lesions.[984]

The study authors hypothesised as follows:

> However, it also seems plausible that the tin weld corrosion inducing inflammatory granulomatosis could also be responsible on a non-exclusive basis, along with adenomyosis, for the pelvic and intercourse pains and bleeding.[985]

Uterine adenomyosis was found on pathological examination in 14 of the 18 patients. In their conclusion, the study authors hypothesised:

> The presence of foreign body granulomas in contact with the weld zone is, in our opinion, related to wear of the implant weld. This wear phenomenon could explain the high frequency of adenomyosis in the patients we followed (77.8%), but also some local signs of pain and bleeding.[986]

This is one of a number of expansive hypotheses discussed in the study. There was no path of reasoning that I could find in the study relating the finding of granulomas

983 Ibid at 7.
984 Ibid at 3.
985 Ibid at 6.
986 Ibid at 8.

in fallopian tube tissue adjacent to the device and uterine adenomyosis found in 14 patients. The hypothesis seems to be little more than speculation.

946 Robertson relied on the finding of granulomas in Catinon 2022 as evidence that there was active inflammation in those cases. Robertson said:

> But we also see evidence, I think we saw a pretty impressive example of a granuloma this morning where the device is not healed in in the way that the manufacturers intended and now there's capacity for a different kind of outcome.
>
> Are you referring to the Hoogendam article?---Yes, I am.
>
> That's one example, isn't it, and it's not the typical fibrotic tissue formed from chronic inflammatory development?---That's one, but there was about another 12 in the list this morning. Was it Catinon? Yeah, Catinon, p3 shows us in 18 patients all but two have a granuloma response.[987]

For the following reasons I do not accept this evidence.

947 First, in her reports Robertson said that granuloma were part of the foreign body response leading to the foreign material being separated from the rest of the body.[988] She said that '[w]hen associated with implants, a large number of [foreign body giant cells] accumulated around the device cause[s] formation of a foreign body granuloma, that in turn give[s] rise to the formation of the fibrous capsule'.[989] Robertson's evidence suggests that granuloma can be part of a normal foreign body response that progresses to healing.

948 Second, when Sokol was cross-examined about Catinon 2022, the following exchange occurred:

> But there's also granuloma which is identified in the other column, isn't it?---M'hmm.
>
> And granuloma tends to suggest a more active inflammatory state, doesn't it, it's got clusters of cells?---A history of an active inflammatory state, not necessarily active.
>
> But it's more than - it's notable - it's of some relevance to the assessment of

987 T3020 (TRA.500.031.0001_2 at 0094_2).
988 Robertson at 22 (EXP.001.001.0127).
989 Ibid at 111.

> ongoing active or some active inflammation; isn't that right?---A history of active inflammation.[990]

Sokol's evidence is consistent with Robertson's general evidence about the role of granulomas in the foreign body response.

949 Third, no other observation is recorded in Catinon 2022 following histopathological examination to indicate that active inflammation was occurring in the observed granuloma.

950 Robertson said that the results of Goodwin 2023 were consistent with and strengthened the evidence for her opinion that metal ions and particles were present in higher concentrations in tissues adjacent to Essure.[991] She said that the detection of tin particles in the same vicinity as findings of chronic inflammation associated with Essure in other studies indicated the likelihood that local immune cells were being directly impacted by the tin ions and particles.[992] Robertson said:

> In my opinion, [Goodwin 2023] provides compelling evidence showing both effects of the Device on the fallopian tube environment, and effects of the fallopian tube environment on the Device. In my opinion, the degree of both elements of this twoway interaction and its consequences are likely to progressively increase over time and to make a causal contribution to the pathophysiological mechanisms by which the Device affects the immunology and reproductive physiology, and risk of adverse health symptoms, of women with Essure Devices.
>
> In my opinion [Goodwin 2023] supports the likelihood of interdependence between both elements of this two-way interaction – both Device effects on tissue and tissue effects on the Device – that would progressively increase the adverse health effects of the Device over time. Ongoing corrosion of the Device (or its parts) would provoke increasing tissue injury and inflammation over time, which in turn is likely to increase the rate of corrosion, because of the hostile effects on metal integrity of tissue components and substances that are elevated in inflammatory environments[.] In turn, corrosion and metal ion and particle release increases inflammation[.]
>
> In my opinion, [Goodwin 2023] provides compelling evidence that corrosion of Essure Device components and leaching of metal ions and particles from the Device are promoted by the fallopian tube environment. The extent of impact of the fallopian tube environment is likely to increase over time after placement. I previously opined on the limitations of in vitro testing of Essure

990 T4114 (TRA.500.041.0001_2 at 0032_15).
991 Robertson at 7 [9] (EXP.001.002.0020_2).
992 Ibid at 9 [16].

> Devices particularly when the test conditions do not reproduce the in vivo environment, or recapitulate the specific interactions between bodily tissues and fluids and the Device[.] The data reported in the article further emphasise the limitation of in vitro testing for understanding Device performance in the in vivo setting. This supports the opinions I expressed in my first report and second report that FDA testing standards were not adequate to evaluate safety and risks of the Essure Device, as they do not recapitulate the in vivo environment of the fallopian tube.[993]

951 In her first report, Robertson outlined three categories of possible outcomes for women implanted with Essure. The third category was that implantation leads to sub-clinical adverse effects that the women are unaware of and which do not result in overt symptoms.[994] She said:

> Having considered the article from [Goodwin 2023] (and the articles cited therein), and based on the additional opinions I have formed, I now have greater confidence that many women with Essure Devices in category 3 do indeed have adverse health effects due to the Device, even though they may not experience obvious signs or symptoms.[995]

952 A preliminary observation is that Goodwin 2023 records results based on examination of tissue and explanted Essure devices from only four women. The authors stated that limitations of the study included the small group of participants and uncertainties about procedures used to obtain the samples from individual participants. The scope and limitations of the study do not seem to justify the weight that Robertson attributed to the findings recorded in it.

953 An example is Robertson stating that Goodwin 2023 showed a consistent relationship between the concentration of metal ions in tissue and proximity to the device. The study reported metal concentrations at three points of the fallopian tube. The study found the highest concentration of tin in tissue at the region of the solder joint, but no statistical difference in the concentrations of iron, titanium, nickel or chromium between sections.[996]

954 It is not clear what findings reported in Goodwin 2023 Robertson relied on to support

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993 Ibid at 13-4.
994 Ibid at 15 [34].
995 Ibid.
996 Goodwin 2023 at 11 (MSC.001.002.0013).

her opinion. The study was blinded to specific patient factors, including wear time.[997] The study found significant concentration of tin in tissue close to the solder joint. However, the authors noted that tin has not been thoroughly studied as a biomaterial and that the inflammatory process associated with it is unknown.[998] Goodwin 2023 does not consider whether the fallopian tube environment is relevant to the observed rate of corrosion. There is no support in the study for Robertson's opinion that 'the extent of impact of the fallopian tube environment is likely to increase over time'. Further, it is not clear how the Goodwin 2023 data emphasises the limitation of in vitro corrosion testing. There is no obvious inconsistency between the data and the corrosion bench test or Aslan 2022.

955 Chrzanowski said that tissue surrounding an Essure insert will receive an undiluted load of metal elements due to leaching and corrosion. He said that the local accumulation and concentration of metal elements can be substantially higher than that measured in the corrosion bench test.[999]

956 Chrzanowski said that release of several metal elements simultaneously into local tissue, some of which have toxic effects, is a factor that may trigger an adverse reaction to the device.[1000] He said that the local release of metal ions results in the upregulation of the immune response, oxidative stress and localised cell death, which contributes to and prolongs the chronic inflammatory response.[1001]

957 Chrzanowski agreed with Robertson that the levels of metal ions and particles required to elicit a harmful immune response is usually far less than the levels required to elicit 'toxicity' as commonly understood.[1002]

958 Sokol explained that metal particles released from the device would be taken up by

997 Ibid at 29.
998 Ibid at 27.
999 Chrzanowski at 8 (EXP.001.002.0012).
1000 Ibid.
1001 Chrzanowski at 25 (EXP.001.001.0082).
1002 Biomaterials JER at 7 (EXP.500.001.0006).

macrophages in a foreign body response.[1003] She said that the ongoing leaching of metal ions could trigger ongoing active inflammation, but could also activate the anti-inflammatory immune response.[1004]

959 Sokol responded to Chrzanowski's evidence about oxidative stress and toxicity as follows:

> It is noted in Professor Chrzanowski's report that metal ions from the Essure Device can "induce oxidative stress and toxicity, thus trigger the immune response"[.] If this is the case, one would expect to see evidence of chronic inflammation. As previously discussed, this could be identified using laboratory measurements of CRP, hsCRP, ESR, and/or fibrinogen. Alternatively, one would expect to see evidence of active inflammation in the fallopian tube, which would be evidenced by the presence of excessive neutrophils in the tissue[.] In the absence of evidence of active inflammation with either systemic markers (e.g., CRP) or tissue markers (e.g., neutrophils), it cannot be assumed that the immune response is inappropriately activated.[1005]

960 Eiselstein said that there was no evidence of pitting corrosion of stainless steel or nitinol in the corrosion bench test, the retrospective evaluation of data from the Phase II study and Pivotal trial, or the corrosion studies. He said that corrosion was only observed on the tin solder. He said that the corrosion bench test showed a rate of release of nickel and tin from Essure that was many times lower than the standard subsequently set by the FDA for the tolerable intake/exposure levels for those metals, and that these metal release rates were subsequently confirmed in Aslan 2022.[1006]

961 Eiselstein said that Robertson did not provide any basis for the asserted toxicity of the metals released from Essure, or the level at which they become toxic and noxious.[1007]

962 Eiselstein said that the metals used in Essure are commonly used in other implants. He said that there was no evidence of elevated metal ion release rates from Essure compared to other implants currently available.[1008]

1003 T4230 (TRA.500.042.0001 at 0008).
1004 T4231 (TRA.500.042.0001 at 0009).
1005 Sokol at 5 (EXP.500.500.0004).
1006 Eiselstein at 79 (EXP.001.002.0004).
1007 Ibid at 98 [11.5.1] (EXP.001.002.0004).
1008 Eiselstein at 14 [17] (EXP.001.002.0017).

Submissions on Essure corrosion studies

Turner

963 The corrosion bench test revealed pitting corrosion of the tin-silver solder joint and a continuing and non-linear release of nickel and tin at the 180-day point. The potentiodynamic test showed corrosion of the solder in each device and corrosion of the nitinol outer coil of one device. Chrzanowski said, in relation to the results of the corrosion bench test:

> So these results clearly show the device corrodes, releases the metal element, releases the metal ions. As I mentioned earlier, there was no reference really to evaluate this against the ingested levels and the concentration in the metals which are eluted into the tissues which are surrounding the device will be contributing to the ongoing inflammatory process. While the process can be considered slow, it might not be considered slow for the cells which we stomach and are unable to digest it and exclude from the cells and rather accumulate it and build up the cumulative responses to these. So this test shows that there was an ongoing corrosion process in some places relatively severe and I don't think we can deny this from these results.[1009]

964 Chrzanowski said that the samples in the potentiodynamic testing did not pass the acceptance criteria, and that taking into account the body's electrical potential, the device would corrode inside the body.

965 The Court should accept Chrzanowski's evidence that the features of the Essure design, including its high surface area and combination of metals, heightened the risk of corrosion. Eiselstein, by comparison, sought to downplay the extent and significance of Essure corrosion.[1010] There is compelling objective evidence in the corrosion studies which supports Chrzanowski's view that Essure corrodes in vivo and releases metal ions and particles into surrounding tissues and fluids:

(a) Catinon 2020 showed the presence of tin-based particles in five out of 10 patients, the presence of nickel, chromium, iron and titanium on mineralogical analysis, and observations that the tin-silver solder was degraded. Under cross-examination, Eiselstein limited his concern about metal contamination of

1009 SBM.001.001.0004 at 91 [253]; T3245 (TRA.500.033.0001_2 at 0088_1-14).
1010 SBM.001.001.0004 at 92 [256].

specimens during sample preparation from the tissue sample staining only to iron, and not to the presence of tin, titanium, chromium or nickel.[1011]

(b) Parant 2020 showed statistically significant high concentrations of nickel and chromium in tissue closer to the device, and compelling evidence of leaching of those metals from the device years after implantation. Eiselstein accepted in cross-examination that the concentrations of nickel and chromium in tissue closer to the device were statistically significant.[1012]

(c) Parant 2022 found significantly higher concentrations of nickel, chromium and tin in the fallopian tube tissue in the symptomatic patient group. Further, the study did not reveal a clear downward trajectory for concentrations of nickel and chromium over the long-term.

(d) Catinon 2022 showed evidence of metal particles, often in clusters, in the fallopian tube tissue of each patient.

(e) Aslan 2022 showed a continuously increasing release of nickel and titanium, with no evidence of a plateau. The study found the tin-silver solder and the nitinol outer coil showed varying amounts of corrosion. Observations of the nitinol coil indicated that corrosion was occurring.[1013]

(f) Finally, Goodwin 2023 showed that concentrations of tin were highest in the region of the solder, and that iron and other metal ions were also present. The study found corrosion of the tin-silver solder, signs that the surface oxide thickness or composition of the nitinol coil had been altered, and evidence of stainless steel corrosion that was likely produced by fretting between the coils. The study found particles containing tin, iron, phosphorous and sodium integrated into the inner tissue surrounding the device.[1014]

1011 Ibid at 96.
1012 Ibid at 95 [265](a).
1013 Ibid at 94 [262].
1014 Ibid at 95 [263].

966 The totality of the published studies provides convincing evidence that there is ongoing leaching of nickel, chromium, tin, titanium and iron from Essure into the surrounding tissues and peritoneal fluid, and that there is accumulation of these metals in ion or particulate form in the tissues and fluid surrounding the device for years following implantation. These studies show that the device continues to corrode in vivo and that this corrosion is not limited to the tin-silver solder.[1015]

967 As Robertson explained, metals present in ionic or particulate form that leach from devices are more likely to provoke chronic inflammation. She explained that the phenotype of macrophages is highly responsive to metals leached from biomedical devices, and that phagocytosis of metal particles can lead to inflammatory and tissue destructive reactions of varying degrees. The inflammatory response can be perpetuated by the continued presence of a high concentration of ions and by the phagocytosis of metal particles. Robertson's evidence about these matters is further strengthened by the results of Goodwin 2023.[1016]

968 Robertson's observation that the highest concentrations of metal ions and particles were found in the same vicinity as immune cell infiltrates strengthens a causal connection between the two.

Defendants

969 Eiselstein's evidence should be preferred to that of Chrzanowski and Robertson to the extent of any inconsistency between them. First, Eiselstein is better qualified than Chrzanowski and Robertson to give evidence about corrosion and leaching. This is because he has more than 40 years' experience as a metallurgist and corrosion engineer, and specialises in materials science as applied to product design and material testing and evaluation.[1017] By comparison, Chrzanowski is a professor of nanomedicine, with a particular research interest in the development of

1015 Ibid at 95 [264].
1016 Ibid at 46.
1017 SBM.500.001.0003_2 at 478 [4.4].

nanoengineered biomaterials with biological applications.[1018] Further, as she acknowledged, Robertson is unqualified to provide opinions on the corrosion studies and on metal ion/particle release from biomedical devices.[1019]

970 It is accepted that some leaching and corrosion of the metal components of Essure occurs. However, the extent of that corrosion and leaching is limited and Turner has failed to discharge her onus of proving that there are any material adverse consequences flowing from it.[1020]

971 Chrzanowski relied on Aslan 2022 to demonstrate the risk of galvanic corrosion between different elements of Essure, and the need to consider stressors that are placed on the device in vivo when assessing its corrosion properties. As to the first issue, Aslan 2022 notes that the tin-silver solder acted as an anode in the galvanic corrosion that occurred. That is consistent with Eiselstein's evidence that the solder acted as a sacrificial anode protecting other elements of the device.[1021] The Court should also accept Eiselstein's evidence that the metal release rates reported in Aslan 2022 and the corrosion bench test were significantly below the FDA limits.

972 In relation to the second point made by Chrzanowski, Eiselstein's evidence was that:

(a) he did not consider mechanical loading to be relevant to the *in vivo* experience of an Essure Insert;

(b) *in vivo*, Essure Inserts would not be subjected to sufficient fatigue cycles to cause fatigue damage – which is supported by the lack of evidence of fatigue cracking in any explanted Essure Inserts; and

(c) he is "unaware of anyone that did, for instance, metal release rate testing under the fatigue loading conditions";

and therefore, Professor Chrzanowski's criticism was not appropriate.[1022]

973 It should be concluded that both Catinon 2020 and Catinon 2022 are unreliable on the basis of the criticisms expressed by Eiselstein, and because of the unexplained failure

1018 Ibid at 479 [4.4](c).
1019 Ibid at 480 [4.4](e).
1020 Ibid at 480 [4.6].
1021 Ibid at 483.
1022 Ibid at 486 [4.30] (citations omitted).

by the authors of both studies to disclose an obvious material conflict.[1023]

974 No weight should be given to Goodwin 2023. The authors themselves noted that the results were preliminary and that no final conclusions can be drawn from the data until the entire 522 study is complete. Further, the data was collected from only four patients, and the authors noted that the results from this relatively small group may not include all the ways in which the device and body interact, or the frequency with which any observed phenomenon occurs.[1024]

975 Eiselstein's evidence analysing and critiquing the findings in Goodwin 2023 should be accepted.[1025] This undermines Robertson's reliance on that study to show that elevated metal ion levels were found in tissue surrounding the Essure device,[1026] and as evidence that corrosion and leaching of metal ions and particles from the device are promoted by the fallopian tube environment.[1027]

976 In her supplementary report, Robertson said:

> In my opinion, [Goodwin 2023] provides compelling evidence showing both effects of the Device on the fallopian tube environment, and effects of the fallopian tube environment on the Device. In my opinion, the degree of both elements of this twoway interaction and its consequences are likely to progressively increase over time and to make a causal contribution to the pathophysiological mechanisms by which the Device affects the immunology and reproductive physiology, and risk of adverse health symptoms, of women with Essure Devices.
>
> In my opinion [Goodwin 2023] supports the likelihood of interdependence between both elements of this two-way interaction – both Device effects on tissue and tissue effects on the Device – that would progressively increase the adverse health effects of the Device over time. Ongoing corrosion of the Device (or its parts) would provoke increasing tissue injury and inflammation over time, which in turn is likely to increase the rate of corrosion, because of the hostile effects on metal integrity of tissue components and substances that are elevated in inflammatory environments[.] In turn, corrosion and metal ion and particle release increases inflammation[.]
>
> In my opinion, [Goodwin 2023] provides compelling evidence that corrosion

1023 Ibid at 493.
1024 Ibid at 495 [4.59].
1025 Ibid at 496.
1026 Ibid at 496 [4.63].
1027 Ibid at 499 [4.75].

> of Essure Device components and leaching of metal ions and particles from the Device are promoted by the fallopian tube environment. The extent of impact of the fallopian tube environment is likely to increase over time after placement. I previously opined on the limitations of in vitro testing of Essure Devices particularly when the test conditions do not reproduce the in vivo environment, or recapitulate the specific interactions between bodily tissues and fluids and the Device[.] The data reported in the article further emphasise the limitation of in vitro testing for understanding Device performance in the in vivo setting. This supports the opinions I expressed in my first report [and] second report [that] FDA testing standards were not adequate to evaluate safety and risks of the Essure Device, as they do not recapitulate the in vivo environment of the fallopian tube.[1028]

For two reasons, the conclusions expressed by Robertson do not bear analysis. First, as she has repeatedly conceded, she is not a metallurgist and does not have specialised knowledge in how 'metal devices break down in the body'.[1029] Second, Robertson does not provide an intelligible methodology or scientific basis for concluding that any asserted inflammation in the fallopian tube will create 'the hostile effects on metal integrity' described in her supplementary report.[1030] Robertson's inability to explain her methodology and reasoning for her bare assertion that Essure will corrode in the fallopian tube environment is of little surprise considering that she does not have the relevant specialist training, knowledge or experience in this field.[1031]

977 Robertson and Chrzanowski rely on Parant 2020 in support of two hypotheses: first, that there are higher levels of nickel and chromium ions in the immediate vicinity of the Essure inserts; and second, that there is a causal relationship between the leached metal ions and adverse consequences experienced by wearers of Essure. For the following reasons, the study does not support these hypotheses. First, the study authors specifically accept that a cautious approach should be taken to the issue of causation.[1032] Second, Eiselstein's evidence about the significant limitations on the reliability of the findings in Parant 2020 should be accepted.[1033]

1028 Robertson at 12 (EXP.001.002.0020_2) (footnotes omitted).
1029 SBM.500.001.0003_2 at 501 [4.78].
1030 Ibid at 502 [4.80].
1031 Ibid at 504 [4.85].
1032 Ibid at 507 [4.100].
1033 Ibid at 508 [4.101].

978 Parant 2022 is not a reliable evidentiary foundation for the assertion that there are elevated levels of tin, chromium and nickel in the fallopian tube and peritoneal fluid of women with Essure, compared to women without.[1034] First, as Eiselstein noted, the finding of metal in tissue surrounding the Essure devices is to be expected.[1035] Second, the study did not include patients undergoing laparoscopic removal of Essure inserts without symptoms as a control group. Third, the authors accept that the study does not demonstrate a causal link between symptomatology and the concentration of metallic elements.[1036] Fourth, the authors do not explain why the control group without Essure devices were having laparoscopic surgery, or what if any symptoms they were experiencing.[1037]

Analysis

979 The Essure device, like all biomedical devices with metal components, corrodes in vivo.

980 There is no doubt that galvanic corrosion occurs in vivo between the tin-silver solder of the device acting as an anode, and the nitinol outer coil acting as a cathode. That conclusion is supported by the results of the corrosion bench test, Aslan 2022 and the potentiodynamic test, and with the outcomes of the other Essure corrosion studies. Each of the tests and studies showed that the tin-silver solder experienced the most significant corrosion, which resulted in the highest rate of metal release.

981 There is no evidence of crevice, pitting, fatigue, fracture or stress corrosion to the 316L stainless steel or nitinol components of explanted Essure devices examined in any of the studies.[1038]

982 Chrzanowski relied on Goodwin 2023 as evidence that fretting corrosion occurred. The single reference to fretting in Goodwin 2023 is ambiguous and uncertain. The

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1034 Ibid at 509 [4.102].
1035 Ibid at 509 [4.105].
1036 Ibid at 510 [4.109].
1037 Ibid at 511 [4.110].
1038 Eiselstein at 12 [1.7] (EXP.001.002.0004).

body of the study records evidence of tissue adhered to the stainless steel coils that contained particles of tin, iron, phosphorous and sodium. After cleaning, the stainless steel coils had an as-manufactured appearance with some tissue remnants on the surface, which were etched into the surface or an adhered layer, or both.[1039] The metal ions present in one structure were analysed using EDS. However, it is not clear how any findings of the surface analysis were considered by the authors to be relevant to the likelihood that fretting had occurred. Further, I note Eiselstein's concerns about the efficacy of the EDS analysis and his evidence as to other possible explanations for the presence of metal ions that were found. No other test or study records evidence of fretting. The uncertainty associated with the single mention of the likelihood of fretting is not a sufficient basis to conclude that corrosion of the Essure device in vivo has been accelerated by, or has resulted from, a process of fretting.

983 I accept Eiselstein's evidence that the results of the tests and corrosion studies showed that the rate of metal release from the device decreased with time.[1040] Eiselstein conducted a careful analysis comparing the results of the corrosion bench test with Aslan 2022. I accept his conclusion that the outcome of those tests is consistent, and shows a decreasing rate of release of relevant metals from the device over the test period. The results of Parant 2022 are not inconsistent with a slowing rate of metal release over time. The study relevantly shows accumulation of metals in tissue proximate to the device. The evidence points to the conclusion that the metal deposits are accumulated over time, and do not reflect metal release being maintained at the same rate.

984 Chrzanowski was critical that there had been no corrosion testing under mechanical loading. He said the comments in Aslan 2022 supported his opinion that this should have occurred. However, I accept Eiselstein's opinion that there is no evidence that the Essure device is subject to mechanical forces in vivo that are sufficient to induce

1039 Goodwin 2023 at 19-20 (MSC.001.002.0013).
1040 T4361 (TRA.500.043.0001_2 at 0034).

stress corrosion.

985 I do not attach great weight to the potentiodynamic test conducted by CTL in 2012. The authors said, and Eiselstein strongly reinforced, that a potentiodynamic test is not a reliable basis for projecting real-world corrosion behaviour. I accept Eiselstein's evidence that the most significant corrosion in the test was of tin.

986 The maximum rate of release of nickel and tin measured in the corrosion bench test and in Aslan 2022 is far below the current FDA guidance recommendation for parenteral exposure to those metals. Chrzanowski was critical of the bench test on the basis that the test solution did not mimic in vivo conditions. However, he accepted that the test solution may have been more corrosive than the fallopian tube environment. In any event, there is no evidence on which it could be concluded that the rate of metal release in vivo is higher than was shown in the corrosion bench test or Aslan 2022. I accept, as Eiselstein said, that there is no evidence that the release rates of nickel, chromium, titanium or iron from Essure were higher than for other currently available biomedical devices.

987 Parant 2020 found no relationship between reported symptoms and the concentration of metal elements. The authors said that the study simply highlighted the presence of nickel and chromium, and that it was not certain these metals were responsible for any adverse effects.[1041] Parant 2022 did not show any correlation between the concentrations of metal elements and symptomology. The authors pointed out the difficulty of determining whether metal particles or the combination of several metals can cause adverse effects. They said that long-term epidemiological studies and non-clinical animal models were needed to answer this question.

988 For reasons I have already expressed, I place very little weight on the Catinon studies.

989 Evidence from the studies suggests that at least some of the metal particles and ions that corrode from the device accumulate in local tissue. I accept Sokol's evidence that

[1041] Parant 2020 at 4 (PUB.001.001.3197).

there will be a foreign body response to corroded metal particles, and that metal ions will trigger an immune response that may involve active inflammation or that may be anti-inflammatory. The immune response to corroded particles and ions may explain why the foreign body response to Essure takes longer than expected to resolve. However, the corrosion evidence does not, without more, establish the likelihood that Essure caused ongoing pathological chronic inflammation.

990 Corrosion of Essure in vivo is potentially relevant to Turner's case in two further ways. First, I accept the evidence of Robertson and Sokol to the effect that DTHR can result from a level of corrosion far below the FDA parenteral dosage recommendation.

991 The second matter is Turner's argument that there was a risk of breakage or fragmentation of the device resulting from corrosion and/or fatigue. The studies are evidence that there was significant corrosion of a solder joint in vivo. However, there is no evidence in the studies of that joint failing in vivo resulting in the device coming apart. Further, the studies do not suggest a level of corrosion or fatigue affecting the nitinol or stainless steel components of the device to a degree that results in a risk of breakage or fragmentation.

992 Further consideration of the relevance of corrosion to the inflammatory response to Essure, incidence of DTHR and whether there was a risk of device breakage or fragmentation in vivo is set out in Chapter XVIII.

XIV. OTHER PROPOSED MECHANISMS CAUSING ONGOING CHRONIC INFLAMMATION

993 Turner submitted that there are various physical and chemical features of Essure, and of the fallopian tube and uterine tissues at the intended site of device insertion, that interact at the time of insertion and afterwards to contribute to incomplete would healing in some women. She submitted that these features of the device and its location increased the risk that it would cause an ongoing chronic inflammatory

response in at least some women.

994 Some of the mechanisms for which Turner contended are dealt with in the above reasons. I consider the further mechanisms in the following paragraphs.

Micro-movements causing ongoing mechanical injury

995 Turner submitted that the outer nitinol coil of the Essure device was designed to cause initial injury to the fallopian tube upon implantation, and therefore had the potential to cut into, erode and cause ongoing tissue injury and inflammation in the event of movement. Both Chrzanowski and Robertson described the nitinol outer coil edges as 'sharp'. Turner submitted that the device was at least sharp enough to cause bleeding and damage to the inner layers of the fallopian tube, and therefore to cause ongoing injury and chronic inflammation.[1042] I note that neither Chrzanowski nor Robertson had examined an Essure device when they expressed these opinions.

996 The defendants submitted that Chrzanowski and Robertson's evidence in relation to this issue amounted to a hypothesis without proper evidentiary support.[1043]

997 Chrzanowski and Robertson said that the peristaltic action of the fallopian tube and mechanical loading during normal daily activities could cause micro-movements at the interface between the device and adjacent tissue. They said that these micro-movements created a risk of ongoing micro-injury and chronic inflammation causing an incomplete fibrotic response.

998 Robertson explained peristaltic activity as the complex network of longitudinal and circular muscles in most tubes in the body, including the fallopian tube, coordinating rhythmically to propel things up and down the tube.[1044] In the fallopian tube, this includes delivering sperm in an upwards direction to where the ovum will be or, in the second half of the menstrual cycle, moving an early embryo down the tube into the uterus. She said that peristalsis occurs throughout the day and had the potential

1042 SBM.001.001.0004 at 48.
1043 SBM.500.001.0003_2 at 175 [1.11](f).
1044 T3177 (TRA.500.033.0001_2 at 0020).

to cause micro-movement between the device and surrounding tissue.[1045] Robertson disagreed with Badylak's opinion that after implantation and the fibrotic process, peristaltic action, at least in that area of the fallopian tube, would no longer occur. She said that the outer muscularis layer of the fallopian tube would be largely intact at least for the first several months. She said that the presence of the device could possibly interfere with the coordination of muscles, but even if the muscles were dysregulated or uncoordinated, the contractile activity would still occur.[1046]

999 Chrzanowski explained that stiffness/hardness is the characteristic of a material. He said that 'compliance' refers to how a device bends or conforms under load.[1047] He said that both stiffness/hardness and compliance influence micro-movements and the potential for micro-injury:

> So your stiffness of the surface influences direct responses of the cells which contact the device. Your compliance is considered as the, in a sense, mechanical force which is applied potentially to the cells. So you have contact versus pushing and the pushing comes from the compliance and the contact comes from the mechanical properties of the surface. So your mechanical properties of the surface are communicating, are talking to the cells what to do, but also mechanical stress which is applied through the bending of the device which is associated with the compliance of the device and the lack of compatibility which we sometimes refer as the lack of biomechanical compatibility with the tissues which generates these micromovements is a push, mechanical push on the cells.[1048]

1000 Chrzanowski explained that 'Young's modulus' is a measure of the stiffness or hardness of a material. He said that there were two orders of magnitude difference between the stiffness or hardness of the Essure metal components and adjacent tissue, which meant that micro-movements were expected to occur and cause continuous disruption and irritation of the tissue, promoting an immunological response.[1049] He added:

> While in the documentation provided to me, I have not seen the evidence for the micromovements of the Essure device in the soft tissues, based on my

1045 T3178 (TRA.500.033.0001_2 at 0021).
1046 T3180 (TRA.500.033.0001_2 at 0023).
1047 T3166 (TRA.500.033.0001_2 at 0009).
1048 T3167 (TRA.500.033.0001_2 at 0010_3-17).
1049 T3162 (TRA.500.033.0001_2 at 0005).

> expertise in biomedical engineering it is my expectation that micromovement[s] happen and contribute to the inflammatory responses. The rapid build-up of the fibrotic tissue around the Essure device gives a confidence that the micromovements (and potentially microinjuries) occur and they contribute to the chronic inflammatory response.[1050]

He said that the tissue between the coils would become squashed because of the different ways the inner and outer parts of the device bend.[1051]

1001 Chrzanowski further explained in his oral evidence:

> So during the normal physical activity, walking, running, squatting, these muscles will be perpetuating forces towards the fallopian tube. These forces naturally will be then transferred to the Essure Device and will be interacting with the Essure Device. So what it means is that the tissue will be subjected to certain forces which will deform the tissue. But then we have the implant which is sitting within the tissues, which is much stiffer, which is made of completely different material than the tissues, so it's deformation is very different, the rate of deformation is different. Therefore there will be micromovements at the interface between the implant and the surrounding tissues. So all this will contribute to relative movements of the tissue and the implant, and understanding that there is a capsule around the implant, there is a possibility that this implant will be dislocated and has the tendency, or may have a tendency, for small dislocations.[1052]

1002 In his primary report, Eiselstein responded to Chrzanowski's evidence on this topic as follows:

> I disagree with Dr. Chrzanowski's many statements with respect to device micromovements against the fallopian tube and the substantial differences between the elastic moduli of metallic Essure components compared to soft tissue. Dr. Chrzanowski's statements regarding substantial differences in elastic modulus are misguided as his statements hold true for most, if not all implantable medical devices. For instance, stainless steel stents and pacing leads are placed in vessels of the beating heart, where they are subjected to micromotions and have the same "order of magnitude difference in Young's modulus between soft tissues and the outer metal coil" he is concerned about. Yet many millions of these procedures have been performed[.] Furthermore, it is not the difference in elastic modulus that is important but the stiffness of the device with respect to the fallopian tube tissue. I have observed having handled an Essure Device, that these devices are quite flexible—i.e., very compliant, like tissue, and bend under their own weight. This is inconsistent with Dr. Chrzanowski's thoughts regarding the differences in elastic modulus between the device and tissue and that this difference somehow suggests an increase in micromotion. If this were an issue it becomes hard to explain why

1050 Chrzanowski at 16 (EXP.001.001.0082).
1051 T3165 (TRA.500.033.0001_2 at 0008).
1052 T3159-60 (TRA.500.033.0001_2 at 0002_31-0003_18).

> any metals would be used for medical devices and all metals have significantly higher elastic modulus compared to tissue. I also note he states: "in the documentation provided to me, I have not seen the evidence for the micromovements of the Essure device in the soft tissues". Further, even if micromotion does occur he notes that "micromovements are microinjuries such as abrasion, lesion, which leads to the formation of a fibrotic scar tissue." The formation of scar tissue likely helps to seal the fallopian tube which is the purpose of the Essure device.[1053]

1003 Eiselstein disagreed with Chrzanowski's explanation of relevant terms. He explained that stiffness and compliance relate to the geometry of an object, whereas the elastic modulus is a property of the material from which an object is constructed.[1054] He said that Essure is quite compliant along its length, but is more rigid in the radial direction. He said that stiffness/compliance was the design element of a device which was most relevant to the potential for micro-movement. He said that when an Essure device was activated, the outer coil expanded into the tissue of the fallopian tube. He said that this was similar to other devices such as cardiovascular stents. His suspicion was that there would be no movement if the device was stuck in tissue. He said he could not find any technical literature on the degree of compliance or motion of the fallopian tube.[1055] He said that the device would stiffen the fallopian tube in the radial direction and possibly in the longitudinal direction.

1004 Eiselstein said it appeared to him that the edges of the outer nitinol coil were rounded. He said that 'sharpness' was a relative term, and would depend on the radius of the curvature.[1056] He said that he was not aware of any evidence supporting Robertson's statement that the outer coil of the device can cut into and erode the inner layers of the fallopian tube.[1057]

1005 Badylak challenged the idea that the outer nitinol coils had a sharp edge that would cut into tissue. He said that the device was designed to expand to a point that it compresses and embeds itself within the wall of the fallopian tube, just like a nitinol

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1053 Eiselstein at 87 [10.4.1] (EXP.001.002.0004).
1054 T3186 (TRA.500.033.0001_2 at 0029).
1055 T3192 (TRA.500.033.0001_2 at 0035).
1056 T3157 (TRA.500.032.0001_2 at 0125).
1057 Eiselstein at 95 [11.1] (EXP.001.002.0004).

stent would do in a coronary artery, ureter or oesophagus. He said that the purpose of the device was to become embedded so that it would not move.[1058] Badylak said that he was not aware of any scientific paper or discussion raising the possibility of micro-motion in relation to Essure or in the context of other devices that have similar modes of action.[1059] He said the body's response to any micro-movements that did occur would be irritation leading to fibrous tissue deposition and scarring, which would not be of concern.[1060]

1006 There is no evidence to support the theories of Robertson and Chrzanowski linking injury caused by the edges of the outer nitinol coil of the Essure device and/or by micro-movements between the device and adjacent tissue, to the risk of ongoing micro-injury and active chronic inflammation. There is no evidence about the degree of forces that would be applied to the fallopian tube by normal physical activity, or the impact those forces would have on tissue surrounding an implanted Essure device. I accept the evidence of Eiselstein and Badylak that there is no scientific literature or studies that raise the possibility of this mechanism in relation to Essure or other devices that operate in a similar way, or that compare the design features of the device to other biomedical devices to show why, in the case of Essure, micro-movements and micro-injury to tissue are likely to contribute to persistent chronic inflammation. The lack of mention in scientific literature would be surprising if there were a real risk of micro-movements and micro-injury resulting in active chronic inflammation in Essure and other biomedical devices.

1007 I accept Eiselstein's evidence that 'sharpness' is a relative term. Eiselstein had the advantage of being able to examine an Essure device when he prepared his primary report. I accept his evidence that the edges of the outer nitinol coil were rounded. As Eiselstein and Badylak said, there is no evidence that the outer coil of the device is sufficiently 'sharp' to cut into or erode fallopian tube tissue.

1058 T3153 (TRA.500.032.0001_2 at 0121).
1059 T3193 (TRA.500.033.0001_2 at 0036).
1060 T3196 (TRA.500.033.0001_2 at 0039).

1008 I accept Eiselstin's explanation of the terms 'stiffness', 'compliance' and 'elastic modulus', and his application of those concepts to implanted biomedical devices including Essure. I found Eiselstein's explanation of the science to be clearer and more logical than Chrzanowski's.

1009 I conclude that the evidence of Chrzanowski and Robertson on this issue does not rise above unsubstantiated theory.

Vulnerability of the fallopian tube and uterus to incomplete wound healing

1010 Robertson gave the following reasons for why the fallopian tube and uterus are vulnerable to incomplete healing and formation of a chronic wound:

> In my view, given the special physiological features of [the] fallopian tube, it is counterintuitive to expect that injury to the fallopian tube as caused by the Essure device could be achieved without substantial impact on reproductive physiology.[1061]

1011 Robertson said that 'the uterus and fallopian tube have an unusual hypervigilant immune response and propensity to inflammation' ('hypervigilance theory').[1062] She said that the specialised immune response associated with cycling between pro-inflammatory and anti-inflammatory states conferred a 'hypervigilant immune capacity' on the uterus and fallopian tubes that is likely to promote a robust pro-inflammatory response to a medical device and any materials leached from it. In her primary report, Robertson said:

> Fertility and healthy pregnancy depend on a remarkable ability of the uterine immune response to cycle between pro-inflammatory (estrogen-dominated) and anti-inflammatory (progesterone-dominated) states. This fluctuation in responsiveness to inflammatory cues confers upon the uterus a hyper-vigilant immune capacity, and allows it to sense and respond selectively to gametes, embryos, microbes, and foreign entities or noxious stimuli. Its sophisticated discriminatory capabilities mean that the uterus can mount highly coordinated and precisely controlled immune responses that accept and tolerate some entities (eg. sperm and embryos), while rejecting others (eg. pathogenic microbes), at appropriate stages of the menstrual cycle.
>
> …

1061 Robertson at 77 [288] (EXP.001.001.0127_2).
1062 Ibid at 12 [8].

> In women with a chronic wound response and persistent chronic inflammatory response to the Essure Device, the ongoing pro-inflammatory stimulus would be expected to change the behaviour (phenotypes) of immune cells not just in the immediate vicinity, but also more broadly in the tissue. This happens because the pro-inflammatory mediators affect the proliferation and function of immune cells in the lymph nodes draining the fallopian tube and uterus … and the cells produced in this site then recirculate to become disseminated in nearby tissue sites in the female reproductive tract (elsewhere in the uterus, fallopian tubes and ovaries) and elsewhere in the body.[1063]

Robertson said that the fallopian tube had a dynamic and selective immune response that equipped it 'with a similar hypervigilant immune response to the uterus'.[1064]

1012 In her primary report, Sokol responded to Robertson's evidence as follows:

> I take issue with the hypothesis that the immune response in the uterus is hypervigilant. There are no data to support the hypothesis that the immune response in the fallopian tube is particularly hypervigilant under normal, or homeostatic, conditions or even under conditions of injury that do not involve the presence of an antigenically distinct embryo or infectious agent. The [study by Wang et al referenced by Robertson] consists of a review discussing the immune response to fallopian tube ectopic pregnancies. Ectopic pregnancies are defined by the implantation of a fertilized egg in a location outside of the uterus where its development into a viable pregnancy cannot be supported by the body. But the Essure Device is not an ectopic pregnancy. It does not have proteins that could be identified as "non-self" by the immune system. It does not grow, progressively penetrate, and link vascular systems as an ectopic pregnancy does. And it is important to note, that just as the immune response can reject the presence of antigenically distinct embryos in the fallopian tube, it can reject the presence of antigenically distinct tissue transplants in other organs. This is a central immune property and does not indicate any specialization or vigilance of the immune system in the fallopian tubes. There simply are not data to support Dr. Robertson's hypothesis that the immune system of the fallopian tube is hyper-vigilant.[1065]

1013 In evidence-in-chief, Badylak said the fundamental basis of the immune response in all tissues was the same. He said:

> There is nowhere that I've ever heard that it's hypervigilant in the fallopian tube. It's different, only to the extent that it's got a different function in life. But it's not more sensitive to the presence of infectious agents or foreign materials than say the lung or the ureter, which is the tube which connects the kidney to the bladder. They're all responsive, it's their job.[1066]

1063 Ibid at 67 [248], [251].
1064 Ibid at 77 [287].
1065 Sokol at 17 (EXP.001.002.0001).
1066 T3459 (TRA.500.035.0001_2 at 0034_22).

1014 Sokol and Badylak were not cross-examined about this evidence.

1015 In her reply report, responding to Sokol's criticism, Robertson stepped back from her hypervigilance opinion:

> Dr Sokol argues that the fallopian tube immune response should not be characterised as hypervigilant. The descriptor 'hypervigilant' applies because as a mucosal tissue, the fallopian tube has a greater surveillance capability that non-mucosal tissues. This surveillance capacity is required to defend epithelial barrier integrity and also contribute to reproductive quality control. The critical point is that fallopian tubes are just as competent at mounting robust inflammatory responses as any other tissue in the body, or even more so by virtue of being a mucosal site and responding to sex steroid hormones that promote immune effector functions[.] In my opinion, whether or not 'hypervigilant' is an appropriate descriptor is not important - the pivotal issue is that it has a perfectly competent and functional mucosal immune response, and is able to deploy this following insult or injury, for example in the presence of an Essure device.[1067]

1016 In her oral evidence, Robertson said that the uterus and fallopian tube, as with other mucosal and epithelial surfaces such as the skin, the lung, the gut and the airways, have a very reactive and competent immune response.[1068] She said that the uterus and fallopian tube have developed a special feature to ensure implantation and development of only the best gametes and embryos, and it was this capability that she was particularly referring to when discussing hypervigilance. She contrasted this capability with the previous scientific understanding that, in order to allow successful implantation of an embryo, the uterus was immunosuppressed.

1017 I accept Sokol and Badylak on this issue. There is no evidence of substance to substantiate Robertson's hypervigilance theory. Robertson proposed this theory in her primary report as a foundation of her opinion that Essure caused an ongoing chronic inflammatory response in some women. The lack of substance to the theory removes part of the foundation of Robertson's opinion.

1018 A related aspect of Robertson's evidence was that at certain stages of the menstrual cycle, parts of the female reproductive tract were 'primed towards a pro-inflammatory

1067 Robertson at 27 [33] (EXP.001.002.0015_2).
1068 T3388 (TRA.500.034.0001_2 at 0102_6).

immune response'.[1069] She said that this evidence related to oestrogen production, which pre-disposed immune cells in the endometrium to inflammation.[1070] Robertson said that at those stages of the menstrual cycle, the uterus and fallopian tube have a propensity to progress into a persistent chronic inflammatory response.[1071] She said that the elevation of oestrogen could extend the inflammatory phase of wound healing and contribute to progression to a chronic wound response.[1072] Robertson said that the phase of the menstrual cycle when Essure insertion occurred could have an impact on the response to the device, but that as far as she was aware, 'there is absolutely no data on that'.[1073] Robertson suggested this effect was most likely to occur during the late secretory phase just prior to menstruation.[1074]

1019 For the following reasons, I do not place any weight on this evidence from Robertson.

1020 First, Sokol said there was 'no convincing human data to suggest such a state of priming in the fallopian tubes under homeostatic conditions or under conditions of tissue injury'.[1075] Robertson acknowledged the lack of data.

1021 Second, Robertson's hypothesis relates to the effect of hormones present in the uterus on endometrial tissue. There was dispute among the experts about whether those hormones are present in the fallopian tube and their effect on fallopian tube tissue.

1022 Third, the Essure PTMs direct that the device implantation procedure be carried out in the early proliferative phase of the menstrual cycle. Robertson agreed that the direction to physicians was to implant the Essure device at a phase of the cycle when it would not, according to her hypothesis, be primed to a pro-inflammatory response. She said that this did not 'guarantee there weren't devices placed at that time'.[1076]

1069 Immunology JER at 15 (EXP.500.001.0004_2).
1070 T4134 (TRA.500.041.0001_2 at 0052).
1071 Robertson at 22 [56] (EXP.001.001.0127_2).
1072 Ibid at 100, footnote 231.
1073 T4139 (TRA.500.041.0001_2 at 0057).
1074 T4138 (TRA.500.041.0001_2 at 0056).
1075 Immunology JER at 16 (EXP.500.001.0004_2).
1076 T4145 (TRA.500.041.0001_2 at 0063).

1023 Robertson said, in associated evidence, that when macrophages arrive at a wound site, they have a pro-inflammatory M1 phenotype, and must quickly acquire an anti-inflammatory or M2 phenotype for healing to occur. She said:

> In my view the critical macrophage progression from M1 to M2 is more difficult to achieve in a wound repair program in the uterus and fallopian tube. In part, this is because estrogen acts to suppress formation of the M2 phenotype, and instead sustains macrophages in the pro-inflammatory M1 phenotype.[1077]

1024 Robertson and Sokol agreed that tests can be administered to determine the phenotype of macrophages. Sokol said that her search for articles or studies including such tests yielded no results, and that 'although the initial placement of the Essure device may lead to acute inflammation, there is no evidence that [she was] aware of that Essure placement leads to chronic or irreversible induction of pro-inflammatory macrophages'.[1078]

1025 When it was put to her in cross-examination that there was no data to support her macrophage phenotype theory, Robertson said:

> There's no data with lineage defining phenotypic markers. There is evidence in relation to phagocytosis and uptake of metal particles which is much more a characteristic feature of an M1 or pro-inflammatory macrophage. There is maybe a little bit of evidence when it comes to the sort of phenotype or shape of phagocytic cells that are likely to be macrophages. There's also a little bit of evidence in relation to their physical proximity to the device and physical proximity to neutrophils from which we can infer information about their likely pro-inflammatory state. But there is not immunohistochemical staining with lineage defining or phenotypic markers, it's not been done.[1079]

1026 I accept Sokol's evidence. There is no evidence of substance to substantiate Robertson's macrophage phenotype theory and I place no weight on it.

Scar-free wound healing of the uterus and fallopian tube

1027 Robertson said that because of menstruation, the uterus and SUTJ region of the fallopian tube have an unusual and specialised form of wound healing which is

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1077 Robertson at 24 [64])EXP.001.001.0127_2).
1078 Sokol at 19 (EXP.001.002.0001).
1079 T4025 (TRA.500.040.0001_2 at 0035_6-18).

regenerative without the formation of fibrotic scar tissue ('scar-free wound healing theory'). She explained that the scar-free wound healing response was of importance because the device traverses the SUTJ region and trails into the uterus. In her primary report, Robertson said:

> Because of the requirement to accommodate regular menstruation, the uterine wound-healing response causes the endometrial functionalis to regenerate and regain its characteristic mucosal properties, but without formation of fibrotic scar tissue as occurs at other sites, such as the skin. The extent of scar formation is related to the quality and strength of the immune response, and scar-free healing is thought to reflect a very limited and tightly controlled inflammatory response in the tissue at the time a wound occurs. In the context of the uterus, its typical scar-free healing response after menstruation occurs because the immune cell populations residing in the endometrial surface after tissue shedding at menstruation are tightly controlled in their composition and actions.
>
> …
>
> This feature would impair formation of fibrotic (scar) tissue in the insert, especially in those parts of the Device located within the SUTJ section of the fallopian tube, and within the uterus. …
>
> In my view, given the scar-free wound healing properties of the uterus, it was counterintuitive to depend on a canonical wound healing response in 100% of women in order for the Essure Device to be effective. This special wound healing response of the uterus was identified many decades ago and was regularly noted in the medical literature at the time prior to Essure clinical development and in the early 2000's.[1080]

1028 Robertson said the intramural region of the fallopian tube shares a scar-free healing characteristic with the endometrium to the extent that it 'shares features with the uterus'. In cross-examination, Robertson was asked:

> And you say that that's a specific reason for why the fallopian tube and uterus are vulnerable to incompletely healing and formation of a chronic wound?---I think I may have said that. I haven't got it in front of me.
>
> Well is that your opinion?---The uterus is - the uterus is very unusual in that it has a capacity to undergo regular menstruation and not form scars in healthy people at least. It's really important that it has that capability because otherwise every time we bleed we would form scars and then we wouldn't have a healthy endometrium to accept an embryo in the next cycle.
>
> Do you rely upon that in forming the opinion that there's this propensity for the fallopian tube to be vulnerable to the incomplete or abnormal response,

[1080] Robertson at 70 [259], [262]-[263] (EXP.001.001.0127_2).

> immune response, so that the scar tissue won't develop?---I think that the biology is not fully settled on the fallopian tube but I would draw on my understanding to form the opinion that the SUTJ region of the, where the uterus abuts the fallopian tube, would have features reminiscent of the uterus in terms of scar-free healing.[1081]

Robertson was challenged on the basis that she had not identified any scientific studies that demonstrate that factors which she said inhibit fibrosis and scar formation in the uterus also operate in the fallopian tube. Robertson said:

> The fact that those studies have not been conducted does not mean this does not occur. There's a lot of biology that still needs to be done about these tissues.[1082]

1029 In her primary report, Robertson cited a number of articles as authority for her scar-free wound healing theory. One of the articles investigated differences in mammals between wound healing in embryos and wound healing in adults ('Ferguson 2004').[1083] It was put to Robertson:

> The article is dealing with the difference in the embryo the immune system was developing?---The article is summarising the current state of knowledge about scar-free healing and extrapolating about its significance more broadly in biology.
>
> Where does the article do that?---Let's have a look at the - usually the last sentence in the abstract or the last sentence in the discussion will say, you know, the reason we need to understand this is because it will have applications in other tissues and if we learn about how this works we will be able to understand the biology of those other tissues and will be able to leverage this knowledge to improve, you know, scar-free healing in appropriate medical settings. I think, you know, it is reasonable to refer to an article that describes a type of biology that has broader implications to support the statement that I made, together with another statement that draws it into the uterine setting and provides, begins to provide an explanation for a big biological question that people were struggling with at that time about how it was possible for a uterus to menstruate every month and not get scarred. The reason that that work was being done was to understand how bleeding disorders arise and what might be done to improve treatment thereof.[1084]

Robertson could not identify any extrapolation by the authors of Ferguson 2004 that

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1081 T2704-5 (TRA.500.029.0001_2 at 0050_16-0051_4).

1082 T2709 (TRA.500.029.0001_2 at 0055_27).

1083 Mark W J Ferguson and Sharon O'Kane, 'Scar-free healing: from embryonic mechanisms to adult therapeutic intervention' (2004) 359(1445) *Philosophical Transactions of the Royal Society of London (Series B, Biological Sciences)* 839 (PUB.001.001.3804); T2713 (TRA.500.029.0001_2 at 0059).

1084 T2715-6 (TRA.500.029.0001_2 at 0061_18-0062_10).

was relevant to her scar-free wound healing theory.

1030 In cross-examination it was put to Robertson that another article on which she relied[1085] did not concern anything beyond the role of enzymes that characterised the commencement of menstruation. Robertson said:

> My recollection is that somewhere in this article - you know, I can't read it all in the few minutes we've got - but somewhere in this article Lois Salamonsen, who lives here in Melbourne and I know well, has made a comment about scar-free healing.[1086]

Robertson was unable to identify the section of the article she relied on to support her hypothesis. She said:

> But, look, there was discussion at that time of the significance of Mark Ferguson's work and the discovery of TGF beta 3 and its implications for understanding menstruation, and if for some reason I have not cited the best articles, I apologise for that, but it certainly doesn't mean that there was not discussion of these elements ongoing at that time. I absolutely recall them and the evidence is there.
>
> Well why didn't you cite those instead of these articles that don't support the proposition? You're a careful editor who reviews scientific literature and your extensive experience that you've referred to, the importance of being careful about citing articles that support the propositions they're cited for? ---Everybody makes a small error, and it certainly doesn't mean that the point doesn't stand and there is substantial evidence that the scar-free - I mean all you have to do is talk to anybody about how a uterus works and it is evident to everybody that there is scar-free healing in a uterus.[1087]

1031 Murdock described the normal menstrual cycle as a regenerative process that does not involve fibrosis. She said she does not use the term 'scar-free'.[1088]

1032 Robertson and Murdock disagreed about whether the intramural or SUTJ region of the fallopian tube contained endometrial tissue. Murdock's evidence was that the intramural region of the fallopian tube did not contain or comprise any uterine endometrial tissue. Murdock gave this evidence by reference to the figure reproduced

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1085 Lois A Salamonsen, 'Current Concepts of the Mechanisms of Menstruation: A Normal Process of Tissue Destruction' (1998) 9(8) Trends in Endocrinology & Metabolism 305 (PUB.001.001.4013).
1086 T2717 (TRA.500.029.0001_2 at 0063_17).
1087 T2718 (TRA.500.029.0001_2 at 0064_12-30).
1088 T2753 (TRA.500.029.0001_2 at 0099).

at [32] above that included photographs of fallopian tube sections that she took herself. Murdock also relied on her very frequent examination of fallopian tube tissue. I prefer her evidence on this point.

1033 Robertson relied, in the alternative, on circulation of soluble mediators from the uterus as being relevant to the extension of scar-free healing to the fallopian tube. She later accepted in cross-examination that the occurrence of this process was not yet understood.[1089]

1034 The articles relied on by Robertson are not relevant to the scar-free wound healing theory. There is no evidence that scar-free wound healing operates in the intramural region of the fallopian tube, or that it is relevant to resolution of the foreign body response to Essure. I conclude no weight should be placed on Robertson's scar-free wound healing theory.

Hypoxic state of the uterus and fallopian tube

1035 Robertson explained that the uterus and fallopian tube have a characteristic hypoxic state ('hypoxia theory'). She said that low oxygen content is recognised as a risk factor for poor wound healing and increases the risk of a chronic wound developing.[1090] In her primary report, Robertson said:

> The uterus (and the fallopian tube) have an unusually low oxygen (O2) concentration, and are considered hypoxic tissues. This is important for development of the fertilized ovum and early embryo, and [sic] has been shown to impair immune defence against bacterial infection in the fallopian tube.
>
> Hypoxia (low oxygen concentration) in tissues is considered a risk factor for poor wound healing and increases the chance of a chronic wound developing.
>
> In my view, given the hypoxic nature of the uterus (and fallopian tube) it is counterintuitive to depend on a canonical wound healing response in 100% of women in order for the Essure Device to be effective. The hypoxic nature of the uterus and fallopian tube was identified in the early 1990's and was discussed in medical literature at the time prior to Essure clinical development, and in the early 2000's.[1091]

1089 T2708 (TRA.500.029.0001_2 at 0054_25).
1090 SBM.001.001.0004 at 43-44.
1091 Robertson at 72 [264]–[266] (EXP.001.001.0127_2).

1036 Sokol agreed that the fallopian tube has often been described as hypoxic compared to other tissues.[1092] She said that depending on the degree of hypoxia, it can be a risk factor in poor wound healing.

1037 Sokol was asked in cross-examination about an article by Zhao et al ('Zhao 2016') that Robertson relied on in relation to the issue of hypoxia.[1093] She said:

> Right, but this really gets to that important point, it depends on the level of hypoxia. What they're talking about here is vasculopathy, so actual diseases of the blood vessels. We see this all the time in medical practice, that you squeeze down those blood vessels so you can't have as much red blood cell flow, you really starve the tissues of oxygen. It's not talking about the normal tissues that may be less - may have less oxygen than others. Like the skin has less oxygen than some other tissues. This is a specific set of factors.
>
> I was talking about local tissue hypoxia though?---Yes, this is absolutely talking about local tissue hypoxia but not all levels of hypoxia are the same. It really depends on what degree of hypoxia you're talking about.
>
> You wouldn't disagree with the - it might be talking about a more extreme example, but you wouldn't disagree with the proposition that hypoxia does disrupt wound heal[ing]?---Severe hypoxia caused by vasculopathies certainly can lead to problems with wound healing. However, the human body is pretty amazing in that the tissues of the human body are capable of healing even tissues that under normal physiologic conditions might have less oxygen than other tissues.[1094]

She said that the hypoxia data usually comes from lower extremity skin wounds in diabetes patients which leads to vasculopathy.[1095] It was put to Sokol:

> But you don't disagree with the general proposition - I think you have agreed with it, that broadly speaking, regardless of the severity of it, hypoxia is something which can impact on a wound healing?---No, I disagree with that. I disagree with the point of regardless of the severity of it. I agree that severe hypoxia caused by a medical condition like vasculopathy can lead to difficulty with wound healing, however physiologic levels or variations in the oxygen content would not.[1096]

1038 Sokol responded to Robertson's hypothesis in her report as follows:

1092 T4055 (TRA.500.040.0001_2 at 0065_16).
1093 Ruilong Zhao et al, 'Inflammation in Chronic Wounds' (2016) 17(12) *International Journal of Molecular Sciences* (PUB.001.001.4077) ('Zhao 2016').
1094 T4055-6 (TRA.500.040.0001_2 at 0065_31-0066_23).
1095 T4057 (TRA.500.040.0001_2 at 0067_10-1).
1096 T4057 (TRA.500.040.0001_2 at 0067_12-20).

> … Dr Robertson hypothesizes that the low oxygen concentration of the uterus and fallopian tubes after Essure placement would interfere with the macrophage ability to induce healing in the "M2" phenotype. However, again I am aware of no data to support this specific hypothesis. Indeed, macrophages in the hypoxic human uterus have been described as anti-inflammatory. In the absence of any data to the contrary, it is not even logical to expect that this same environment would somehow prevent this transition after Essure placement.[1097]

1039 Badylak responded to Robertson in his primary report as follows:

> With respect to Professor Robertson's repeated claim that the uterus has an unusually low oxygen concentration and that this results in impaired wound healing, this is simply not true. Although environmental oxygen (the air we breathe) is at a concentration of near 21%, the oxygen concentration in almost every tissue of the body is approximately 1.5-3.0%. In fact, the citation given to support her claim [Roth et al, 2010] uses the figure of less than 5% for the uterus and does not state that this concentration is "unusually low" nor in fact, different tha[n] other tissues.[1098]

1040 Robertson did not cite any scientific article or study which contained evidence that the oxygen concentrations in the fallopian tube and uterus were unusually low. Ultimately, she did not disagree with Badylak's evidence about oxygen concentrations in peripheral tissues.[1099]

1041 Robertson did not cite any study supporting the proposition that low oxygen concentration levels in fallopian tube and uterine tissue were likely to adversely affect wound healing. I reject Turner's submission that Zhao 2016 supports Robertson's theory that low oxygen concentrations in normal tissue are a risk factor for poor wound healing and increase the chance of a chronic would developing. The study clearly considers the impact of hypoxia caused by vascular insufficiency on wound healing. For example, in relation to arterial ulcers, the study says: '[n]arrowing of arterial lumen reduces perfusion, leading to ischemia and hypoxia'.[1100] In relation to diabetic ulcers, the study says that wound healing is disrupted by factors including 'micro and macro circulatory dysfunctions leading to poor oxygen perfusion'.[1101] The

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1097 Sokol at 19 (EXP.001.002.0001).
1098 Badylak at 18 [52] (EXP.001.002.0007).
1099 T3387 (TRA.500.034.0001_2 at 0101_16).
1100 Zhao 2016 at 2 [2.2] (PUB.001.001.4077).
1101 Ibid at 3 [2.4].

study notes local tissue hypoxia as a factor in the development of chronic wounds.[1102] The study says:

> Many chronic wounds occur on a background of local tissue hypoxia due to vasculopathies such as atherosclerosis and venous hypertension, or periwound fibrosis which reduces perfusion. Local tissue hypoxia is well known to profoundly disrupt wound healing.[1103]

I conclude that Zhao 2016 is consistent with Sokol's evidence about the role of vascular insufficiency causing hypoxia which may be a factor in chronic wound development. The article did not consider the possible contribution of otherwise normal oxygen concentrations in tissue to chronic wound development.

1042 Again, I conclude no weight should be placed on Robertson's hypoxia theory.

XV. EPIDEMIOLOGY

1043 As Spigelman CJ said in *Seltsam Pty Ltd v McGuiness*[1104] *('Seltsam')*:

> Epidemiology provides two types of material: first, the statistical measurement of an association between exposure and disease and, secondly, interpretation of the data to determine general causation. The second function may be performed by an epidemiologist who had no association with the study or studies which provide the raw data.[1105]

Spigelman CJ explained general causation as being the question: 'Is the agent capable of causing the disease?'.[1106]

1044 The main focus of the epidemiological evidence was studies that compared outcomes for women who had hysteroscopic implantation of Essure with outcomes for women who had laparoscopic sterilisation. Korda and As-Sanie agreed that laparoscopic sterilisation is considered to be acceptably safe, and that scientific studies do not show an association between laparoscopic sterilisation and CPP or AUB. They agreed that

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1102 Ibid at 5 [4].
1103 Ibid at 6.
1104 49 NSWLR 262 ('*Seltsam*').
1105 Ibid at [62].
1106 Ibid at [22].

laparoscopic sterilisation was an appropriate comparator to assess whether there was an association of those adverse outcomes with Essure. Gordon agreed that laparoscopic sterilisation is treated as being acceptably safe and was therefore the most sensible and meaningful comparator group for Essure.

1045 Turner submitted that the epidemiological evidence in relation to Essure was not a reliable foundation for conclusions about general causation. Turner submitted that the comparative studies were low on the hierarchy of epidemiological evidence and of relatively poor quality, and that no randomised controlled trial ('RCT'), which is the 'gold standard' in epidemiological evidence, was conducted in relation to Essure.[1107] Turner observed that Carney was an author of two of the comparative studies and that Bayer had provided financial support for other studies relied on by the defendants. She submitted that as a consequence, those studies were infected by conflicts of interest.

1046 The defendants emphasised that Turner bears the onus of proving causation. They characterised her attempt to do so without demonstrating a statistically significant association between Essure, CPP and AUB as 'novel'.[1108] The defendants submitted that because the comparative studies examine the experiences of over 100,000 women and demonstrate a similar, if not lower, rate of CPP and AUB reported by women who underwent hysteroscopic sterilisation (principally by use of Essure) compared to those who underwent laparoscopic tubal ligation, Turner's case that Essure causes a risk of those adverse outcomes is without merit.[1109] The defendants submitted that it logically follows that Turner has not established an association, let alone a causative effect, between Essure and the pleaded adverse outcomes. The defendants submitted that the most probable explanation for the observation of those adverse events following Essure implantation was that they were part of what is colloquially known as 'background rates' of those conditions in women of reproductive age, and as such

1107 SBM.001.001.0004 at 168 [532], 169 [536].
1108 SBM.001.001.0003_2 at 5 [1.7].
1109 Ibid at 5 [1.8].

were unrelated to Essure.[1110]

Key terms

1047 Gebski and Gordon agreed to the following glossary of relevant terms:

> **alternative hypothesis -** this is usually the point of interest in a study. It is generally phrased in terms of the null hypothesis (of no treatment effect) not being true. If the objective of a study is to 'compare Drug A with placebo' then the null hypothesis would be that there is no difference between the two treatments and the alternative hypothesis would be that there is a difference[.]
>
> **bias -** a process which systematically overestimates or underestimates a measurement or a parameter.
>
> **confidence interval -** a range of values for a parameter (such as a mean or a proportion) that are all consistent with the observed data. The width of such an interval can vary, depending on how confident we wish to be that the range quoted will truly encompass the value of the parameter. Usually '95% confidence intervals' are quoted. These intervals will, in 95% of repeated cases, include the true value of the parameter. In this case, the confidence coefficient (or confidence level) is said to be 95% (or 0.95). Confidence intervals are a preferred method of presenting estimates of parameters, while significance tests compare those parameters with arbitrary values.
>
> **covariate -** a variable that is not of primary interest but which may affect response to treatment. Common examples are subjects' demographic data and baseline assessments of disease severity
>
> **endpoint -** a variable that is one of the primary interests in a study. The variable may relate to efficacy or safety. The term is used almost synonymously with efficacy variable or safety variable but not, for example, with demographic variable.
>
> **forest plot -** A name sometimes given to a type of diagram commonly used in meta-analysis, in which point estimates and confidence intervals are displayed for all studies included in the analysis. An example from a meta-analysis of clozapine v other drugs in the treatment of schizophrenia is shown in Fig. 65.

[1110] Ibid at 6 [1.8].

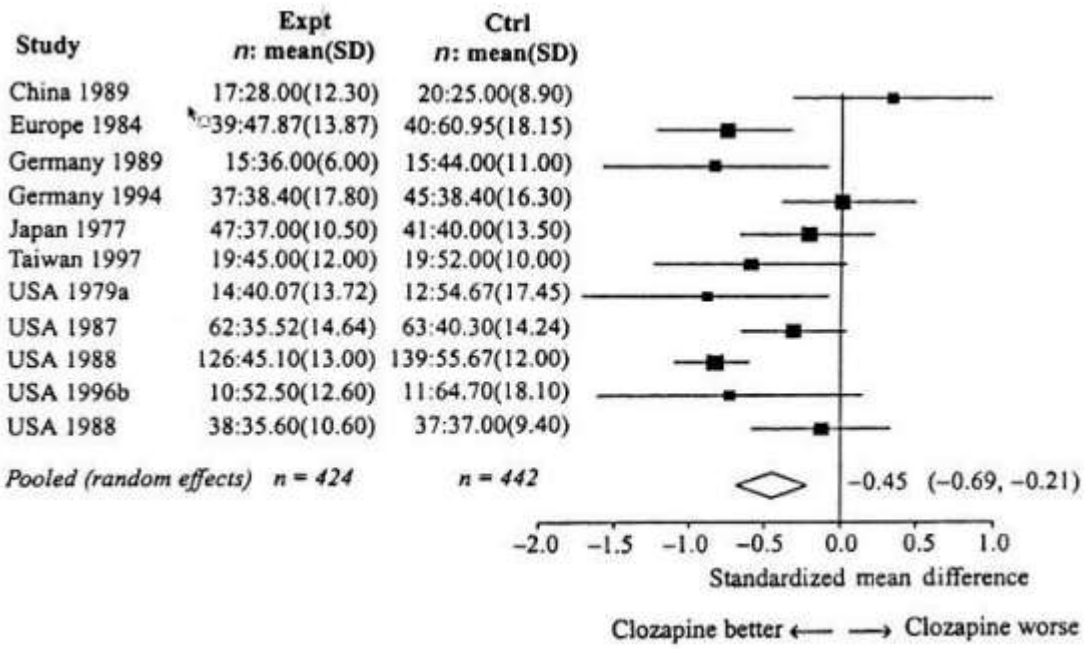

Fig. 65 Forest plot.

hazard rates - the hazard function at any particular point in time[.]

hazard ratio - the ratio of two hazard rates or of two hazard functions, either at a particular point in time or averaged over a long period.

hypothesis testing - A general term for the procedure of assessing whether sample data is consistent or otherwise with statements made about the population.

interim review - a review of data part way through a study, often to check on data quality and completeness rather than in the sense of a formal interim analysis.

loss to follow up - a subject who supplies some data for a study but for whom, after a certain time, no more data are available. The term usually also implies that there is no known reason why the subject supplies no more data.

null hypothesis - the assumption, generally made in statistical significance testing, that there is no difference between groups (in whatever parameter is being compared). Evidence (in the form of data) is then sought to refute (or reject) this null hypothesis.

outcome - usually the primary variable of a study. Although an outcome would generally be an event (≈ outcome event), the term is frequently used to refer to the primary variable whatever the measurement scale.

parameter - the true (but often unknown) value of some characteristic of a population. The most common parameter that we wish to estimate in clinical trials is the size of the treatment effect.

power - in statistical significance tests, the probability that the null hypothesis will be rejected if it is not true.

> **propensity score -** Propensity scores are used to adjust nonrandomized comparisons for covariates. For medical devices, they can be useful when an experimental device is compared with a historical control using patient-level information in the two data sets. In this context, the propensity score is the probability that a subject is assigned to the experimental device treatment. It is modeled as a function of the covariates. Adjustment for the covariates can be achieved by blocking on propensity score strata. The comparison is adjusted for the covariates in the sense that given the propensity score, the covariate distribution is independent of treatment assignment. In comparison with merely regressing the response variable on the covariates, an advantage of propensity score adjustments is that overfitting of the propensity score model is permissible and even desirable. For example, a logistic regression of the propensity score on the covariates can include higher-order terms and interactions.
>
> ***P*-value -** The probability of the observed data (or data showing a more extreme departure from the null hypothesis) when the null hypothesis is true.
>
> **randomization -** the process of randomizing a set of data values, subjects, treatments, etc.
>
> **statistical significance -** the claim that is generally made when the calculated *P*-value from a statistical significance test is less than a prespecified significance level (often meaning $P < 0.05$) so that the null hypothesis is rejected.[1111]

Null hypothesis

1048 Gordon said that when testing inferences, statisticians often concern themselves with a 'null hypothesis' - that is, a hypothesis of 'no effect'. In the context of this proceeding, an example of a null hypothesis is that the true difference in pregnancy rates between laparoscopic and hysteroscopic sterilisation is zero (which means effectively that the rates are the same). Adopting this example, Gordon said that if the 95% confidence interval for the estimated difference spans the null hypothesis value, which is zero, 'we would conclude that [there is] no statistically significant difference at the 5 per cent level between the two procedures with respect to pregnancy rate'.[1112]

Non-inferiority margin

1049 Gordon and Gebski agreed that adverse outcomes might be considered from a 'non-inferiority' point of view. Gordon explained:

> This means that the study is designed so that if the two interventions have the same true rate of an adverse outcome (e.g. abnormal vaginal bleeding), the

1111 MSC.500.001.0028.
1112 T3558 (TRA.500.036.0001_2 at 0016_14).

> study will have a high probability of concluding that the Essure device is no worse than laparoscopic tubal ligation.[1113]

Gordon said that in this case, a non-inferiority margin means 'that we may conclude that Essure is no worse than laparoscopic tubal ligation, even if the results of the study are consistent with a small difference in that direction'.[1114] He explained that if a non-inferiority margin is set at a small value of 1.5%:

> Then we will conclude that Essure is no worse than laparoscopic tubal ligation if the one-sided 95% confidence interval for the difference in percentages (Essure minus laparoscopic) is less than or equal to 1.5%.[1115]

The value chosen in a study for the non-inferiority margin affects the required sample size. The smaller the margin, the larger the required sample size.[1116]

Statistical power

1050 Gordon said the statistical 'power' is the chance that a study will conclude that there is a difference in a parameter, when there is a true difference of a given magnitude away from the null hypothesis. Gordon explained that if, for example, the true difference between the rates of adverse events following hysteroscopic and laparoscopic sterilisation is 2%, the null hypothesis is zero and the statistic power is 80%, the study has an 80% probability of declaring a statistically significant result (even though the true difference is only 2%). Generally, the higher the power, the greater the sample size required. To have an adequately large power in a study with a small sample size, the study generally needs to detect a large difference between the two parameters.[1117]

Significance

1051 Gebski explained that the level of significance is the probability, if the intervention is actually detrimental by at least the non-inferiority margin, that the study will declare that the intervention is actually non-inferior. He said that a study with a 5% level of

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1113 Regulatory JER at 6 [16] (EXP.500.001.0003_2).
1114 Ibid at 6 [17].
1115 Ibid at 6 [18].
1116 Ibid at 7 [22].
1117 T3563-5 (TRA.500.036.0001_2 at 0021_29-0023_10).

significance for detriment means that 5% of the time the study will declare that the intervention is non-inferior when in fact it is detrimental.[1118]

Bias

1052 A factor or covariate that differs between the groups being compared may result in the systematic overestimation or underestimation of the parameter being measured. That factor or covariate may be known or unknown. Examples of covariates that are often known include age, ethnicity and socioeconomic status.

1053 Gordon said:

> I've referred a number of times now to this idea of drawing an inference about an unknown population parameter, a quantity of interest, a scientific quantity of interest which might be something like the true difference in pregnancy rates or adverse event rates comparing laparoscopic versus hysteroscopic. It's very important to always keep in mind that from the statistical point of view we have this sort of quantity lurking there in the background that we never actually see, we draw an inference about it with associated uncertainty. Bias or lack of bias relates to whether we are estimating that unknown quantity in a biased way or not. If we're doing it in an unbiased way it means that we think that in a long run repeated sampling sense, if we did the same thing over and over again, the average of the results we're getting in the studies we actually can conduct would be right on that true parameter value. They would be neither too high nor too low on average. Now they'll deviate a bit because of sampling variation, we're never going to get exactly on the right number, but we don't have a systematic tendency for the result of our study to be in one direction away from the true parameter value, the systematic. It's only the random component.[1119]

1054 Gordon gave the following example of bias:

> Kaplan, Chambers and Glasgow (2014), sounding a cautionary note on big data and bias, state that "Despite the advantages of big studies, large sample size can magnify the bias associated with error resulting from sampling or study design." Their article starts with the example I usually use to reinforce the point. The Literary Digest, in 1936, predicted that Alf Landon would win the US Presidential election, based on a survey of 2.4 million respondents. The prediction was that Landon would win in a landslide, with 57% of the vote. In fact, Roosevelt won in a landslide, and Landon's actual percentage was 38%; the survey was out by 19 percentage points (= 57 minus 38). But if a 95% confidence interval was calculated for the estimate of, say, 57.0%, it would be (56.9% to 57.1%), very narrow because of the huge sample size, but a

1118 Regulatory JER at 10 [39].
1119 T3568 (TRA.500.036.0001_2 at 0026_3-25).

completely misleading inference, due to the very large bias.[1120]

Gordon explained that because the survey was carried out during the Great Depression and targeted owners of cars and phones, the survey was biased towards people who were inclined to vote Republican.

Hierarchy of epidemiological evidence in medical research

1055 Gordon and Gebski agreed on the evidence hierarchy in the National Health and Medical Research Council ('NHMRC') guideline for assessing medical interventions. The level of evidence is set out in the following NHMRC table:[1121]

Table 1.3 Designation of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pretest/post-test.

Medical devices are within the definition of 'intervention' for the purposes of the guideline.[1122]

1056 There was significant debate between Gordon, Gebski and Brandwood about whether an RCT could feasibly have been undertaken in relation to Essure and, if so, whether

1120 Gordon at 22 [104] (EXP.001.002.0014).
1121 Regulatory JER at 3 [3] (EXP.500.001.0003_2).
1122 Ibid at 4 [5].

that should have been done. However, there was no dispute about the nature of the Essure statistical evidence that exists. Gordon and Gebski agreed:

> In relation to the comparison between the Essure device and laparoscopic tubal ligation, there is no level I, level II or level III-1 evidence; the available evidence is at level III-2 or lower.[1123]

Experiments

1057 Gordon said that there was an important distinction between experiments and non-experimental studies. He said that the experiment is one of the most fundamental ideas of scientific research, and involves measurements and observations obtained under controlled conditions. He said that many medical studies are experiments, and are distinguished from observational studies which involve collection of data from historical or contemporaneous observations.[1124]

Randomised controlled trials

1058 Gordon said that an RCT is an experiment in which the allocation of interventions to units (with units typically being humans in medical studies) is done using a random process, such as a random number generator. He said that 'randomised trials are universally regarded as the best and most reliable research strategy for comparing interventions'.[1125] He said:

> [T]he theory of a randomised control trial is that the presence of other factors which might influence the outcome are removed precisely by determining the treatment through a chance process only, and so that means that all the other things are on average balanced, whether you know about them or not, measured or unmeasured characteristics that could be relevant to the outcome.[1126]

He said that in an RCT, comparisons between groups are unconfounded by other factors or covariates because the potentially distorting effects of those factors has been removed by randomisation. Gordon said that it was important to recognise that this

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1123 Ibid at 4 [7].
1124 Gordon at 20 [57](EXP.001.001.0418).
1125 Ibid at 21 [61]-[62] (EXP.001.001.0418).
1126 T3569 (TRA.500.036.0001_2 at 0027_4-10).

applied to known factors, even if unmeasured, and to unknown factors.[1127]

Cohort studies

1059 Gordon said that a cohort study is a broad type of observational study, and refers generally to a study in which individuals are followed over time for health outcomes of interest but without the feature of randomisation.

1060 Gordon explained what he said was an important practical difference between prospective and retrospective cohort studies:

> It can be very difficult, and sometimes impossible, to obtain measurements of interest from individuals at a time-point in the past, which may be decades ago. Even identifying the relevant individuals may be a problem. The quality of a retrospective study relies, in part, on the standards of record-keeping that are relevant: whether they ever existed, and, if so, whether they have been preserved. Relevant information may have been recorded in an ad hoc manner, according to the standards of the person creating the records, rather than according to a systematic protocol.
>
> On the other hand, a prospective study can be consciously designed, and the identification of subjects and measurement of their characteristics and health outcomes can be planned carefully. Therefore, the quality of the data is commonly better than in a retrospective study.[1128]

1061 The Essure comparative studies are all retrospective cohort studies and are therefore in the III-3 level of evidence, according to the NHMRC guideline.

Unadjusted comparisons

1062 Gordon explained that an 'unadjusted comparison' is an attempt to draw an inference from data in an observational study with no attempt to control for the factors that may differ between the groups being compared.[1129]

Propensity score matching

1063 'Propensity score matching' is an attempt to adjust for factors that may differ between the groups being compared.[1130] It attempts to approximate the balancing which occurs in an RCT by modelling known probabilities to adjust for covariates such as

1127 T3569 (TRA.500.036.0001_2 at 0027).
1128 Gordon at 24 [79]-[80] (EXP.001.001.0418).
1129 T3570 (TRA.500.036.0001_2 at 0028_15-25).
1130 T3571 (TRA.500.036.0001_2 at 0029).

age, ethnicity or income. This can be done in a number of ways, but is limited to variables which are known and have been measured in the study.[1131]

1064 Gordon described propensity score matching as an attempt to deal with differences between groups which have not been randomly allocated. He said it is a desirable and necessary step, because failing to do so means including subjects in a study who cannot be properly compared to subjects in the other group. He explained that excluding subjects on this basis is related to their eligibility for proper comparison.[1132] Gordon explained that propensity score matching involves modelling the probability of an individual getting one treatment versus the other by reference to known characteristics at the time of allocation. If the probability of the individual choosing either treatment is the same after this exercise, a fair comparison can then be made between the two treatments.[1133] If the reason for a subject's treatment choice is a characteristic — for example age, a pre-existing condition such as diabetes, cardiac history, or other comorbidities — which cannot be matched in the other treatment group, the individual is excluded.[1134] That comparison of outcomes occurs down the track, after propensity matching. Gordon said it was 'crucial to understand that the outcomes play no part in determining the propensity score matching'.[1135]

1065 Gebski agreed with Gordon's explanation, but said that while 'propensity score matching does give you a comparable set in probability, [it] may not be comparable in reality'.[1136] He said that using propensity score matching may result in 'throwing away' most of the measured events in an attempt to obtain a quasi-randomised comparable group. He said that it was an exploratory tool rather than a confirmatory one, and the real question was how much weight the analysis should be given.[1137]

1131 Ibid.
1132 T3858 (TRA.500.038.0001_2 at 0041_14).
1133 T3860 (TRA.500.038.0001_2 at 0043).
1134 T3858 (TRA.500.038.0001_2 at 0041_7).
1135 T3860 (TRA.500.038.0001_2 at 0043).
1136 Ibid.
1137 T3860-1 (TRA.500.038.0001_2 at 0043_21–0044_6).

Systematic reviews, meta-analysis and data pooling

1066 Gordon discussed the different approaches in medicine and epidemiology to the review of a body of literature on a given research question:

> One approach may be described as a "literature review". This is the traditional approach, practised not only in medicine but in science generally. It entails a narrative summary of evidence on a given topic, citing relevant documents, but without any overt commitment to systematic or comprehensive coverage of the available research.
>
> A second approach is a "systematic review"; in this case there is usually a focus on a particular research question, such as the comparison of a designated intervention with placebo, or another intervention. The term 'systematic' is used to indicate that the review attempts to reference and review *all* of the relevant information on the topic. This means accessing relevant studies as comprehensively as possible. Usually, this will involve – at least – electronic searches of reference databases, using keyword searches. It might also involve checking trial registries, or writing to authors in the area and asking them about their knowledge of any studies not yet unearthed. There may, in practice, be some exceptions to the comprehensive coverage, but these must be treated with caution. For example, systematic reviews sometimes do restrict their scope to publications in English. This entails the assumption that any study that has important evidence on the topic will have at least one informative document in English.
>
> The third approach adds a further dimension to the previous type. This is a "systematic review, with meta-analysis". Meta-analysis is a statistical technique for combining the information about a common research question, from different studies. It is commonly applied to research questions about the efficacy and safety of interventions.
>
> In its simplest form, meta-analysis seeks to provide an estimate of a parameter of interest, such as the difference in the percentages of an adverse outcome, between two interventions. The term "parameter" here refers to a fixed but unknown population quantity, which we seek to estimate by appropriate research studies. Several studies of the two interventions may each give an estimate of the difference. Meta-analysis combines the several estimates into a single 'meta-estimate'. The intended benefit is statistical efficiency: the combined estimate, it is hoped, will be more precise than the separate estimates from the individual studies.[1138]

1067 Gordon said that data from different studies may be 'pooled' to provide a meta estimate that is an average of the study-specific estimates.[1139] I will return to this issue when considering Gebski's pooled analysis and Gordon's criticisms of it.

1138 Gordon at 26-27 [90]-[93] (EXP.001.001.0418).
1139 Ibid at 27 [94].

Fixed effect analysis

1068 Gebski used a 'fixed effect' approach in his pooled analysis. Gordon said that this approach is based on an assumption that each study contributing to a meta-analysis is estimating the same 'true' treatment difference. He said that standard practice in meta-analysis is to avoid making this assumption, and allow for heterogeneity between studies.[1140]

Random effects analysis

1069 A random effects meta-analysis accounts for the expected variation between studies. Gordon said that it had long been the recommended approach. He said that it was particularly important to use a random effects analysis where there were marked differences in some of the outcomes considered. He said that this was the case with Gebski's pooled analysis, where the 95% confidence intervals for the treatment comparisons in different studies did not overlap.[1141]

1070 In cross-examination, Gebski gave the following description of a random effects analysis:

> [W]hat random effects tries to do is says if you have a population of trials there and you select a bunch of them at random, then you have to account for the fact, it's a sampling problem, that you have to account for the fact that you haven't got all the trial that you've sampled. So there's variability in that. Now we haven't done that. We've taken all the studies that we know, or at least we could identify, so there was nothing random about selection of the studies, it's not from a population of studies, it is the studies, it is the population. So the argument is that if you try to be as inclusive as you can it makes no sense to do further adjustments for something that doesn't exist, that is the random part. That was the reason I chose the fixed effect.[1142]

When asked about the choice between the two methods of analysis, Gebski said:

> [T]he argument is what are you trying to estimate? You're trying to estimate some unknown difference, if you like, and that unknown difference is fixed. We just don't know it. It's a population thing. You have this difference. It doesn't have any variability. It's a fixed number. The proponents of random effects put actually a distribution around that number, that's how well-known it's unknown, and that comes from some other distribution. That's where the debate lies. So the question is if you get one answer that says one thing and

1140 Gordon at 39 [199] (EXP.001.002.0014).
1141 Ibid.
1142 T3755 (TRA.500.037.0001_2 at 0072_2-16).

> another answer that says another thing, I think you need to go back to saying what am I trying to do and what's the most appropriate way? And I think either approach is fine but it's not arbitrary.[1143]

1071 Gordon said that Gebski's characterisation and application of the random effects approach was demonstrably false.[1144] Gordon said he had authored numerous meta-analyses and read hundreds more, yet could not think of a single instance where the studies used in the meta-analysis were a random sample from a wider set of studies. He said the purpose of a meta-analysis is to draw from the complete set of available studies. Gordon explained that in cases where there is a clear disparity between the individual studies and their outcomes, demonstrated either by a test of heterogeneity or an inspection of the forest plots from the studies, a random effects model is required.[1145] He said that if a fixed effect analysis is used in those circumstances, the resulting confidence interval will be too narrow and what is expressed as a 95% confidence interval around the final estimate might only be a 40% or 50% confidence interval.[1146]

1072 Gordon said that the heterogeneity between studies is related to their empirical differences. The random effects analysis takes the view that there is variation within and between the studies caused by factors that are not being explicitly accounted for.[1147] He said:

> [If] we can imagine a hyper-population of studies, and they would all have their variation due to the different features of the study, where they were conducted, the protocols, the way things were measured and so on, and so the best handle we've got on that is the variation we see in the studies that we've actually got. That's a different matter from saying that the studies we've actually got is in fact a random sample from such a hyper-population.[1148]

1073 When asked to comment on Gordon's evidence, Gebski said:

> Look, I don't disagree with Professor Gordon's statements. Mine was

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1143 T3756 (TRA.500.037.0001_2 at 0073_3-16).
1144 T3847 (TRA.500.038.0001_2 at 0030_26).
1145 T3849 (TRA.500.038.0001_2 at 0032).
1146 Ibid.
1147 T3851 (TRA.500.038.0001_2 at 0034).
1148 T3852 (TRA.500.038.0001_2 at 0035_7-15).

qualifying, tried to qualify why he used fixed effects.[1149]

Gebski said while he accepted Gordon's reasoning for using a random effects analysis, both were appropriate, and that he used fixed effect because 'it was simpler to say this is what you're trying to estimate'.[1150]

1074 The evidence demonstrated that Gordon had a clearer understanding of fixed and random effect analysis, and that he was able to give a reasoned explanation for why it was necessary to use the latter when undertaking a meta-analysis. Gebski's description of a random effects analysis in cross-examination was inaccurate. The only explanation Gebski gave for using a fixed effect analysis was because it was 'simpler'. There was no path of reasoning to that conclusion, which seems inconsistent with the exactitude that would be expected to be applied to a complex statistical analysis.

Essure comparative studies

Conover 2015

1075 The objective of a 2015 study by Conover et al ('Conover 2015') was to compare the incidence of opioid-managed pelvic pain within 12 months after hysteroscopic and laparoscopic sterilisation.[1151] The measured outcome was at least two diagnoses for pelvic pain and at least two filled prescriptions for opioid analgesics.[1152]

1076 The data source for the study was the Truven Health MarketScan Commercial Claims & Encounters Database ('Truven database') for the years 2005 to 2012. The Truven database contains de-identified healthcare and pharmaceutical claims from over 150 large employer-provided health insurance plans from across the US. The authors noted that approximately 55% of the US population had employment-based health insurance coverage in 2011 (approximately 170.1 million people), meaning the data

1149 T 3853-4 (TRA.500.038.0001_2 at 0036_31-0037_2).
1150 T 3854 (TRA.500.038.0001_2 at 0037_28-29).
1151 Mitchell M Conover et al, 'Incidence of opioid-managed pelvic pain after hysteroscopic sterilization versus laparoscopic sterilization, US 2005-2012 (2015) 24(8) *Pharmacoepidemiology and Drug Safety* 875 (PUB.500.001.0030) ('Conover 2015').
1152 Ibid at 1.

constituted a substantial portion of the US population with employer-provided insurance.[1153]

1077 Conover 2015 identified a cohort of women aged 18 to 49 years from inpatient and outpatient medical claims, of which 26,927 had undergone hysteroscopic sterilisation and 44,948 had undergone laparoscopic sterilisation. The sources of data were insurance, procedural and diagnosis codes used for the purposes of the claims procedure.

1078 The code for hysteroscopic sterilisation corresponded to claims related to Essure and a second device, Adiana, without identifying which device was placed. Adiana was available on the US market from 2009 until April 2012.[1154] Gordon said that 29,500 Adiana procedures were performed worldwide during that period.[1155]

1079 Starting follow-up 14 days after sterilisation, the authors evaluated opioid-managed pelvic pain using pharmaceutical claims and diagnosis codes associated with service claims. The diagnoses relating to pelvic pain included dysmenorrhea, abdominal pain or symptoms associated with female genital organs. Conover 2015 noted that while the codes relating to the last of those diagnoses may include non-pain symptoms, it was frequently used by physicians to code pelvic pain. The authors said, in relation to their approach to statistical analysis:

> We compared the baseline characteristics of the matched and weighted cohorts by sterilization type to ensure balance of measured covariates of interest. Cox proportional hazards regression models were used to estimate adjusted hazard ratios and 95% confidence intervals for the effect of sterilization type on opioid-managed pelvic pain, accounting for censoring. We compared the cumulative incidence of opioid-managed pelvic pain at 2, 4, 6, 8, 10, and 12 months post-sterilization between treatment groups for the crude, IPTW [inverse-probability-of-treatment-weighting], and matched [propensity score matching] analyses using Kaplan–Meier survival curves.
>
> We conducted 17 sensitivity analyses (SA), including analyses varying the

1153 Ibid at 2.

1154 Patricia I Carney et al, 'Occurrence of Chronic Pelvic Pain, Abnormal Uterine Bleeding, and Hysterectomy Postprocedure among Women Who Have Undergone Female Sterilization Procedures: A Retrospective Claims Analysis of Commercially Insured Women in the US' (2017) 25(4) *Journal of Minimally Invasive Gynecology* 651, 2 (PUB.500.001.0020 at 2) ('Carney 2015').

1155 Gordon at 32 [155] (EXP.001.002.0014).

> outcome definition (SA 1–8), perioperative period (SA 9–12), and look-back (SA 14–15), which are described in detail in Web Appendix 2. We also conducted two stratified analysis, one evaluating effect estimates by quartiles (defined within calendar year) of the propensity score and a second evaluating effect estimates within discrete windows during follow-up.[1156]

1080 Conover 2015 reported that 656 women (0.91%) experienced opioid-managed pelvic pain. This included 236 women in the hysteroscopic group (0.88%) and 420 women in the laparoscopic group (0.93%). In the crude analysis, the cumulative incidence of this outcome was greater in the hysteroscopic group at six months, but approximately equal between the two groups at one year. The study used two propensity score adjustment methods, propensity score matching, and stabilised inverse-probability-of-treatment-weighting ('IPTW'). IPTW involves balancing the distribution of measured covariates across treatment groups in order to control confounding. The IPTW analysis in the study was similar to the crude analysis, while the propensity score matched analysis indicated marginally increased risk of opioid-managed pelvic pain for the hysteroscopic sterilisation patients. All bar two of the sensitivity analyses indicated no difference in the risk of opioid-managed pelvic pain between the sterilisation groups. Combining the two remaining sensitivity analyses, which pointed in different directions, yielded results close to null.

1081 Conover 2015 noted the following limitations of the study:

> First, there may be important unmeasured variables that result in residual confounding in the relationship between sterilization and opioid-managed pain outcomes (e.g., body mass index). Second, opioid-managed pelvic pain is only a proxy for true pain outcomes and is likely limited in both sensitivity and specificity. Validated instruments measuring pain/discomfort exist but are impractical in studies with very large sample sizes. We conducted multiple sensitivity analyses to explore alternative outcome definitions, none of which indicated elevated risk in the hysteroscopic sterilization group. Third, in our primary analysis, we restricted evaluation of baseline covariates and exclusions for patient histories with evidence of the outcome-of interest to a six-month look-back period, which may result in under-ascertainment of relevant covariates and residual confounding. Fourth, this study only evaluated outcomes up to 1 year following sterilization. Fifth, by studying pharmaceutical claims, we assume that a prescription fill implies medication use, which may not be the case. However, we sought to reduce this misclassification by requiring two opioid prescriptions for the outcome.

1156 Conover 2015 at 3 (PUB.500.001.0030).

> Finally, the employer-provided insurance plan enrollees studied may limit generalizability because they may differ slightly from the general population in health status and healthcare utilization. However, they are a stably insured population, enabling longitudinal research not possible with conventional data sources.[1157]

Conover 2015 identified that the strengths of the study were its large sample size, highly sensitive and highly specific exposure ascertainment, and the consistency demonstrated by the extensive sensitivity analyses.

1082 The study concluded:

> Among women without recent history of childbirth, we did not find compelling evidence of a clinically meaningful increase in the incidence of pelvic pain requiring opioids during the year after hysteroscopic sterilization. However, effects observed in sensitivity analyses may merit further investigation.[1158]

1083 As-Sanie was asked about Conover 2015 and said:

> You'll see that [the Truven database] was used in multiple studies and thousands of articles have been published widely from this database, not just limited to this topic, but to multiple topics. It is a database of wide use because it looks across the US at patients that have employment based insurance and so this represents about half of the entire US population.[1159]

As-Sanie said that because the database was publicly available, the data could not be manipulated for the purposes of a study.

1084 As-Sanie agreed that because the prescriptions of opioids were not linked to the diagnostic codes for pelvic pain, there was no way of knowing whether the prescriptions were obtained for pelvic pain treatment. She added:

> But what you do know is that on average in a population that appears to be as similar as possible who underwent two different methods of sterilisation that were controlled in every other way that was feasible within the data, there was no difference or a low difference. … So while you don't exactly know what the reason was, the one thing that's different, as best as you can tell between the two groups, is what method of sterilisation that they had. All other things being as similar as possible and the data and you don't see a difference.[1160]

1157 Ibid at 8.
1158 Ibid at 1.
1159 T2531 (TRA.500.027.0001_2 at 0089_12).
1160 T2585 (TRA.500.028.0001_2 at 0048_1).

As-Sanie said that the reason for the prescription would only be relevant if the purpose of the study was to understand, in a given sample, the absolute rate of opioid prescriptions due to pelvic pain. She said that the study was not addressing pain severity, but was intended to determine whether there was a signal in the difference in the number of pelvic pain diagnoses associated with opioid prescriptions between the two groups.[1161]

1085 As-Sanie was asked about the limitations of studies that used combined data for Essure and other hysteroscopic devices such as Adiana. She said that the proportion of data related to Adiana was extremely small compared to Essure; and that while in theory the failure to distinguish between the two devices was a limitation, it was not likely to change the interpretation of the data.[1162]

1086 Korda criticised Conover 2015 for being limited to a 12-month observation period but agreed it was still relevant, together with the other comparative studies, to informing a view about the relationship between Essure and pelvic pain.[1163]

1087 Gordon said that Conover 2015 was unsuitable for assessing the safety of Essure in a comparative way because it failed to separately identify and report those women who had Essure and those who had Adiana.[1164]

1088 Gordon said further that because Conover 2015 is a retrospective registry study, the lack of control of other variables could result in bias affecting the assessment of any difference between laparoscopic and hysteroscopic sterilisation. Gordon said that while the authors had made an attempt to control for identified variables, other variables could account for differences between the laparoscopic or hysteroscopic sterilisation groups. Gordon acknowledged in cross-examination the speculative nature of this observation.

1161 T2585 (TRA.500.028.0001_2 at 0048_24).
1162 T2575 (TRA.500.028.0001_2 at 0038_16).
1163 T2604 (TRA.500.027.0001_2 at 0067_22).
1164 Gordon at 38 [141] (EXP.001.001.0418).

1089 Gordon said that he was not in a position to disagree with the following conclusion in Conover 2015:

> Through the use of administrative claims data, we were able to evaluate the incidence of a rare but serious outcome following sterilization in over 70 000 women from a national, population-based sample over an eight-year period. We found a small but not clinically or statistically significant increase in the incidence of pelvic pain requiring opioid-management during the 12 months after hysteroscopic versus laparoscopic sterilization.[1165]

1090 Gordon accepted that Conover 2015 'lines up as indicative of the possibility that there is no difference'[1166] between laparoscopic and hysteroscopic sterilisation so far as it concerns pelvic pain requiring opioid management. He said that, putting to one side the problem that the study does not isolate hysteroscopic sterilisation to Essure:

> Then it's up towards the higher end of the quality of evidence from observational studies because it makes a series of attempts to control for confounding and it's got a careful, ostensibly careful, albeit registry based, measurement of the outcome.[1167]

Perkins 2016

1091 The objective of the 2016 study by Perkins et al ('Perkins 2016') was 'to compare rates of gynecologic morbidity after laparoscopic and hysteroscopic sterilisation'.[1168]

1092 This retrospective cohort study used data from the Truven database for the years 2007 to 2013. The study included women who had undergone either laparoscopic or hysteroscopic sterilisation during the study period, and who were continuously listed in the database with a single insurance plan for at least 12 months before and after the sterilisation procedure. The study consisted of between one and five years of follow-up data from 27,724 women who underwent hysteroscopic sterilisation and 42,391 who underwent laparoscopic sterilisation.

1093 Insurance codes were again used to identify data. The authors said:

> Menstrual dysfunction outcomes were defined as abnormal vaginal bleeding

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1165 Conover 2015 at 9 (PUB.500.001.0030).
1166 T3726 (TRA.500.037.0001_2 at 0043_1).
1167 T3728 (TRA.500.037.0001_2 at 0045_12).
1168 Rebecca B Perkins et al, 'Gynecologic Outcomes After Hysteroscopic and Laparoscopic Sterilization Procedures' (2016) 28(4) *Obstetrics and Gynecology* 843 (PUB.500.001.0079 at 1) ('Perkins 2016').

> (ICD-9 codes 280, 285.1, 626, and 648.23). Pelvic pain outcomes included dysmenorrhea, dyspareunia, ovulatory pain, low back pain, and other pain associated with gynecologic organs (ICD-9 codes 625.0, 625.2, 625.3, 625.9, 724.2, and 789). The outcomes of menstrual dysfunction or pelvic pain were counted if they occurred two times in the outpatient setting or once in the inpatient setting.[1169]

1094 The study adjusted for known covariates of age, comorbidities, geographic region, urban setting and insurance type. A sensitivity analysis controlling for state instead of region was performed.

1095 Perkins 2016 found that women who underwent hysteroscopic sterilisation were more likely to experience subsequent menstrual dysfunction and hysteroscopic surgery than women who underwent laparoscopic sterilisation. The rates were 11.60 menstrual dysfunction diagnoses per 100 person-years for hysteroscopic sterilisation, compared with 9.72 per 100 person-years for laparoscopic sterilisation in the first year. The cumulative rates were 26.8% compared to 22.3% at two years, and 43.1% compared with 41.1% at five years.

1096 Perkins 2016 found that women were less likely to experience pelvic pain and less likely to undergo intra-abdominal gynaecologic surgery after hysteroscopic sterilisation than after laparoscopic sterilisation. The rates were 9.21 pelvic pain diagnoses per 100 person-years after hysteroscopic sterilisation, compared with 10.80 after laparoscopic sterilisation. The cumulative rates were 21% compared with 25.6% and 36.5% compared with 42.7% at two and five years respectively.

1097 The authors acknowledged that, as with any research that uses data from diagnostic codes, attribution errors could lead to misclassification of events. They said:

> It is highly likely that the bias introduced by such misclassification would be nondifferential and bias our analyses toward the null. Nonetheless, because we cannot know the frequency of misclassification and cannot prove the nondifferential nature of such events, appropriate caution is required when interpreting our results.[1170]

1169 Ibid at 2.
1170 Ibid at 8.

The authors added, in relation to the study limitations:

> Administrative codes lack sufficient detail to determine methods of laparoscopic sterilization, which may affect observed outcomes, nor could we reliably determine whether women may have had diagnoses related to menstrual dysfunction or pelvic pain before sterilization because we could not obtain data on surgeries, contraceptive methods, or other treatments for these conditions that occurred before the start of the study period. These data also do not allow for definitive ascertainment of why surgeries were performed after the initial sterilization procedures. Additionally, the lack of racial-ethnic data and the failure to include patients with public insurance such as Medicaid limits our ability to generalize to populations that may be more vulnerable to adverse health outcomes as a result of socioeconomic status and health care access.[1171]

They said that the large dataset was a strength of the study.

1098 The authors said:

> Women in this study were followed for an average of 2.6 years (range 1–5 years); therefore, additional surveillance will be necessary to define both effectiveness and complications in the longer term.[1172]

1099 Korda agreed that Perkins 2016 was highly relevant to assessing the comparison between hysteroscopic and laparoscopic sterilisation outcomes.[1173]

1100 As-Sanie said that Perkins 2016 was, together with the other comparative studies, among the highest quality of evidence for assessing comparative outcomes between hysteroscopic and laparoscopic sterilisation.[1174] As Sanie identified the control methods used for potentially confounding variables as a strength of the study.[1175]

1101 Gordon said that the study likely included Adiana procedures in the hysteroscopic group of women. While Gordon agreed that the study suggested that there may be no adverse difference between hysteroscopic and laparoscopic sterilisation in relation to pelvic pain, the lack of distinction between hysteroscopic sterilisation procedures meant that the study did not support the conclusion that there is no causal link

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1171 Ibid at 8–9.
1172 Ibid at 9.
1173 T2512 (TRA.500.027.0001_2 at 0070).
1174 T2530 (TRA.500.027.0001_2 at 0088).
1175 T2536 (TRA.500.027.0001_2 at 0094).

between pelvic pain and Essure.[1176]

1102 Gordon agreed that the following sentence in the study suggested that there may not be an adverse difference between laparoscopic and hysteroscopic sterilisation in relation to pelvic pain:

> Our longer term follow-up data indicated that more women experienced menstrual dysfunction and more underwent subsequent hysteroscopic surgery but fewer women experienced pelvic pain and fewer underwent subsequent intra-abdominal gynecologic surgery after hysteroscopic compared with laparoscopic sterilization.[1177]

It was put to Gordon:

> But nonetheless it lines up against the notion - it doesn't prove it, I'm not suggesting that for a moment - it lines up against the notion of there being an adverse difference if you use Essure?---I'm reluctant to gloss over this issue of the difference between hysteroscopic sterilisation and Essure for reasons I've articulated in my report.[1178]

Carney 2017

1103 The objective of a 2017 study by Carney et al ('Carney 2017') was to evaluate the frequency of CPP, AUB and hysterectomy after hysteroscopic sterilisation or laparoscopic sterilisation in the US.[1179] In particular, Carney 2017 investigated the impact of pre-existing pain conditions and AUB diagnoses on the likelihood of being diagnosed with CPP or AUB after sterilisation, or undergoing a subsequent hysterectomy post-sterilisation procedure.

1104 Carney 2017 again used data from the Truven database, in this study for the period from 1 January 2010 to 31 December 2012. Among that study population, 10,224 women underwent hysteroscopic sterilisation and 8,051 underwent laparoscopic sterilisation.

1176 T3730 (TRA.500.037.0001_2 at 0047).
1177 Perkins 2016 at 8 (PUB.500.001.0079).
1178 T3730 (TRA.500.037.0001_2 at 0047_19-25).
1179 Patricia I Carney et al, 'Occurrence of Chronic Pelvic Pain, Abnormal Uterine Bleeding, and Hysterectomy Postprocedure among Women Who Have Undergone Female Sterilization Procedures: A Retrospective Claims Analysis of Commercially Insured Women in the US' (2017) 25(4) *Journal of Minimally Invasive Gynecology* 651 (PUB.500.001.0020 at 1) ('Carney 2017').

1105 Carney 2017 adjusted for covariates including age group, geographic region, health plan type, index claim year, comorbidities and recent use of prescription contraceptives.

1106 The study described the measurement of outcomes as follows:

> Among the study cohorts the proportions of women with CPP postprocedure, defined as >2 diagnoses of pelvic pain/lower abdominal pain with >1 of them occurring at least 2 weeks postprocedure and the other occurring beyond 3 months after the index procedure, were determined. Among women who underwent HS and LS, the proportions of women with AUB postprocedure were determined in the same manner. In the study by [Conover 2015], the occurrence of postprocedural pelvic pain after sterilization procedures was defined as receiving 2 ICD-9-CM diagnosis codes on separate days. For the purposes of the current study, to investigate a distinctly longer-term episode of pain, as opposed to a brief episode, we maintained the requirement for 2 codes but also required that 1 of the codes occur at least 3 months postprocedure.[1180]

1107 The results in Carney 2017 were reported as follows:

> Among women who underwent HS, a greater proportion with a pre-existing pain diagnosis versus those without were diagnosed with CPP within the 24 months after their procedure (Fig. 2A: 19.8% vs 9.3%, p<.001). Similarly, among women who underwent LS, a greater proportion with a preexisting pain diagnosis versus those without were diagnosed with CPP within the 24 months after their procedure (Fig. 3A: 23.8% vs 11.4%, p<.001). …
>
> Among women who underwent HS, a greater proportion with a pre-existing AUB diagnosis versus those without were diagnosed with AUB within the 24 months after their procedure (Fig. 4A: 21.2% vs 7.3%, p<.001). Similarly, among women who underwent LS, a greater proportion with a preexisting AUB diagnosis versus those without were diagnosed with AUB within 24 months after their procedure (Fig. 5A: 15.9% vs 6.4%, p<.001). …
>
> *Hysterectomy in the Follow-Up Period*
>
> Among women who underwent either HS or LS, the frequency of hysterectomy after sterilization was significantly greater among women with a pre-existing AUB diagnosis versus those without (Fig. 4B: HS cohort 6.3% vs 2.4%, p<.001; Fig. 5B: LS cohort 6.8% vs 3.1%, p<.001).[1181]

1108 The authors said in the final discussion:

1180 Ibid at 3 (footnote omitted).
1181 Ibid at 4-7.

> Whether the occurrence of CPP after sterilization is causally related to the procedure or is due to some other etiology cannot be ascertained from this retrospective database claims analysis. …
>
> In conclusion, receiving a diagnosis for a pre-existing pain condition is associated with a higher likelihood of CPP after both HS and LS procedures. Likewise, receiving a diagnosis for pre-existing AUB is associated with a higher likelihood of AUB after both HS and LS procedures. Both pre-existing conditions are also associated with a higher frequency of subsequent hysterectomy after both HS and LS. This information may be of value when counselling women who are planning to undergo permanent sterilization procedures.[1182]

1109 As-Sanie said that the authors' conclusions support the proposition that women with pre-existing CPP are more likely to report those outcomes after the Essure procedure.[1183] She said that while the study did not directly compare outcomes following hysteroscopic and laparoscopic sterilisation, 'the overall incidence [looks] quite similar'.[1184] As-Sanie disagreed with Korda's conclusion that the study was not reliable because the authors had received funding from Bayer. She said that while the funding source was a consideration, Carney 2017 had declared the funding; the study had been peer-reviewed by other clinicians and scientists; the study used data that was publicly available; and there was no evidence of letters to the editor of the publishing journal questioning the validity of the study.[1185]

1110 Gordon said that although Carney 2017 does not present a direct statistical comparison between hysteroscopic and laparoscopic sterilisation, the data in the study can be used to carry out the following comparison:

> … For women without pre-existing abnormal uterine bleeding, the rate of abnormal uterine bleeding at 24 months was 7.3% in the hysteroscopic group and 6.4% in the laparoscopic group. This is a difference (hysteroscopic minus laparoscopic) of 0.9%, with a 95% confidence interval from 0.1% to 1.7%. These are the results used by Professor Gebski in his pooled analysis of abnormal uterine bleeding.
>
> For women with pre-existing abnormal uterine bleeding, the rate of abnormal uterine bleeding at 24 months was 21.2% in the hysteroscopic group and 15.9% in the laparoscopic group. This is a difference (hysteroscopic minus

1182 Ibid at 4–10.
1183 T2556 (TRA.500.028.0001_2 at 0019).
1184 T2556 (TRA.500.028.0001_2 at 0019_13).
1185 T2556 (TRA.500.028.0001_2 at 0019_20).

> laparoscopic) of 5.3%, with a 95% confidence interval from 1.3% to 9.2%.
>
> Since the 95% confidence intervals for the difference exclude zero in both cases, these results are statistically significant at the 5% level.
>
> While this is an unadjusted analysis, these results are not consistent with Dr As-Sanie's conclusion that "In all studies, there is no difference in the incidence of abnormal bleeding one year and longer after Essure placement".[1186]

1111 Gebski said that one must be pragmatic about the conflict of interest issue, as commercial enterprise funds most studies which often leads to some of the biggest scientific advances.[1187]

Bouillon 2018

1112 The objective of a study by Bouillon et al ('Bouillon 2018') was to compare the risk of reported adverse events between hysteroscopic and laparoscopic sterilisation.[1188]

1113 Bouillon 2018 used data from the French national hospital discharge database ('PMSI database') and the health insurance claim database ('SNIIRAM database') which contain information on at least 99% of the French population. The PMSI database contains details of all admissions, outpatient appointments and accident and emergency attendances at all public and private hospitals in France. The SNIIRAM database contains individual data on all reimbursements for patient health expenditure. There is no clinical validation of data from either database.

1114 The study population was women who had undergone a first hysteroscopic or laparoscopic sterilisation between 2010 and 2014. All hysteroscopic sterilisations were performed using Essure.

1115 The measured outcomes of the study included gynaecological and medical outcome events within one year and three years follow-up.

1116 Of the women included in the study, 71,303 underwent hysteroscopic and 34,054

1186 Gordon at 64 (EXP.001.002.0014).
1187 T3788 (TRA.500.037.0001_2 at 0105).
1188 Kim Bouillon et al, 'Association of Hysteroscopic vs Laparoscopic Sterilization With Procedural, Gynecological, and Medical Outcomes' (2018) 319(4) *Journal of the American Medical Association* 375 (PUB.500.001.0014) ('Bouillon 2018').

laparoscopic sterilisation. Bouillon 2018 recorded:

> Women in the hysteroscopic sterilization group were slightly older (mean [SD] age, 41.5 years [3.5] vs 40.8 [3.9]), had a higher socioeconomic status, a more healthful lifestyle, more likely to have diabetes, and more likely to be obese; less likely to have a history of allergy, suicide attempts, gynecological history, and prior pregnancy and were less likely to use an intrauterine contraceptive device (Table 1). Prior to inclusion, the hysteroscopic group consumed few medications, consulted a general practitioner less often (mean [SD] number of consultations, 5.27 [4.9] vs 5.69 [5.2]) but consulted a gynecologist more often (mean [SD], 1.56 [1.5] vs 1.51 [1.5]) and had a lower mean number of sick days than did those in the laparoscopic group (mean [SD], 7.0 [27.4]) vs 8.1 [30.3]). Although these characteristics were statistically different, their absolute difference in percentages or means were small.[1189]

1117 Bouillon 2018 adjusted for covariates including age, medical history and medication use.

1118 Bouillon 2018 found a lower incidence of abnormal vaginal bleeding after hysteroscopic sterilisation compared to laparoscopic sterilisation at one year and three years.

1119 The study measured analgesic prescriptions as a proxy for pelvic pain. Analgesics included opioids, non-steroidal anti-inflammatory drugs and others. Women were included if they had at least two reimbursements of analgesics within the first year of follow-up, and six reimbursements within three years. There was lower incidence of analgesic reimbursement with hysteroscopic sterilisation at one year and three years. Pelvic pain was not separately measured.

1120 The study did not find a significantly increased risk of medical outcomes related to hysteroscopic sterilisation.[1190]

1121 The authors noted the use of administrative databases as a study limitation, and that assessment of the formal validity of the diagnosis codes used was not possible.[1191] They said:

1189 Ibid at 4.
1190 Ibid.
1191 Ibid at 11.

> To take into account the different nature of complaints, both specific (gynecological events, allergy, autoimmune diseases, thyroid disorders, suicide attempts, death) and unspecific (use of analgesics, antimigraines, antidepressants, and benzodiazepines; physician visits; sick day absences) outcomes were studied. Despite the examination of numerous and heterogeneous outcomes, the present findings do not support the concern that increased medical risks are associated with hysteroscopic sterilization.[1192]

Bouillon 2018 further commented that diagnostic codes were regularly checked against patients' medical records and found to be accurate and precise.

1122 Bouillon 2018 said that while a generalisability question may arise because the study only included women with general insurance coverage:

> …because this covers 75% of the French population, these findings are likely to be generalizable, and it is unlikely that the present findings were affected by selection bias, in particular by geographic variability, which was also considered for these analyses. In addition, to further avoid selection bias and to render baseline characteristics more comparable between comparison groups, exclusion criteria had been applied (n = 4942; 4.5% of initial population) and the inverse probability of treatment weighting using the propensity score was performed making comparison groups well balanced. However, residual selection bias and confounding effect of unmeasured or unknown factors cannot be ruled out.[1193]

1123 Korda said that analgesic use was not an appropriate proxy for CPP, and that it was inappropriate to draw conclusions from Bouillon 2018 about its incidence.[1194] He agreed that Bouillon 2018 was relevant for consideration in relation to Essure outcomes but said that it was 'a long bow to equate CPP with analgesic use.'[1195]

1124 Bouillon 2018 was published in the *Journal of the American Medical Association*. As-Sanie described this journal as one of the most prestigious journals in medical science. As-Sanie pointed to the extremely large study sample size drawn from women across France using a very standardised claims databases method. She said that the study made comparison between the two groups as equal as possible using 'very robust methods' to control for confounders.[1196] She concluded 'that if there was some degree

1192 Ibid.
1193 Ibid at 12.
1194 Korda at 7 [16.12]-[16.4] (EXP.001.002.0011).
1195 T2469 (TRA.500.027.0001_2 at 0027_7).
1196 T2553 (TRA.500.028.0001_2 at 0016_28).

of increased pain that would require analgesic use in patients that underwent hysteroscopic sterilisation, we should see a higher rate of analgesic use in that population and we did not'.[1197]

1125 Gordon said that he was not aware of any methodological studies examining whether use of analgesia as a proxy for gynaecological pain was appropriate. He said that such a study was unnecessary to substantiate his criticism that analgesia was too broad and undifferentiated to be a useful proxy for CPP. He regarded it as self-evident that this approach would lead to inaccuracies, and said his criticism was borne out by the empirical results 'because they're so different in terms of the proportions'.[1198] Gordon said that as a consequence Bouillon 2018 should be disregarded when considering the safety of Essure with regard to pelvic pain.[1199]

1126 Gordon agreed that in relation to AUB, Bouillon 2018 lined up indicatively in favour of, or at least not against, hysteroscopic surgery.[1200]

1127 Gordon said Bouillon 2018 was the only comparative study in which the hysteroscopic sterilisation group only included women with Essure. He disagreed with Gebski's evidence that the Adiana 'comparative results would be largely in line with those expected from the Essure device'.[1201]

Steward 2018

1128 The objective of a study by Steward et al ('Steward 2018') was to compare the long-term outcomes, including hysterectomy, CPP and AUB, in women post-hysteroscopic sterilisation and laparoscopic tubal ligation.[1202]

1129 The study data was extracted from the US Medicaid Analytic Extracts (MAX)

1197 T2553 (TRA.500.028.0001_2 at 0016_31).
1198 T3738 (TRA.500.037.0001_2 at 0055_24).
1199 T3739 (TRA.500.037.0001_2 at 0056_14).
1200 T3739–40 (TRA.500.037.0001_2 at 0056-7).
1201 Gebski at 20 [55] (EXP.001.002.0003).
1202 Rachel Steward et al, 'Long-term outcomes after elective sterilization procedures — a comparative retrospective cohort study of Medicaid patients' (2018) 97(5) *Contraception* 428 (PUB.001.001.3895) ('Steward 2018').

Encounters database for the period 1 July 2009 to 31 December 2010. Medicaid provides US public health insurance. Steward 2018 noted that about two-thirds of women in the US aged 18 to 64 years have private health insurance, while 13.2% rely on public insurance. The study noted differences between those groups including that publicly insured women were on average younger when they underwent sterilisation, were more likely to be using an injectable contraceptive, and less likely to be using an oral contraceptive prior to sterilisation.[1203] The study also noted that women with public insurance were more likely to undergo sterilisation than women with private insurance, had a different race profile, were less educated, and more exposed to poverty.

1130 Of the 14,804 women who met the inclusion criteria, 3,929 had undergone hysteroscopic sterilisation, and 10,875 laparoscopic sterilisation.

1131 The primary outcomes measured were the proportion of women who were diagnosed with CPP or AUB or underwent hysterectomy at six, 12 and 24 months post-sterilisation procedure. Post-sterilisation CPP was defined as receiving two or more diagnoses of pelvic pain/lower abdominal pain on at least two separate visits, beginning two weeks post-sterilisation. One of these diagnoses had to be received at least three months after the procedure. AUB was defined as two or more diagnoses at least two weeks post-index procedure with at least one occurring at least three months after the procedure.

1132 Steward 2018 adjusted for covariates including age, ethnicity, comorbidities, geographic region, pelvic pain related conditions, and pregnancy and contraceptive use in the six months prior to sterilisation. A 'multivariable logistic regression analysis was carried out on the entire unmatched sample as a sensitivity analysis to check on the robustness of the findings from the matching analysis'.[1204]

1203 Ibid at 4.
1204 Ibid at 2.

1133 The study concluded as follows:

> In conclusion, our data demonstrate that the incidence of hysterectomy and CPP in publicly insured women is lower after HS compared to after TL. In propensity score matched analyses, HS is associated with lower odds of having a hysterectomy at 24 months or receiving a diagnosis of CPP at 12 and 24 months, but not 6 months, after sterilization compared to TL. The clinical relevance of these findings is uncertain given the small absolute difference in rates. The incidence rates of AUB at 6, 12 and 24 months post sterilization were similar in women who underwent HS compared to TL (Table 3). Logistic regression analyses support these findings.[1205]

The adjusted 24-month data found that CPP was more common in the laparoscopic group than the hysteroscopic group (26.8% versus 23.5%; p = .0050).[1206] The logistic regression analysis supported a lower risk of CPP diagnosis in the hysteroscopic group at 24 months post-procedure (odds ratio 0.91 [95% CL 0.83–0.99]; p = .0336).[1207] The equivalent findings for AUB were adjusted (8.2% versus 7.9%; p = .7629: logistic regression 1.06 [95% CL 0.93–1.21]; p = .3967).[1208]

1134 The authors noted, in relation to AUB:

> Previous researchers found a significant difference in the rate of AUB during the first year following HS versus TL. This potentially may be explained by the need to continue contraception after HS until a confirmation test has demonstrated proper insert location. Therefore, in the first several months after HS, women are still experiencing the effects of taking, then withdrawing from, hormonal contraception, whereas women undergoing TL can cease using contraceptives immediately after sterilization. In our matched analysis, however, the rate of AUB was similar at 6, 12 and 24 months postprocedure.[1209]

1135 Steward 2018 said that study limitations included the potential for coding errors during data entry, the potential for under-reporting because patients may experience AUB and pelvic pain events without consulting a healthcare professional, and limitations associated with the collection of claims data for the purpose of payment and not research.[1210] The authors stated:

1205 Ibid at 5.
1206 Ibid at 4.
1207 Ibid at 5.
1208 Ibid.
1209 Ibid at 4.
1210 Ibid at 5.

> In addition, other variables, such as level of education and socioeconomic status, are known to affect reports of chronic pelvic pain, AUB, and hysterectomy. It is unknown how unmeasured variables such as these would affect these analyses.[1211]

Steward 2018 noted as a strength that the data came from all regions of the US and was therefore likely to be nationally representative.

1136 Korda said that because all studies supported by industry were inherently biased, Steward 2018 could not be relied upon.[1212] In cross-examination, Korda agreed that the study population made it more reliable. He made no criticism of the statistical analysis used in the study.[1213] He agreed that the Medicaid data source was publicly available and not subject to interference. Korda was asked:

> Again, in assessing whether it's biased, you'd look for consistency with independent studies?---Yes.
>
> And it is consistent with the independent studies, isn't it?---It is.
>
> So you'd agree that it's a study that is to be taken into account, cumulative with the other studies, in forming a view?---Sure.[1214]

1137 As-Sanie said that Steward 2018 was a valuable study because it considered a different group of patients and adopted very robust methods for matching patients according to their demographic and medical variables.[1215] She said that Steward 2018 added to the volume of studies comparing pelvic pain and AUB outcomes between hysteroscopic and laparoscopic sterilisation. She said that the Bayer funding was disclosed,[1216] the study was published in a peer-reviewed journal, and the database was publicly available for anyone to test the reliability and reproducibility of the study outcomes.

1138 Gordon was asked:

> And the 24 months for CPP, the 24 months for AUB, are both, if anything,

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1211 Ibid at 5 (footnote omitted).
1212 T2519 (TRA.500.027.0001_2 at 0077_8–9).
1213 T2518 (TRA.500.027.0001_2 at 0076_22).
1214 T2519 (TRA.500.027.0001_2 at 0077_1).
1215 T2557-8 (TRA.500.028.0001_2 at 0020-1).
1216 T2557 (TRA.500.028.0001_2 at 0020).

> indicative of either a benefit from hysteroscopic sterilisation or at least no real difference; is that right?---Taken at face value from this table, yes.
>
> And that again is a study which, for what it is worth, lines up, as indicating, no adverse difference concerning those outcomes for a hysteroscopic sterilisation compared to laparoscopic; isn't that right?---Yes.[1217]

1139 Gebski was asked about an email chain relevant to the study.[1218] The chain involved Carney and other Bayer employees and indicated that the study protocol was settled before Steward was invited to participate. One email read in part:

> We have asked an external KoL [key opinion leader], Dr. Rachel Steward, to participate in the project with us. So I would like to pencil in a meeting for us to review the results together.[1219]

It was put to Gebski that it appeared the study was driven from within Bayer. He replied that 'if [Bayer was] supporting her to do this project and she was a high profile researcher, then [he] would've thought she would still be quite an independent mind'.[1220] He said that because the study included actual numbers and rates, he saw no reason not to include it in his pooled analysis.

1140 The next email in the chain reads in part:

> Do we want to set up a call with KoL after we have the matching results or when we are done with the descriptive analysis?[1221]

The email chain indicates that the results of the study and descriptive analysis was largely complete before Steward's involvement. It was put to Gebski that this raised the possibility of conflict of interest causing a shift in the results. He said:

> It could be the other way. She could be - so we'd like to pencil a meeting so you can explain the results to me. It could also mean that, I don't know.[1222]

1141 Shortly after she was engaged, Steward emailed Bayer expressing her frustration about a journal article that she perceived was unfairly negative to Essure. She

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1217 T3737 (TRA.500.037.0001_2 at 0054_12-20).
1218 BAY-JCCP-3712382.
1219 Ibid at 3.
1220 T3778 (TRA.500.037.0001_2 at 0095).
1221 BAY-JCCP-3712382 at 3.
1222 T3781 (TRA.500.037.0001_2 at 0098_5-8).

concluded her email asking whether anyone from Bayer was 'submitting a letter to the green journal in response' to it.[1223] The Bayer HealthCare Vice President of US Medical Affairs, Women's Health and Neurology, responded as follows:

> A letter from Bayer could potentially be perceived as "self-serving" and due to some of the pending litigation we would most likely not be able to address some of the points that you raised below. I truly believe that a letter from someone who has a lot of real-world experience with Essure would be most impactful as they would be able to speak from experience and not be perceived as biased. This is especially true with a journal like this.[1224]

A few days later Steward responded saying that she had submitted a letter to the editor of the journal 'as an independent physician'.[1225] Gebski initially responded in cross-examination by saying that this demonstrated Steward's independence:

> … because they said, no, let's not rock the boat because of the company's view and she said, 'I'm going to do it anyhow'. First of all, whether Bayer is trying to manage the fact that she's written that, you know, I can't really comment.[1226]

He later said that this exchange did cause him to be a little more circumspect about his reliance on Steward 2018, but added that it was reassuring 'that Professor Steward [had] gone out and demonstrated she's independent'.[1227] When it was put to Gebski that in his email, the Bayer HealthCare Vice President was encouraging Steward to write a letter of complaint about the journal article and that Steward responded by doing so, he said:

> Look, I take your point. I think she obviously felt strongly about it or she may not have, I don't know. I mean whether - I'm not going to defend her, let me say that, I'm not here trying to defend authors, but your point of saying would that cause me to think, the answer would be yes, given this information.[1228]

Gariepy 2022

1142 The objective of a 2022 study by Gariepy et al ('Gariepy 2022') was to evaluate the real

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1223 BAY-JCCP-2515211 at 3.
1224 Ibid at 2.
1225 Ibid 1.
1226 T3782 (TRA.500.037.0001_2 at 0099_19-23).
1227 T3783 (TRA.500.037.0001_2 at 0100).
1228 T3784–T3785 (TRA.500.037.0001_2 at 0101_28-0102_2).

world safety of hysteroscopic compared with laparoscopic sterilisation.[1229]

1143 Gariepy 2022 is a retrospective cohort study of Medicaid claims. The data was restricted to hysteroscopic and laparoscopic sterilisation procedures performed in California between 2008 and 2014. The study identified 5,906 women who had undergone hysteroscopic sterilisation and 23,965 who had undergone laparoscopic sterilisation.

1144 Gariepy 2022 adjusted for covariates including the year of procedure, race, ethnicity, geographic region, age and baseline condition in the two years pre-procedure.

1145 The study measured outcomes including procedural complications, additional surgical procedures, repeat sterilisation procedures, pelvic pain, PID, abdominal pain, non-abdominal pain and AUB.

1146 Gariepy 2022 reported:

> In this analysis of Medicaid claims data from thousands of California women, we found that hysteroscopic sterilization offered some advantages and some disadvantages compared with laparoscopic sterilization. Overall, hysteroscopic sterilization was the safer procedure. Complications within 30 days of procedure (eg, uterine perforation) and additional surgical procedures (eg, hysterectomy) were less common with hysteroscopic sterilization. Women who had hysteroscopic sterilization were also less likely to have claims for pelvic pain or endometriosis, abdominal pain and other gastrointestinal symptoms, and PID. However, hysteroscopic sterilization was more likely to be followed by a repeat attempt at sterilization and an abnormal uterine bleeding claim up to 12 months postprocedure.[1230]

The findings for pelvic pain and AUB were summarised as follows:

> Claims for pelvic pain (adjusted incident rate ratio 0.77, 95%, CI 0.65–0.92 at 2 years), abdominal pain (adjusted incident rate ratio 0.80, 95% CI 0.68–0.93 at 7–12 months), and PID (adjusted incident rate ratio 0.55, 95% CI 0.33–0.93 at 2 years) were less common after hysteroscopic than laparoscopic sterilization. Although abnormal uterine bleeding claims were more common after hysteroscopic than laparoscopic sterilisation up to 12 months postprocedure (adjusted incident rate ratio 1.37, 95% CI 1.06–1.77 at 7–12 months), there were

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1229 Aileen M Gariepy et al, 'Patient-Centred Safety Outcomes After Hysteroscopic Compared with Laparoscopic Sterilization' (2022) 139(3) *Obstetrics and Gynecology* 423 (PUB.500.002.0010) ('Gariepy 2022').

1230 Ibid at 9.

no significant differences between methods 1 year after the procedure.[1231]

1147 The study noted:

> There are a number of limitations inherent in studies of claims data. Claims data likely underrepresent patients' experiences of pain and other symptoms and cannot distinguish between different types of laparoscopic sterilization (eg, titanium clips or bipolar cautery), which may affect experience outcomes (eg, pelvic pain). Patients found to have endometriosis at the time of laparoscopy may have been more likely to have future claims that this study categorized as pelvic pain. Comparisons between hysteroscopic and laparoscopic sterilization are additionally limited because the average woman in this data set undergoing hysteroscopic sterilization had only 28 months of enrolment postprocedure. Thus, caution should be used in interpreting findings for hysteroscopic sterilization procedures beyond 2 years.[1232]

1148 Gariepy 2022 said that the study improved on previous safety analyses following hysteroscopic sterilisation in the following ways:

(a) analysing the Medicaid group that previous US studies had excluded;

(b) excluding post-partum sterilisations that involve different surgical approaches and considerations; and

(c) examining more than five years of post-sterilisation data.

1149 Korda criticised Gariepy 2022 on the basis that it relied on claims data which likely under-represented patients' experiences of pain and other symptoms. Korda agreed that the study was highly relevant to the assessment of the comparative safety of Essure, but said that he had not looked at it very carefully. He agreed that in forming her opinion about whether or not hysteroscopic sterilisation was a cause of adverse outcomes, As-Sanie had correctly considered the study.[1233]

1150 As-Sanie said that the methodology in Gariepy 2022 was extremely well described.[1234] She agreed that while the retrospective claims data would likely under-represent patients' experiences of pain and other symptoms, the effect size would not change

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1231 Ibid at 1.
1232 Ibid at 9.
1233 T2516 (TRA.500.027.0001_2 at 0079).
1234 T2558 (TRA.500.028.0001_2 at 0021).

unless there was a systematic way in which these experiences were under-reported in one group versus another.[1235]

1151 Gordon agreed that CPP and endometriosis data at two years post-sterilisation was favourable to the safety of Essure. He pointed out that there was other study data indicating higher adverse outcome rates in the hysteroscopic group over the laparoscopic group, and cautioned against drawing further general conclusions about the safety of the device from the study.[1236] Gordon was asked:

> [The tables and printed results] don't all have to be the same in order to draw any conclusion about the safety of the device, do they?---One has to make judgments, I guess, based on the overall picture.
>
> Quite. But insofar as this is a form of epidemiology to assist with those who make such judgments, be they regulators before the event or courts afterwards, it is significant, is it not, to pay regard to the apparent differences, if any, between the two arms of the study for the outcomes in which you may be interested?---Yes.
>
> Thus, for example, on p0003, report 426, right-hand column, last paragraph, there is a take out from the data presented in table 3 with respect to claims for pelvic pain, as well as endometriosis, in the two years after sterilisation, do you see that?---Yes.
>
> The plain English of 'hysteroscopic sterilisation less likely' in that sentence shows that with respect to that outcome of two years, if anything, this is a study that lines up in favour of Essure in that regard, correct?---Yes, if anything.[1237]

522 study

1152 As outlined at [310] above, the 522 study is an FDA-mandated PMS study initiated following concerns about the safety of Essure. By design, it is a prospective comparison between Essure and laparoscopic tubal sterilisation with adjustment using propensity score matching. The 522 study is specifically addressed to safety outcomes. A total of about 1,130 patients are enrolled in the study at 60 investigational sites, including about 280 patients who attempted an Essure procedure and 700 patients who attempted laparoscopic tubal sterilisation. The 522 study is ongoing and

1235 T2591 (TRA.500.028.0001_2 at 0054_13).
1236 T3743 (TRA.500.037.0001_2 at 0060).
1237 T3741 (TRA.500.037.0001_2 at 0058_28).

is scheduled to conclude on or around 30 June 2025.

1153 In his reply report, Gordon noted that interim 522 study results made available in late 2022 showed that for the two key outcomes of chronic lower abdominal and/or pelvic pain and AUB, the Essure percentages were higher than for laparoscopic tubal sterilisation.[1238]

1154 Further interim results were released in July 2023 ('2023 interim results'), after the biostatistical concurrent evidence session had concluded. The parties agreed to the 2023 interim results being tendered into evidence and to Gordon and Gebski providing supplementary reports considering those results.

1155 In their supplementary reports, Gordon and Gebski were asked to address the statistical significance of the 2023 interim results in relation to CPP.

1156 Gordon explained:

> In the biostatistical contexts considered here, the inferences about unknown population parameters are generally framed in one of two ways: a confidence interval, or a hypothesis test and an associated P-value.[1239]

He said that the 'P-value' is defined as the probability of a result at least as extreme as that obtained, assuming that the null hypothesis - in this case equivalence of Essure and laparoscopic tubal sterilisation in respect of the outcome under consideration - is true. The answer is expressed as a probability between zero and one. A very small P-value indicates that the result obtained is very unlikely, assuming the null hypothesis is true. The arbitrary threshold for statistical significance that is most used historically is 5%, meaning that a result of P less than 0.05 will be regarded as statistically significant.

1157 Gordon explained that confidence intervals are the second way that results are framed in statistical inference. He explained that by convention, the confidence interval 'can be thought of as a range of plausible values for the true, unknown population

1238 Gordon at 37 [191] (EXP.001.002.0014).
1239 Gordon at 8 [25] (EXP.001.002.0021).

percentage, with correspondence between "plausible" and "95% confident"'.[1240]

1158 Gordon said these measures of statistical significance have been trenchantly criticised in recent literature because:

> It reduces the result of a study down to a very coarse "yes/no" decision, without attention to the size of the effect and a range of plausible values for the population quantity of interest. The arbitrariness of 5% in this determination and its dominance in decision-making and interpretation is also problematic.[1241]

1159 Gordon reported the 2023 interim results for chronic lower abdominal and/or pelvic pain as follows:

> Using the Full Analysis Set, the simplest representation for the outcome chronic lower abdominal and/or pelvic pain (here abbreviated to "chronic pelvic pain") at 10 March 2023 is
> Essure: 39/280 (= 13.9%) and
> 275 LTS: 82/705 (= 11.6%).
> …
>
> Using the Adjusted Full Analysis Set, the simplest representation for chronic pelvic pain at 10 March 2023 is
> Essure: 38/264 (= 14.4%) and
> LTS: 27/264 (= 10.2%).[1242]

1160 Gordon analysed the statistical significance of the full analysis set as follows:

> Treating the two percentages from the Full Analysis Set as being suitable for statistical comparison and inference, the percentages of 13.9% and 11.6% give a P-value of 0.334 for Fisher's exact test; the difference between the percentages (Essure minus LTS) is 2.3%, with a corresponding 95% confidence interval of (−2.4% to 7.0%). The effect is in the direction of Essure being worse. It is not statistically significant at the 5% level, since P = 0.334, and this probability is greater than 0.05.[1243]

He assessed the adjusted full analysis set as follows:

> Using the two percentages from the Adjusted Full Analysis Set for statistical comparison and inference, the percentages of 14.4% and 10.2% give a P-value of 0.185 for Fisher's exact test; the difference between the percentages (Essure minus LTS) is 4.1%, with a corresponding 95% confidence interval of (−1.4% to 9.8%). The effect is in the direction of Essure being worse. It is not statistically significant at the 5% level, since P = 0.185 and this probability is greater than

1240 Ibid at 9 [34].
1241 Ibid at 9 [31].
1242 Ibid at 10.
1243 Ibid at 10 [41].

0.05.[1244]

1161 Gordon set out the results for AUB as follows:

> Using the Full Analysis Set, the simplest representation for the outcome abnormal uterine bleeding at 10 March 2023 is
> Essure: 58/280 (= 20.7%) and
> LTS: 137/705 (= 19.4%).
> …
>
> Using the Adjusted Full Analysis Set, the simplest representation for abnormal uterine bleeding at 10 March 2023 is
> Essure: 57/264 (= 21.6%) and
> LTS: 55/264 (= 20.8%).[1245]

1162 Gordon reported the statistical significance of the raw and adjusted data as follows:

> Treating the two percentages from the Full Analysis Set as being suitable for statistical comparison and inference, the percentages of 20.7% and 19.4% give a P-value of 0.658 for Fisher's exact test; the difference between the percentages (Essure minus LTS) is 1.3%, with a corresponding 95% confidence interval of (−4.3% to 6.9%). The effect is in the direction of Essure being worse. It is not statistically significant at the 5% level, since P = 0.658, and this probability is greater than 0.05.
>
> Using the two percentages from the Adjusted Full Analysis Set for statistical comparison and inference, the percentages of 21.6% and 20.8% give a P-value of 0.915 for Fisher's exact test; the difference between the percentages (Essure minus LTS) is 0.8%, with a corresponding 95% confidence interval of (−6.6% to 7.7%). The effect is in the direction of Essure being worse. It is not statistically significant at the 5% level, since P = 0.915 and this probability is greater than 0.05.[1246]

1163 Gebski reached the same conclusions about the statistical significance of the outcomes for pelvic pain and AUB.

1164 In his supplementary report, Gordon repeated that the 522 study had numerous strengths compared to the other studies of the efficacy of Essure. Gordon said:

> Notably: it is clear that the hysteroscopic treatment used is exclusively Essure, and not a mix of Essure and one or more other hysteroscopic treatments; the study outcomes were defined and designed clearly and intended to be implemented in the same way in the Essure and LTS groups; it is a prospective study, a feature likely to enhance data quality, and propensity score matching has been used in the analysis. It is not a randomised trial, and that is a

1244 Ibid at 11 [43].
1245 Ibid at 15.
1246 Ibid.

> deficiency, but its design is superior to most of the other available observational studies of Essure.[1247]

Gordon did have some reservations about the 522 study. He said that the 2023 interim results had not been published in a way that allowed the usual academic scrutiny of a referee journal. He said the study did not achieve the intended sample size, partly due to the withdrawal of Essure from the market.[1248]

1165 Gordon said that the 2023 interim results only report the occurrence of a relevant outcome at some time between recruitment and the date of interim analysis. He explained that women were recruited for the 522 study between 3 May 2017 and 31 December 2018. The current interim results are reported to 10 March 2023, and therefore reflect a follow-up period between 4.2 years and 5.9 years. He said that analysis is planned at the completion of the study of the time between recruitment and an outcome of interest which was 'a desirable feature, as it allows the most sensitive comparison between the groups'.[1249]

1166 Gebski said the limitations of the 2023 interim results include:

> (a) Unadjudicated interim data: the data is not adjudicated and the interim report itself warns against making any decision based on these results;
>
> (b) No independent peer-review: the data and results contained in the interim report have not been subject to peer-review or been published in a scientific journal.
>
> (c) Selection bias: this study is based on women self-selecting to enroll and choosing the method of sterilization and subject to unmeasured selection bias (such as the impact of women who enroll doing so because they may desire close clinical monitoring).
>
> (d) Poor recruitment/accrual rate: Despite subjects having the choice of their preferred sterilization method and the benefits of close clinical surveillance, over an approximately 34-month period only 985 subjects (non-screen failures) were enrolled. This point was highlighted when the DMC recommended study closure (May 5, 2021) due to the futility of subject recruitment.
>
> (e) Inability to obtain meaningful information regarding patient safety: In their May statement, the DMC concluded that due to the actual numbers in the study

1247 Ibid at 5–6 [9].
1248 Gordon at 49 [17] (EXP.001.001.0418).
1249 Gordon at 6 [10] (EXP.001.002.0021).

> being far below to the originally planned sample sizes, "the study results will not provide any meaningful interpretation, statistically or clinically, regarding the Essure device or procedure's safety".
>
> (f) Patient attrition/loss to follow-up: at the time of the 7-year report, the attrition rate was 50.3% in the Essure and 46.7% in the LTS cohort.[1250]

Gebski said that because of these limitations and the lack of statistically significant outcomes, the 2023 interim results do not support the existence of any association between the CPP and AUB rates of Essure when compared to laparoscopic tubal sterilisation.

1167 Turner noted that Keith Bangerter, a statistician employed by the Bayer defendants to oversee the 522 study, was not called by the defendants to give evidence.[1251] Turner did not identify an inference that should be drawn as a result of Bangerter's absence. The 522 study documents have been tendered. Considerable evidence was given about the study by a number of witnesses, most particularly Gordon and Gebski. Turner has not identified why the defendants were required to call evidence from Bangerter to further explain or contradict evidence that has been given.

Retrospective Analyses

1168 Bayer conducted two observational retrospective cohort studies using data from electronic medical record databases Intermountain Healthcare ('IMH') and MarketScan. The two studies used retrospective analysis of the databases to describe hysterectomy rates in patients who had undergone hysteroscopic or laparoscopic sterilisation. Bayer submitted final reports for the studies to the FDA in February and April 2016.[1252]

IMH database study

1169 The IMH dataset included records for 3.9 million patients who had at least one episode of care and two years of enrolment between 1 January 2000 and 31 March 2015. The study included 584 patients who had undergone hysteroscopic sterilisation and 9,994

1250 Gebski at 6 [8] (EXP.500.500.0009) (document references omitted).
1251 SBM.001.001.0004 at 264.
1252 SBM.500.001.0003_2 at 471.

patients who had undergone laparoscopic sterilisation between 1 April 2005 and 31 March 2015.

1170 The study reported that the two procedures had very similar post-sterilisation patterns. Approximately 8% of hysteroscopic sterilisation patients went on to have a hysterectomy, with that figure being closer to 10% for the corresponding cohort of laparoscopic sterilisation patients. Very few women in the hysteroscopic cohort had procedure codes indicating subsequent salpingectomy or removal of Essure inserts via some other method. Risks of post-sterilisation outcomes including pregnancy, ectopic pregnancy and repeat sterilisation were reportedly similar across the two cohorts.

1171 The study noted several limitations in the interpretation of results. These included that no methods were applied to adjust for confounding (e.g. propensity score matching); the study did not distinguish between Essure and alternative hysteroscopic methods available on the market; the dataset was limited to encounters with the IMH system; there was no defined minimum follow-up period; the collection of data was for administrative purposes; and there was a relatively small number of patients who underwent hysteroscopic versus laparoscopic sterilisation in the dataset.[1253]

MarketScan database study

1172 The MarketScan database study analysed data from the Truven database. Patients who had at least one claim for either the hysteroscopic or laparoscopic sterilisation procedure between 1 January 2010 and 31 December 2012 were included in the study. In addition to calculating the proportion of women who received a hysterectomy after sterilisation, the study also aimed to measure the proportion of women who had diagnoses of CPP or AUB after sterilisation. The overall study enrolment and follow-up comprised 9,184 hysteroscopic sterilisation patients and 5,239 laparoscopic

[1253] BAY-ESSURE-0086934 at 23-26.

sterilisation patients.

1173 The study reported that the overall proportion of women who received a hysterectomy after sterilisation was relatively low. After adjusting the data for patient characteristics, the study found that for patients with at least 12 months of continuous enrolment and follow-up, those who had hysteroscopic sterilisation were less likely to undergo hysterectomy or experience CPP when compared to the laparoscopic sterilisation cohort, but more likely to experience AUB. At 24 months of enrolment and follow-up, the difference in rates of AUB between the patient cohorts was no longer significant. The study noted that the number of women who reported CPP and AUB was higher for those with pre-existing pain and bleeding conditions.

1174 The study noted several limitations including the risk of database coding errors; an inability to confirm causation between diagnoses of pelvic pain or bleeding and the sterilisation procedure performed; that the data did not distinguish between Essure and alternate hysteroscopic sterilisation methods; the lack of a unique CPP database code; and that pre-existing conditions were defined based on a single occurrence of a diagnosis code during the 6 month pre-index period, which was considered baseline for inclusion in the study.[1254]

Utility of Essure comparative studies

As-Sanie's analysis

1175 As-Sanie was asked when briefed to identify studies that examine the incidence of CPP, AUB and dysmenorrhea in women with Essure, compared to women who had laparoscopic sterilisation. She conducted a literature search and identified studies with larger sample sizes and long-term follow-up which she used to form the basis of her conclusions. In her primary report, As-Sanie described the process she used to identify Essure studies relevant to outcomes under consideration, including CPP and AUB:

> A large number of studies have examined the incidence of pelvic pain and

[1254] BAY-ESSURE-0087834; SBM.500.001.0003_2 at 472.

abnormal uterine bleeding in women undergoing permanent contraception, including the Essure device. In order to draw upon the highest quality of research, I have relied primarily on the studies with large sample size (>1000 participants) with longer-term follow-up (12 months or more) in my expert analysis. However, I have also reviewed smaller studies (<1000 participants) or those with short-term follow-up (< 12 months) when reviewing studies reporting perforation, device expulsion and migration. Some of these are single-arm studies that examine only Essure, while other are comparator studies comparing Essure (hysteroscopic sterilization (HS)) to tubal ligation (laparoscopic sterilization (LS)). In order to identify the appropriate pool of studies, I conducted a literature review using PUBMED using key search terms of ["hysteroscopic sterilization" OR "Essure"], AND ["pelvic pain" OR "dysmenorrhea" OR "abnormal bleeding" OR "vaginal bleeding" OR "migration" OR "expulsion" OR "perforation" OR "malposition"] and have identified the studies in this report as the relevant and appropriate group of studies. I also reviewed the publicly available data provided on the FDA website regarding Essure sterilization as it relates to abnormal bleeding, pelvic pain, device perforation and migration.[1255]

1176 As-Sanie's analysis of the studies that she identified as relevant to CPP is as follows:

> The outcome of chronic or persistent abdominal and/or pelvic pain was examined in the following clinical trials and large-scale observational studies:

Study Design	**Study**	**Outcome**
Essure Clinical Trials (FDA Executive Summary 2015, p. 15)	Phase II	In the Phase II trial, 12/206 (5.8%) of women with at least one insert reported episodes of period pain, ovulatory pain, or changes in menstrual function.
	Pivotal Trial	In first year of reliance: • Abdominal pain / abdominal cramps: 3.8% (18/476) • Back pain / low back pain: 9.0% (43/476) • Arm/leg pain: 0.8% (4/476) • Dysmenorrhea/menstrual cramps (severe: 2.9% (14/476) • Pelvic / lower abdominal pain (severe): 2.5% (12/476) • Pain / discomfort — uncharacterized: 2.9% (14/476)
Single-Arm Studies	Povedano (2012)	• Persistent abdominal pain: 0.02% (1/4108 women)
	Berral (2014)	• 7 out of 4,274 women who underwent Essure sterilization (0.16%) presented with chronic pelvic pain requiring removal
	Kamencic (2016)	• Following Essure placement, 27/1430 women had new-onset pain; of these: ○ 15 had surgical or pathology findings consistent with a painful gynecological condition ○ 8 seemed to be related to a perforation or migration of Essure ○ 4 had no other obvious cause for new-

1255 As-Sanie at 30 [108] (EXP.001.002.0005).

		onset pain • 11/1430 women had worsening pre-existing pain
	Cabezas-Palacios (2017)	• "A total of 1014 of the 1064 patients who had the Essure device inserted (95.3%) attended their 3-month post-insertion check-up; 161 (15.1%) reported having an adverse effect during this period. The most common event, occurring in 87 of the 1064 women was pelvic pain or discomfort (8.2%). Only nine patients (0.85%) continued experiencing discomfort at 3 months of the insertion, and two had pain that required analgesic treatment (0.19%)." • Over 9 years' experience at the hospital study site, two additional women had devices removed due to chronic pelvic pain.
Comparator Studies	Conover et al. (2015)	HR (Essure v. LS): **1.08 (0.90, 1.31)** [26,927 women with Essure, 44,948 with LS]
	Perkins et al. (2016)	HR (Essure vs. LS): **0.83 (0.80, 0.85)** [27,724 women with Essure, 42,391 with LS]
	Bouillon et al. (2018)	HR (Analgesic use at 1 year with no prior history of pain): 0.96 (0.93-0.99) HR (Analgesic use at 3 years with no prior history of pain): **0.83 (0.70, 0.97)** [71,303 women with Essure, 34,054 with LS]
	Carney (2018)	"During baseline 23.3% and 26.9% of women with HS and LS, respectively, had a pre-existing pain diagnosis. Among both HS and LS study cohorts, greater proportions of women with a pre-existing pain condition versus those without had CPP in the 24 months afterward (HS cohort: 19.8% vs 9.3%, p < .001; LS cohort: 23.8% vs 11.4%, p < .001)." [10,224 women with Essure, 8,051 with LS]
	Steward (2018)	OR (Essure vs. LS): **0.91 (0.83, 0.99) at 24 months** • CPP at 6 months post-procedure: 5.5% of women with Essure and 6.8% of women with LS had CPP (p=0.0043) • CPP at 12 months: 13.2% of women with Essure and 16.5% of women with LS had CPP (p < 0.0001) • CPP at 24 months: 25.7% of women with Essure and 29.6% of women with LS had CPP (p < 0.0001) [3,929 women with Essure, 10,875 with LS]
	Gariepy (2022)	IRR (Incident Risk Ratio) of Pelvic Pain or Endometriosis (Essure vs LS**): 0.77 (0.65, 0.92) at 13-24 months** [5,906 women with Essure, 23,965 with LS]

Based on these data, I conclude that in large, comparator studies, the incidence of chronic pelvic pain following Essure hysteroscopic sterilization was similar to or lower than the incidence of chronic pelvic pain following laparoscopic sterilization. A history of chronic pain prior to any form of sterilization is

associated with a higher risk of chronic pelvic pain following sterilization.[1256]

1177 As-Sanie's analysis of the studies relevant to AUB is as follows:

> The clinical trials and the following large-scale observational studies examined abnormal uterine bleeding:

Study Design	Study	Outcome
Essure Clinical Trials (2015 FDA Executive Summary, p. 15)	Phase II	In the Phase II trial, 12/206 (5.8%) women with at least one insert reported episodes of period pain, ovulatory pain, or changes in menstrual function.
	Pivotal Trial	First Year of Reliance (N=476 women with at least one Essure insert): • Persistent increase in menstrual flow: 1.9% • Abnormal bleeding – time not specified (severe): 1.9% • Dysmenorrhea/menstrual cramps (severe): 2.9% • Menorrhagia / prolonged menses (severe): 1.1%
	Chudnoff 2015	Over 5 years of follow-up: "Irregular bleeding affected 5% to 12% of women over the 5 years of follow-up. Intermenstrual bleeding occurred frequently in the first 3 months after placement (23.6%). After the use of alternative contraception, intermenstrual bleeding was reported in 6% to 9% of women. By year 5, no participants had persistent irregular or intermenstrual bleeding. At the 5-year follow-up visit, 20% of women reported heavier menses and 11% reported lighter menses."
	ESSTVU Study 16974 "TVU Study" (2015 FDA Executive Summary)	In 597 women studied: • Menorrhagia: 3.9% • Dysmenorrhea: 2.5% • Vaginal hemorrhage: 2.3% • Uterine hemorrhage: 1.5% • Metrorrhagia: 0.8% • Dyspareunia: 0.7% • Menstrual irregularity: 0.5% • Amenorrhea: 0.5% • Dysfunctional uterine bleeding: 0.3%
Single-Arm Studies	Cabezas-Palacios (2017)	• 40/1014 patients who attended their 3-month post-insertion checkup reported spotting or period bleeding (3.8%)
Comparator Studies	Bouillon (2018)	HR (Essure vs. LS, 1 year of follow-up): 0.71 (0.52, 0.96) HR (Essure vs. LS, 3 years of follow-up): 0.83 (0.70, 0.97) [71,303 women with Essure, 34,054 with LS]
	Carney (2017)	During baseline 11.7% and 6.4% of women with HS and LS, respectively, had pre-existing AUB. Among cohorts, greater proportions of women

1256 Ibid at 33-5.

		with preexisting AUB versus those without had AUB in the 24 months afterwards (HS cohort: 21.2% vs 7.3%, p < .001; LS cohort: 15.9% vs 6.4%, p < .001). [10,224 women with Essure, 8,051 with LS]
	Steward (2018)	OR (Essure vs. LS): **1.06 (0.93, 1.21) at 24 months** • At 6 months, 2.2% of Essure users and 1.2% of LS women had AUB (p < 0.0001) • At 12 months, 4.8% of Essure users and 3.8% of LS women had AUB (p=0.0059) • At 24 months, 9.3% of Essure users and 8.8% of LS women had AUB (p=0.3145) • "The rates of AUB diagnoses after sterilization procedure was significantly more common in the HS group than the laparoscopic TL group at 12 months (P=0.0059) but not at 24 months (P=0.3145) (Table 2)." [3,929 women with Essure, 10,875 with LS]
	Gariepy (2022)	IRR (Incident Risk Ratio) of Abnormal uterine Bleeding (Essure vs LS): **1.01 (0.84, 1.22) at 13-24 months** • Compared to LS, "Women who had hysteroscopic sterilization were more likely to have claims for abnormal uterine bleeding in unadjusted analyses (Table 6), but in propensity-weighted, fully adjusted models there were only significant differences up to 12 months post procedure (adjusted incident rate ratio 1.37, 95% CII.06–1.77)." There was no difference in abnormal uterine bleeding one year and longer after the procedure. [5,906 women with Essure, 23,965 with LS]

> Based on the above large, comparator studies, I conclude that the incidence of abnormal bleeding following Essure hysteroscopic sterilization is *variable in the first year after sterilization- it is reported to be similar in some studies and slightly higher in other studies in the first year after the procedure. In all studies, there is no difference in the incidence of abnormal bleeding one year and longer after Essure placement.* A history of abnormal bleeding prior to any form of sterilization is associated with a higher risk of abnormal bleeding following sterilization.[1257]

1178 In the gynaecology JER, As-Sanie discussed the reliability of the Essure comparative studies as follows:

> Dr As-Sanie says these 6 studies are reliable because they contain relevant knowledge regarding pelvic pain and bleeding. She acknowledges that no single study is definitive to answer the question regarding the relationship between the Essure device and the conditions of bleeding and pain. But the consistent results across multiple studies with large sample sizes (ranging

[1257] Ibid at 35–7.

> between approximately 15,000 and 100,000 patients who underwent permanent sterilization) suggest high reliability of the findings. All of these studies were peer-reviewed, used sound statistical analyses, and used publicly available databases with very large sample sizes across diverse real-world clinical populations. The two studies that were funded by Bayer (the Steward and Carney studies) were among these peer reviewed studies and used publicly available data bases. These databases are not data produced by Bayer — and produced similar results to the studies not funded by Bayer. She also says health insurance administrative data are an important source of information for medical research. While all studies have individual strengths and weaknesses, health insurance claims studies are widely accepted as a valid form of research information. Claims data record diagnostic codes and treatments given and have the advantage of using very large sample sizes using diverse, representative real-world clinical populations receiving treatment. She also says that claims data have been shown to exhibit high congruence between medical records data compared to patient surveys performed by both telephone and mail. The discussion sections of all these studies specifically outline the strengths and weaknesses of interpreting studies based on insurance claims data. She says that the findings in the reports are consistent with her clinical experience. For these reasons she considers them to be reliable.[1258]

1179 Gordon criticised As-Sanie's reliance on the comparative studies and the conclusions she reached from that data, and said:

> … Dr As-Sanie has assembled data from non-randomised comparisons of hysteroscopy and laparoscopy, without regard to data quality and without concern about lack of randomisation. She has conducted a qualitative assessment and arrived at a judgment that is not supported by the data.[1259]

Sample size and study quality

1180 Gordon criticised As-Sanie's reliance on sample size and what he said was a lack of attention to study quality:

> Dr As-Sanie equates study quality with sample size, and also follow-up length. She has not considered the hierarchy of evidence, the quality of the studies or the effects of study quality on her review of the evidence.
>
> Published systematic reviews and meta-analyses do not use study size as a selection criterion, and they often consider studies of size much smaller than 1000.[1260]

1181 Gordon said that an assessment of study quality begins with consideration of study design, whether it is an RCT, cohort study, case control study or case series. He said

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1258 Gynaecology JER at 13 [44] (EXP.500.001.0001).
1259 Gordon at 66 [400] (EXP.001.002.0014).
1260 Ibid at 62 [364]–[365].

whether the study is prospective or retrospective can affect the quality of the data. Quality is also affected by the way in which variables are measured and whether the data accurately reflects the outcome under consideration. He said that definitions of outcomes, implementation of the data design, the actual logistics, and the control over the quality of data collection are all important.[1261]

1182 Gordon said that non-randomised, retrospective studies are always problematic because of the inability to balance unknown variables which may influence the outcome. He said that without knowledge from the time of the studies of the processes used in them, he could not say much about the unknowns. He said that prospective studies were somewhat better than retrospective studies in terms of the ability to consider variables and attempt to control them as best as possible, but that there would still be unknown variables which could not be controlled for without randomisation.[1262]

1183 Gordon said sample size does not trump randomisation.[1263] In cross-examination, he was asked:

> To use one of your own expressions, all other things being equal, large sample size tends to reassure, rather than trouble you about making decisions; is that correct?---Yes, if all other things being equal means the absence of bias.[1264]

1184 Gordon agreed that a serious attempt had been made in the Essure comparative studies to adjust and account for identified variables. He acknowledged the speculative nature of his observation that unknown variables may have resulted in the outcomes of each of the studies being biased.

1185 I reject Gordon's criticism that As-Sanie ignored study quality. It is clear that As-Sanie turned her mind to study quality and considered relevant matters including that the studies were peer-reviewed, used sound statistical analyses that included propensity

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1261 T3693 (TRA.500.037.0001_2 at 0010).
1262 T3691 (TRA.500.037.0001_2 at 0008).
1263 Ibid at 28 [133]–[134].
1264 T3579 (TRA.500.036.0001_2 at 0037_2-5).

score matching to account for identified variables, were based on large sample sizes across diverse real-world clinical populations, and that there were strengths associated with the use of health insurance administrative data. As-Sanie also pointed to the consistency of results across multiple studies and with her own clinical experience. As-Sanie made further comments about the quality of individual studies, some of which are set out in the above paragraphs dealing with those studies. As-Sanie agreed that an RCT would be the best quality evidence to compare Essure and laparoscopic sterilisation outcomes. As-Sanie's approach, in the absence of a relevant RCT, was to identify the highest quality studies available and consider what conclusions relevant to general causation could be drawn from those studies. This was a reasonable approach to take.

Period of analysis

1186 Gordon said it was necessary to assess the long-term safety of Essure:

> For long-term safety outcomes, there are different considerations, however. This is because the Essure device remains in a woman's body for her lifetime, in general. We therefore need to consider, in principle, the possibility of adverse outcomes occurring for the rest of her life, and after (sometimes, long after) the desired outcome of contraception is relevant. While this can be true for many interventions, the permanent nature of Essure suggests that alertness to the possibility of long-term impacts is especially pertinent.[1265]

Gordon said, after reviewing the available studies, that there was a lack of data to assess the long-term safety of Essure. He said that there were changes to a woman's reproductive system with age and the onset of menopause, and that:

> A study which limits follow-up to a relatively short time span will not be able to identify any side effects that are related to the reproductive life cycle and changes in later life.[1266]

He said a 10-year follow-up time should be considered in the evaluation of a life-long device such as Essure.[1267] Gordon noted that follow-up times in studies that rely on hospital and/or claims data may be constrained 'by practical limitations such as

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1265 Gordon at 47-48 [164] (EXP.001.001.0418).
1266 Gordon at 48 [271] (EXP.001.002.0014).
1267 Ibid at 48 [267].

availability, data quality and data volume'.[1268]

1187 There is a logical basis for Gordon's criticism that long-term follow up was necessary to determine whether there were any risks associated with Essure. However, this criticism is less relevant to the risks pleaded by Turner. It is not clear why, if the risks of inherent defects, failure defects and adverse events existed, they would not be apparent in the period following Essure implantation covered by the comparative studies.

Registries and codes

1188 Gordon agreed that large registries often contain data used in observational studies. He agreed that observational studies based on registry data may be designed to take into account confounding biases and data accuracy so as to contribute to the question of causality, but added the qualification that in his observation and experience this was often beset by difficulties.[1269] He was asked:

> Almost by definition nobody's perfect because of the unknowns?---That's right, but registries are particularly problematic, I would say.[1270]

1189 Gordon said that the methods of recording in insurance databases do not assist the purposes of analysing the data from an epidemiological point of view. He said the purpose of insurance codes are to claim recompense from the insurer, and that use of the data for an epidemiological purpose was problematic. He said:

> We have this data here that we think may be useful for an epidemiological purpose, but that's an entirely [different] thing from conducting in a careful way an epidemiological study where you attempt to measure things with defined scales and questions or even clinical examinations of the subjects.[1271]

Gordon said if the codes were recorded correctly they could in principle be used for an epidemiological purpose, however, this assumption could not safely be made. He said without checks on the quality of coding, biases of the clinicians recording the

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1268 Ibid at 48 [266].
1269 T3715 (TRA.500.0037.0001_2 at 0032).
1270 T3715 (TRA.500.0037.0001_2 at 0032_27-9).
1271 T3733 (TRA.500.037.0001_2 at 0050_21-31).

codes, or of the patients, could easily be introduced.[1272]

1190 As-Sanie agreed there were some limitations to the retrospective studies because of the way the registry data had been collected. However, she added that the registry databases were widely used and supported in medical science to understand relationships between interventions and outcomes because they had the distinct advantage of having a large sample size. She said studies that cross-referenced data from the registries with actual medical records of patients found that the registry data was relatively accurate and reflective of what patients had reported to physicians during consultations.[1273] As-Sanie said her opinion did not rely on a single study and was based on multiple studies with consistent outcomes.

Measured outcomes

1191 Gordon and Gebski agreed that the definitions of CPP and AUB are broad and imprecise, making measurement of these outcomes in retrospective observational studies difficult.[1274] Gebski said the nature of pain measurement is that it is very difficult to distinguish between patients who are actually suffering clinically verifiable pain, and those who are simply reporting pain to their doctors, rendering accurate classification of patients nearly impossible.[1275]

Publication bias

1192 Gebski was cross-examined about publication bias and conflict of interest by reference to chapters from a clinical training handbook that assists study investigators to minimise bias, published by Cochrane Training ('*Cochrane*').[1276] Gebski agreed that the publication of studies was influenced by the nature and direction of the results, and that studies with statistically significant results were more likely to be published than those with non-significant results.[1277] Gebski agreed with the following quote

1272 T3734 (TRA.500.037.0001_2 at 0051).
1273 T2574 (TRA.500.028.0001_2 at 0037).
1274 T3765 (TRA.500.037.0001_2 at 0082).
1275 Regulatory JER at 22 [115] (EXP.500.001.0003).
1276 MSC.001.002.0085 at 2; MSC.001.002.0084.
1277 T3772 (TRA.500.037.0001_2 at 0089).

from *Cochrane*:

> By examining a cohort of 164 trials submitted to the FDA for regulatory approval, Rising and colleagues found that trials with favourable results were more likely than those with unfavourable results to be published.[1278]

1193 Gebski agreed bias may arise from conflicts of interest, and agreed with the following from *Cochrane*:

> A particularly important piece of information is the funding source of the study and potential conflicts of interest of the study authors.[1279]

He further agreed with the following observation in *Cochrane*:

> The authors of a study concluded that trials funded by a drug or device company were more likely to have positive conclusions and statistically significant results and that this association could not be explained by differences in risk of bias between industry and non-industry funded trials.[1280]

1194 Gebski said that he only used the raw numbers from the studies in his pooled analysis because of the potential for statistical manipulation in those studies. I asked:

> HIS HONOUR: Does that mean that the devil's in the detail and the detail's not always obvious?---The detail can be very, very transparent or very opaque, agreed.
>
> MR GUO: In fact sometimes the necessary detail might not even be published at all?---I agree.[1281]

1195 Gebski was shown an internal Bayer document called the 'Essure® Global Publication Plan'.[1282] Gebski said a chart in the document that mapped out the universe of Essure literature and studies, indicating whether studies were positive or negative, sounded like 'scientific marketing', which was an attempt identify problems and where the value is for the company. He was asked:

> The value as in the value of targeting subsequent research for publication?---Could be, yeah.[1283]

1278 MSC.001.002.0085 at 8; T3772 (TRA.500.037.0001_2 at 0089_27-30).
1279 MSC.001.002.0084 at 11; T3773 (TRA.500.037.0001_2 at 0090_18-20).
1280 MSC.001.002.0085 at 19; T3773 (TRA.500.037.0001_2 at 0090_24-9).
1281 T3775 (TRA.500.037.0001_2 at 0092).
1282 BAG.001.001.2526.
1283 T3786 (TRA.500.037.0001_2 at 0103_24-5).

As-Sanie's approach

1196 Gordon made the following further criticism of As-Sanie's approach:

> Dr As-Sanie's approach to evaluating the evidence in relation to each of the outcomes of interest is to tabulate the results from the studies she has identified and to draw a qualitative conclusion based on her own descriptive 'synthesis'. She does not use a quantitative methodology, such as meta-analysis, to combine results.[1284]

1197 Gordon did not agree that assessment of an intervention was practically enhanced by an increased number of indicatively favourable studies, because each of the studies may be subject to the same bias or biases. It was put to him that the greater the number of studies, the less chance they would all be subject to the same undetected or uncontrolled biases.[1285] He said it was possible that consideration of a number of studies would lead to 'unwelcome precision around a biased estimate'.[1286] He said that an analysis of the design and results of the studies may not be sufficient to discover common undetected or uncontrolled biases. However, Gordon agreed that consistent results from a number of observational studies assessed to be of reasonable quality, taken together, may add something to the assessment of causality.[1287]

1198 Gordon said in relation to the safety of Essure that the epidemiological evidence on causality was quite poor.[1288] The following exchange occurred with Gordon in relation to RCTs and observational studies:

> In this case you're not suggesting, are you, that RCTs themselves can attribute causality, are you?---I am saying that.
>
> So an RCT without more, no biological considerations - - - ?---Well - - -
>
> - - - to attribute causality; is that right?---That's the scientific paradigm, yes.
>
> That's what you include in the idiom gold standard?---Yes.
>
> When you say it's the scientific paradigm, you mean to convey to His Honour that without it you can't attribute causality; is that right?---I think it's very challenging to do so, yes.

1284 Gordon at 62 [366] (EXP.001.002.0014).
1285 T3711 (TRA.500.037.0001_2 at 0028).
1286 T3711 (TRA.500.0037.0001_2 at 0028_22).
1287 T3720 (TRA.500.0037.0001_2 at 0037).
1288 Ibid.

> In this case you see that as an insurmountable challenge, without the RCT you can't attribute causality; is that right?---There are many problems with the observational studies which lead me to that conclusion, yes.
>
> So your conclusion, for His Honour, is there's nothing to attribute causality in this case?---Well - - -
>
> There's no RCT and the studies are too problematic?---I think that - let me rephrase that, if I may, Mr Walker. I think that's too binary a conclusion.
>
> Yes?---Within the non-randomised studies there are better and worse studies and the studies that are better among the observational studies may give us a guide to causality.[1289]

He said that better quality observational studies were those where a serious attempt had been made to adjust for confounding variables, and where the definitions of outcomes were clear and had been well measured.

1199 Gordon agreed that in the absence of a properly conducted meta-analysis, individual studies remained of some value in assessing causality. I asked Gordon:

> And so you either do a proper meta-analysis?---Yep.
>
> Or you consider what you can glean from an individual study?---Yes, and you may consider more than one individual study in that way without doing a proper meta-analysis.
>
> I see. So it might be that you can identify three individual studies?---Yes.
>
> Which, upon consideration of the way in which they were done and the size of the study group which questions the way it was done, you say, 'Well I can glean something from that in terms of causality. And if I can glean something from this one and this one and this one, then that adds to the picture in terms of causality'?---That's right, Your Honour, and I would say that what you've described is pretty much exactly what used to be done before meta-analysis was more widely used. It's of some value. It remains of some value.[1290]

In the above evidence, Gordon described the approach that As-Sanie took to analysis of the comparative studies and causation.

Gebski's pooled analysis

1200 The defendants asked Gebski to give an opinion on the broad question:

1289 T3716-7 (TRA.500.037.0001_2at 0033_26–0034_18).
1290 T3718 (TRA.500.037.0001_2 at 0035_9).

> By reference to the available data, comment on the risk benefit profile of the Essure device, including when compared to alternative methods of permanent female contraception.[1291]

Gebski said that in response to that question he conducted a pooled analysis of appropriate results from published observational studies comparing Essure outcomes with laparoscopic sterilisation.[1292] He said:

> I use the term a 'pooled' analysis rather than a 'meta-analyses, as I interpret the latter to be a more extensive synthesis. A meta-analysis would typically include estimates of unpublished studies, publication bias, tests of heterogeneity among the studies being analysed, numbers needed to treat, and, formal sensitivity analyses. I have not performed analyses to this level of detail.[1293]

1201 In his reply report and the biostatistical JER, Gordon made numerous criticisms of the pooled analysis in Gebski's primary report. Gebski prepared an amended pooled analysis in a supplementary report exchanged just prior to trial responding to some of Gordon's criticisms ('amended pooled analysis').

1202 The AUB rates in Gebski's amended pooled analysis are set out in the following table:[1294]

	Laparoscopic			hysteroscopic			difference		
Author	N	events	rate (%)	N	event	rate %	(%)	weight	weight*diff
Boullion	34054	364	1.069	71303	613	0.860	0.209	2325251.5	4863.9
Carney	7536	482	6.396	9025	659	7.301	-0.905	64748.5	-586.6
Steward	10875	955	8.782	3929	366	9.315	-0.534	34642.2	-184.9
							Sum	2424642.1	4092.4

1291 Gebski at 18 (EXP.001.002.0003).
1292 Ibid at 19.
1293 Ibid at 20.
1294 Gebski at 8 (EXP.500.500.0006_2).

$$\text{Pooled difference (\%)} = 100 * \frac{4092.4}{2424642.1} = \underline{0.17\%}$$

$$\text{Lower 95\% confidence interval = pooled difference} = 100 * \{(\frac{4092.4}{2424642.1}) - 1.96\sqrt{\frac{1}{2424642.1}}\}$$

$$= \underline{0.04\%}$$

$$\text{Upper 95\% confidence interval = pooled difference} = 100 * \{(\frac{4092.4}{2424642.1}) + 1.96\sqrt{\frac{1}{2424642.1}}\}$$

$$= \underline{0.29\%}$$

Gebski explained the relevance of the figures in the table:

> For laparoscopic procedures from a total of 52,465 patients, abnormal bleeding was reported in 1,801 patients, a rate of 3.43%. For the hysteroscopic procedures 1,638 cases of abnormal bleeding were reported from a total sample size of 84,257 or 1.94%. Differences in the proportions for abnormal uterine/vaginal bleeding are displayed in the forest plot… The pooled estimates for the difference between abnormal bleeding rates are 0.17% lower for those undergoing the hysteroscopic procedure, 95% confidence interval being 0.04 - 0.29%.[1295]

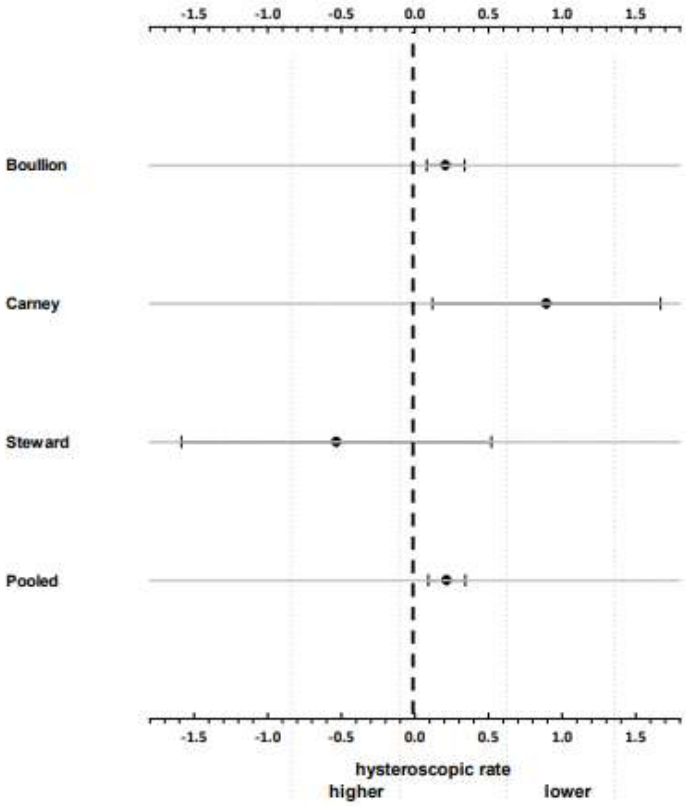
1203 Gebski concluded:

> …the rates of abnormal bleeding do not demonstrate any statistical evidence of an [increase in] the rate of long term abnormal uterine/vaginal bleeding for the hysteroscopic procedures. The estimated pooled difference shows a small but statistically significant reduction of 0.17%.[1296]

1204 Gebski included forest plots in his primary report showing the 95% confidence interval for the individual studies and the pooled figures. The following is the forest plot for AUB rates:[1297]

1295 Ibid at 8 [80].
1296 Ibid at 8 [82].
1297 Gebski at 27 (EXP.001.002.0003).

Fig 2 Forest plot of the difference in abnormal uterine/vaginal bleeding rates between laparoscopic and hysteroscopic procedures together with the 95% confidence interval for the difference (measure of uncertainty



For studies whose confidence intervals cross the zero line the is no statistical difference between the laparoscopic and hysteroscopic procedures

1205 Gebski's amended pooled analysis of CPP rates is as follows:[1298]

	Laparoscopic			Hysteroscopic			difference		
Author	N	events	rate (%)	N	event	rate %	(%)	weight	weight*diff
Boullion	34054	17379	51.03	71303	33228	46.601	4.433	92352.3	4093.54
Carney	5887	671	11.4	7842	729	9.296	2.102	35833.61	753.19
Conover	44948	420	0.93	26927	236	0.876	0.058	1891857.15	1096.70
Perkins	42391	18101	42.7	27724	10119	36.50	6.20104	70762.6	4388.02
Steward	10875	3223	29.6	3929	1010	25.71	3.93	14752.8	579.86
							Sum	2105558	10911.31

1298 Gebski at 9 (EXP.500.500.0006_2).

$$\text{Pooled difference (\%)} = 100 * \frac{10911.31}{2105558} = 0.518\%$$

$$\text{Lower 95\% confidence interval = pooled difference} = 100 * \{(\frac{10911.31}{2105558}) - 1.96\sqrt{\frac{1}{2105558}}\}$$

$$= 0.38\%$$

$$\text{Upper 95\% confidence interval = pooled difference} = 100 * \{(\frac{10911.31}{2105558}) + 1.96\sqrt{\frac{1}{2105558}}\}$$

$$= 0.65\%$$

Gebski said:

> Five reports, [Boullion 2018, Carney 2017, Conover 2015, Perkins 2016, and Steward 2018] provided information on the rates of pain requiring prescription analgesics resulting in health insurance claims. A report by Povedano only provided information on pain from hysteroscopic devices and, as no differences from the laparoscopic procedure were provided, this study was not included in the meta-analysis. For reports on 138,155 patients undergoing the laparoscopic procedure, chronic pelvic pain was assigned to 39,794 patients (28.80%). For 142,031 patients undergoing the hysteroscopic procedure, chronic pelvic pain was assigned to 45,477 (32.02%) patients.[1299]

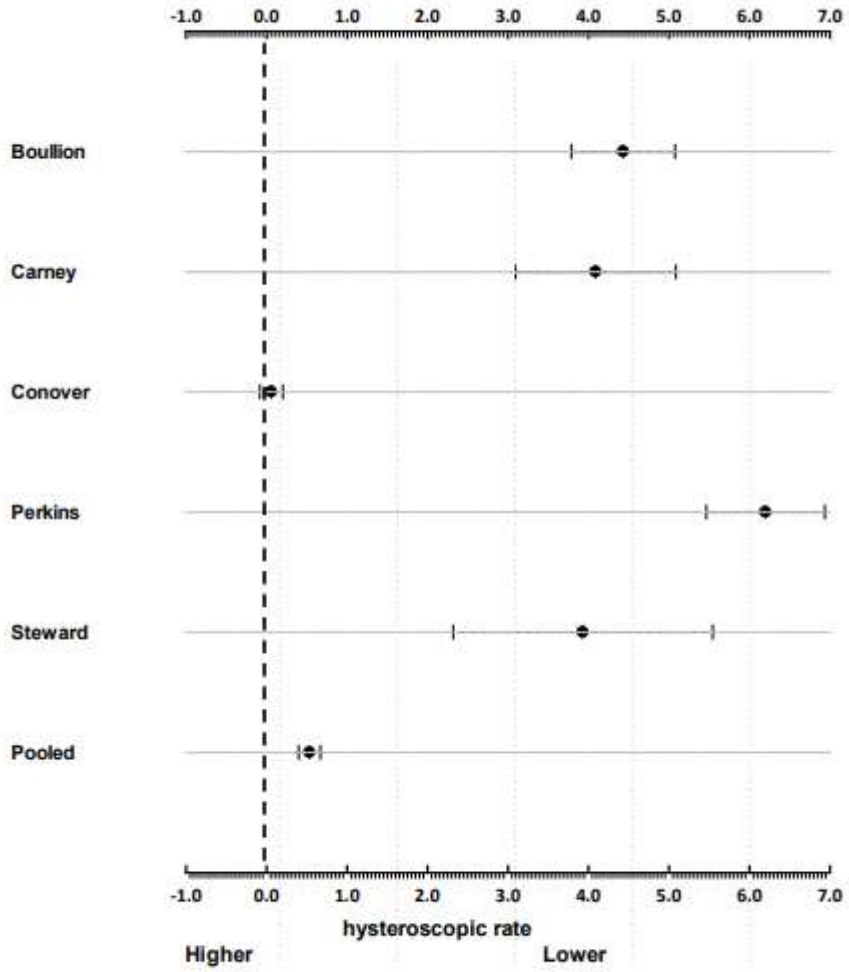
1206 Gebski reached the following conclusion relevant to CPP based on his pooled analysis:

> The interpretation of this result is analogous to the previous graphs. The pooled difference between the two procedures shows a 0.518 lower pain rate for the hysteroscopic group, 95% confidence interval 0.38% - 0.65%, with the pooled laparoscopic rate being estimated as 41.27%.[1300]

1207 The CPP forest plot produced by Gebski in his primary report is set out below:[1301]

1299 Ibid at 10 [85].
1300 Ibid at 10 [88].
1301 Gebski at 29 (EXP.001.002.0003).

Fig 3 Forest plot of the difference in chronic pelvic pain rates between laparoscopic and hysteroscopic procedures together with the 95% confidence interval for the difference (measure of uncertainty)



For studies whose confidence intervals cross the zero line the is no statistical difference between the laparoscopic and hysteroscopic procedures

1208 Gebski said that he made assumptions in performing the analysis, including:

(a) 'laparoscopic procedure/device' was assumed to refer to tubal ligation performed laparoscopically;

(b) hysteroscopic procedures were assumed to imply the use of Essure;

(c) whenever feasible, adverse events within three months post-sterilisation procedure were excluded on the basis that the key question of interest was longer term adverse events;

(d) where a study included data for different time periods, only information from the longer time period was used on the basis that this would better reflect the 'lifelong' outcome rates in patients;

(e) 'only patient groups experiencing adverse events that were reported not to be present prior to the procedures were used in the pooled analysis as these would more accurately reflect the incidence of adverse events which could be attributed to the device'.[1302]

1209 Gebski said that the pooled analysis was a guide as to whether there are differences in the rates of adverse outcomes following the different procedures, and not an analysis determining the precise magnitude of any differences that exist. He said that the pooled analysis showed there was little evidence of any substantial differences between Essure and laparoscopic sterilisation for the outcomes of CPP and AUB. He said:

> With reports, comparisons and complex statistical analyses derived from very large databases totalling in excess of 440,000 patients, the prospect that a single RCT would provide results which differ to these in these reports is at best, very remote.[1303]

1210 Gebski emphasised this evidence by reference to the likely outcome of an RCT, if it were conducted:

> Pragmatically any RCT designed to evaluate differences between laparoscopic and hysteroscopic procedures would comprise of at least 3000 patients. It is inconceivable that results for [an] RCT comprising of < 1% of the population of patients having these procedures would outweigh those from the large databases/reports based on > 440,000 cases. To suggest that results from observational studies are somehow inadequate undermines the whole concept of large disease registries and the methods underlying data science. Discrepancies between the results from RCTs and those from large databases would point to the generalizability of RCT results rather than question the appropriateness of results from these databases. Additionally, I suspect that there would be a high chance the results from the two study designs would corroborate each other with and little extra scientific/clinical information would be gained.[1304]

1302 Ibid at 21.
1303 Ibid at 35.
1304 Ibid.

Criticisms of Gebski's pooled analysis

Re-operation

1211 Turner criticised Gebski's failure to include re-operation in his pooled analysis, and tendered an aide memoire which applied the methodology used in his primary report to analyse re-operation rates as reported in the relevant studies. This aide memoire is reproduced in Schedule 2 to these reasons.

Study quality and sample size

1212 The following evidence is relevant to a consideration of the comparative studies and As-Sanie's analysis.

1213 Gordon criticised Gebski's inattention to the quality of the studies he sought to combine in the pooled analysis, and to the impact poor quality observational studies may have on the reliability of the combined meta-estimate of parameters such as AUB and CPP. Gordon said:

> It is not my view that meta-analyses of observational studies should never be carried out. If they are done, however, they should focus a lot on the quality of the studies and be carried out carefully and with a lot of attention to detail. Where possible, they should pay attention to, and use, comparisons that are adjusted for differences between the groups being compared. This is required because comparative observational studies are not designed to have the balance between other important group differences that RCTs ensure.[1305]

The thrust of Gordon's criticism was that a lack of adjustment for known and unknown variables made retrospective observational studies prone to biases and that pooling of the individual study data would be infected by those biases, and may therefore be misleading. He said that sometimes, if a study was of very poor quality, it should not be included in the meta-analysis at all. He said that a sensitivity analysis of the data may be necessary to examine the quality of the studies used, and the effect of leaving subgroups of data out of the analysis.[1306]

1214 In his reply report, Gordon said:

1305 Gordon at 23 [106] (EXP.001.002.0014).
1306 T3694 (TRA.500.037.0001_2 at 0011).

> The limitations in using retrospective record data and issues in measurement of adverse events are acknowledged by Professor Gebski in paragraph 113. The impact of these issues on the reliability of the analyses he reports is not discussed explicitly. Usual practice in reporting a meta-analysis is to consider such issues on a case-by-case basis, and to evaluate study quality.
>
> Professor Gebski, while giving broad acknowledgement to these issues, effectively sweeps them under the carpet in terms [of] their potential impact on the interpretation and reliability of the analyses he has conducted. Again this does not meet the usual standards of academic rigour or peer review.[1307]

1215 Gebski referenced several studies to support the proposition that the information provided by observational data had value. Gordon said in reply:

> None of this literature is convincing evidence for any change in the hierarchy of evidence in my opinion. Nor do the authors argue for that. Based on a few tens of specific cases, it is observed that sometimes the results of randomised studies are similar to non-randomised studies, and sometimes they are not, and there is no clear indication of factors that determine which of these scenarios applies to a specific research topic.[1308]

He added that the literature clearly suggested 'that any reliance on non-randomised studies should focus on studies of high quality'.[1309]

1216 Gordon said that Gebski's suggestion that observational studies with large sample sizes were more representative of the population than RCTs, and resolved any issues of bias, was not valid. He said a biased estimate of a treatment effect is worse when it arises from a large sample.[1310] He gave the following example:

> Suppose (hypothetically) the difference between a laparoscopic device and Essure is found to be +3% for uterine bleeding (laparoscopic worse), from a very large cohort study. Suppose, further, that due to selection biases, this estimate is biased and the difference should be lower by 2 percentage points; it should be only 1% worse for laparoscopic. If the study is very large, the 95% confidence interval around the +3% might be (+2.6% to +3.4%). The large sample size leads to a narrow confidence interval around a biased estimate, and that is an unhelpful and undesirable conclusion.[1311]

1217 Gebski said there was no evidence about what biases were present in the comparative studies, or the extent to which those biases may cause concern in interpreting the

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1307 Gordon at 41-2 [222]-[223] (EXP.001.002.0014).
1308 Ibid at 21 [98].
1309 Ibid at 22 [100].
1310 Gordon at 22 [101] (EXP.001.002.0014).
1311 Ibid at 22 [102].

study results.[1312] Gebski agreed there were unknowns about women's reproductive health,[1313] that could cause bias in the data.[1314] Gebski said, however, that this was not necessarily a confounding factor, adding:

> But there's this perception, I think, that because it's an observational study a bias must exist and that's been shown not to be necessarily true. In fact there is research saying that the results from observational studies match very closely those from randomised trials. That's been published in the New England Journal of Medicine, a very highly respected journal. There's been essentially the whole thing of saying, well, we need to adjust for all these variables. We don't know - my definition of confounding of, of a confounding variable is if that individual variable impacts on outcome. We mentioned, say, age will impact on an outcome. We don't know that. We just don't. So just saying that because it's observational, because we haven't adjusted for it, somehow it's bad, I don't accept. I can accept it's not as pristine as a randomised trial, I don't disagree with that, but it has enormous value and we don't know, for instance, in all of these studies, we don't know that there's bias. Coming back to Professor Gordon's example of the Roosevelt thing, that's a sampling problem. You ask a potential voter which way they're going to vote and they're in control. In these databases the patients aren't in control. They put in a claim that goes into a database and that database is then interrogated. So therefore they don't have a choice whether their data is used or not, whereas they do have a choice of whether they're going to respond to a survey. I think that analogy is not – it shows bias, but it shows bias for a totally different problem. This is not a sampling issue, it's an issue of collection.
>
> I'm not suggesting it's a sampling issue, I'm just talking about whether this phenomenon could affect the numbers that have been reported in the studies and on which you rely?---Well, I mean it could. We don't know whether it does.
>
> To use the Rumsfeldian term, an unknown unknown?---Unknown unknown, yeah.
>
> You just would be speculating if you were to attempt to be precise about the effect?---Yes.[1315]

1218 The first study relied on by Gebski is Concato et al ('Concato 2000') which considered five research questions for which RCTs and observational studies were available, which concluded that the average results of observational studies were remarkably

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1312 Gebski at 47 [160] (EXP.001.002.0003).
1313 T3614 (TRA.500.036.0001_2 at 0072).
1314 T3790 (TRA.500.037.0001_2 at 0107).
1315 T3790–2 (TRA.500.037.0001_2 at 0107_8-0109_14).

similar to those of RCTs.[1316] In fact, Concato 2000 found:

> … the summary results of randomized, controlled trials and observational studies were remarkably similar for each clinical topic we examined ... Viewed individually, the observational studies had less variability in point estimates (i.e., less heterogeneity of results) than randomized, controlled trials on the same topic ... In fact, only among randomized, controlled trials did some studies report results in a direction opposite that of the pooled point estimate, representing a paradoxical finding …[1317]

Concato 2000 found the data presented in the study was consistent with three other types of available evidence:

> For example, previous investigations have shown that observational cohort studies can produce results similar to those of randomized, controlled trials when similar criteria are used to select study subjects. In addition, data from nonmedical research do not support a hierarchy of research designs. Finally, the finding that there is substantial variation in the results of randomized, controlled trials is consistent with prior evidence of contradictory results among randomized, controlled trials.[1318]

Concato 2000 said a possible explanation for observational studies being less prone to heterogeneity than RCTs related to them including a broad representation of the population at risk. The authors concluded:

> Randomized, controlled trials will (and should) remain a prominent tool in clinical research, but the results of a single randomized, controlled trial, or of only one observational study, should be interpreted cautiously. If a randomized, controlled trial is later determined to have given wrong answers, evidence both from other trials and from well-designed cohort or case–control studies can and should be used to find the right answers. The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals.[1319]

1219 The second study is Shrier et al ('Shrier 2007') which considered whether observational studies should be included in meta-analyses in addition to RCTs.[1320]

1316 John Concato et al, 'Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs' (2000) 342(25) *New England Journal of Medicine* 1887 (PUB.500.001.0369); Gebski at 13 [32] (EXP.001.002.0003).

1317 Ibid at 4.

1318 Ibid.

1319 Ibid at 6.

1320 Ian Shrier et al, 'Should Meta-Analyses of Interventions Include Observational Studies in Addition to Randomized Controlled Trials? A Critical Examination of Underlying Principles' (2007) 166(10) *American Journal of Epidemiology* 1203 (PUB.500.001.0393).

Shrier 2007 found that both randomised controlled trials and observational studies had strengths and weaknesses, and that both should be included in any systematic review or meta-analysis.

1220 I conclude that Concato 2000 and Shrier 2007 support Gebski's proposition that observational studies have value. Further, the conclusions of Concato 2000 and Shrier 2007 support As-Sanie and Gebski's reliance on the comparative studies in this case.

1221 Gebski said that he distinguished between a pooled analysis and a more extensive meta-analysis, and that Gordon had conflated the two. He said:

> The pooled analysis is an exploratory analysis attempting to gain insight into differences between the AE and failure rates rather than assuming to develop strict rules as to which studies may/may not be included in the pooling. Other than the requirement that the study should be published in a peer-reviewed journal and no further assessment of study quality is made. Due to the exploratory nature of the pooled analysis studies would be included which use strong surrogates for some outcomes, for example, the frequent use of prescription analgesics as a surrogate for chronic pelvic pain as opposed to multiple radiological scans. The pooled analysis was never intended to be a comprehensive and rigorous synthesis of the information, and this was outlined in some detail in my first report.[1321]

1222 Gordon said that Gebski's statement that 'despite the variations across the reported studies, the pooled analysis does give some indication of the direction of the estimates of difference in outcomes between the laparoscopic and hysteroscopic devices'[1322] was misleading. Gordon said that a poorly conducted pooled analysis can be biased, and that Gebski's claim that a properly conducted systematic review would be consistent with the results of his pooled analysis was pure speculation.[1323]

1223 Gordon said that while sample size was important, it was a secondary consideration and did not trump issues of bias and study quality. He said:

> Accurate quantification of effects is the cornerstone of rigorous statistical science. Professor Gebski's view that his analyses are informative because they

1321 Regulatory JER at 19 [97] (EXP.500.001.0003).
1322 Gebski at 34 [111] (EXP.001.002.0003).
1323 Gordon at 41 [220] (EXP.001.002.0014).

provide *guides* and *some indication* is deeply flawed.[1324]

Gordon added:

> When the evidence is inadequate or poor, and inconsistent, claims of the absence of differences are not well-founded.[1325]

1224 In relation to Gebski's claim that criticism of observational studies undermines the concept of large disease registries and the methods underlying data science,[1326] Gordon responded:

> This is a confusion between the roles of well-designed comparative studies (RCTs) and registries. Disease and treatment registries have an important role in monitoring health events for a diseased or treated population. They are not however, a substitute for RCTs in attributing causality to interventions.[1327]

1225 While Gebski acknowledged that the comparative studies were subject to biases, 'patient selection bias being the foremost', he concluded:

> Such large sample sizes will provide estimates of the rates of pregnancy and adverse events which would closely reflect the population levels of women undergoing sterilisation using these procedures (such as body mass index, physical fitness, lifestyle factors etc).[1328]

Gebski said that some caution was required when assessing the existence of adverse events, noting that self-reported adverse events are highly variable in both reported severity and 'attribution of the adverse event to surgical procedure'.[1329] Gebski said that the published studies had not identified significant differences between laparoscopic and hysteroscopic procedures based on patient demographic variables such as race or ethnicity, or other baseline variables, that suggested the presence of selection bias. He said that the impact of biases would be present in both procedure groups and would therefore be minimised.[1330]

1324 Ibid at 42 [227].
1325 Ibid at 42–43 [231].
1326 Gebski at 35-6 [119] (EXP.001.002.0003).
1327 Gordon at 44 [241] (EXP.001.002.0014).
1328 Gebski at 22 [61] (EXP.001.002.0003).
1329 Ibid at 22 [62].
1330 Ibid at 23 [65].

1226 Gebski concluded:

> Despite the variations across the reported studies, the pooled analysis does give some indication of the direction of the estimates of difference in outcomes between the laparoscopic and hysteroscopic devices. The volume of patients together with reports from different countries adds to the generalizability of the results, and while a systematic review may allow for increased clarity in interpretation of the differences in outcomes, I believe that these would be consistent with the results presented in this report.
>
> Despite of the drawbacks of lack of randomized comparisons and selection bias, the volume of participants in receiving either the laparoscopic and hysteroscopic procedures would nevertheless provide estimates of failure rates for both procedures (unwanted pregnancies) as well as short- and long-term adverse events representative of this population of women.[1331]

Comprehensive meta-analysis

1227 Gordon said that the first step in carrying out a meta-analysis was to comprehensively search for Essure studies. He said this was necessary to ensure that relevant studies were not omitted, and to avoid 'publication bias'. Gordon said it was fundamental to a meta-analysis that all relevant results on a given topic be considered. He said that because no such comprehensive search had been attempted, Gebski's analysis did 'not meet minim[um] standards of good statistical practice' and 'would not be considered suitable for publication in an academic journal'.[1332]

1228 Gebski responded by saying his pooled analysis was never intended to be a comprehensive and rigorous synthesis of information in the comparative studies, but was 'an exploratory analysis attempting to gain insight into differences between the [adverse event] and failure rates'.[1333]

Inclusion of Adiana device

1229 Gordon criticised Gebski's use of data from studies that did not differentiate between Essure and Adiana hysteroscopic procedures. He rejected Gebski's explanation that the comparative results would be largely congruent with expected Essure results, and noted that Essure and Adiana were quite different in their construction and function.

1331 Ibid at 34–35.
1332 Gordon at 41 [149]-[214] (EXP.001.002.0014).
1333 Regulatory JER at 19 [97] (EXP.500.001.0003_2).

1230 Gebski responded that it was known Essure comprises the vast majority of devices used in hysteroscopic sterilisation, and described Gordon's criticism as an over-reaction. He said:

> As a hypothetical example, if out of the 26,927 patients undergoing hysteroscopic sterilization in the Conover 2015 study, all but 100 patients had the Essure device, should that study be excluded? As we do not know the proportion of Essure devices in the Brandi et al. (2018), [Carney 2017], [Perkins 2016], [Steward 2018] and [Conover 2015] studies, the approach adopted was to include them in the pooled analysis wherever possible. This was a pragmatic decision as I am not aware on any evidence of a differential [adverse event] and pregnancy rate between devices from different manufacturers.[1334]

Analgesic use as a proxy for pain

1231 Gordon criticised Gebski for equating CPP with analgesic reimbursements in his pooled analysis, as reported in Bouillon 2018. Gordon said that this was a fundamental measurement error, noting that 'analgesics may be taken for many reasons, which need not be pelvic pain, chronic or otherwise'.[1335]

1232 Gebski responded that because of the nature of pain it would be almost impossible to distinguish patients who are actually suffering from CPP. He said a patient requiring prescription analgesics may also be experiencing medically managed CPP. Gebski said:

> Reimbursements for analgesics (particularly over long periods of time) may be an accurate surrogate for chronic pelvic pain.[1336]

He added that in his understanding, the strength of prescription analgesia was strongly associated with pain intensity, and that 'the need for prescription analgesia is a common surrogate indicator when monitoring pain after clinical procedures in the absence of more specialized approaches of pain assessment'.[1337] Gebski concluded that using the analgesic surrogate was a pragmatic consideration 'so as not to exclude information which could mask differences between the two devices'.[1338]

1334 Ibid at 20 [99].
1335 Gordon at 36 [181] (EXP.001.002.0014).
1336 Regulatory JER at 22 [116] (EXP.500.001.0003_2).
1337 Ibid.
1338 Ibid.

Heterogeneous outcomes

1233 Gordon criticised Gebski's pooled analysis for significantly confusing units and types of variables. He pointed to Gebski's consideration that a rate of pelvic pain per 100 person-years as reported in Perkins 2016 could 'somehow "correspond" to a prevalence (percentage) of pelvic pain at a point in time'.[1339] Gordon said that 'the rate per 100 person-years could be larger than 100, reflecting the fundamentally different natures of a rate per time and a percentage at a point in time'.[1340]

1234 Gebski acknowledged that the definitions used and outcomes reported in the comparative studies were 'not ideal', adding:

> Despite these reservations, [if] pooling [of] this information is still feasible, this pooling would help to clarify the profile of chronic pelvic pain experiences for each of the device, particularly in a more diverse patient population.[1341]

1235 In an associated criticism, Gordon said that the outcomes studied in a meta-analysis should be the same in each included study. In Gebski's pooled analysis, the percentage for the outcome treated as CPP for laparoscopic sterilisation ranges from 47% in Bouillon 2018 down to 1% in Conover 2015. Gordon said that '[t]hese percentages are so divergent that they cannot be measuring the same outcome'.[1342]

1236 Gebski said in response:

> Professor Gordon has highlighted the heterogeneity among studies in outcome assessment, particularly pain and I agree with his observations. This raises the question of whether any of these studies should be combined at all. Given that these studies do provide information regarding outcomes, and, many studies are based on tens of thousands of patients, not to obtain some overall estimate may also be unwise, particularly for future decision making.[1343]

Excluded data

1237 Gordon criticised Gebski's decision to ignore adverse events in the first three months following the sterilisation procedure as unreasonable, on the basis that the short-term

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1339 Gebski at 30 [93] (EXP.001.002.0003).
1340 Gordon at 37 [185] (EXP.001.002.0014).
1341 Regulatory JER at 22 [114] (EXP.500.001.0003_2).
1342 Gordon at 38 [194] (EXP.001.002.0014).
1343 Regulatory JER at 23 [118] (EXP.500.001.0003_2).

effects remain relevant.

1238 Gebski responded as follows:

> The size of the effects of [adverse events] associated with the procedure would be confounded by physician experience, or patient characteristics (e.g., advice to abstain from engaging in sexual intercourse for a period post insertion) and attribution of [adverse events] observed in the period at or just after insertion to be entirely due to the device. Having a time buffer after insertion is a sensible decision to help isolate the attribution of [adverse events] or pregnancies to the device.[1344]

1239 Gordon disagreed with Gebski's exclusion of patient groups experiencing adverse events with a pre-sterilisation history of CPP or AUB. Gordon pointed out that Essure or laparoscopic sterilisation could exacerbate or reduce symptoms of CPP or AUB, and that this was important to evaluate.

1240 Gebski responded as follows:

> If some of the [adverse events] of interest were originally present at baseline, it would be difficult to attribute the [adverse events] post implantation to the particular implant. Professor Gordon suggests that the implant/procedure may worsen or ameliorate the severity of an [adverse event]. If a change in [adverse event] status were observed post implant, the cause of this change would be completely unknown.[1345]

Gebski said that the change could be due to a range of factors including the disease history, an alteration of patient/behaviour factors post-surgery, an impact of the procedure such as anaesthesia, or the sterilisation device itself.

Use of unadjusted data

1241 Gordon criticised Gebski for using 'raw data' from the comparative studies (being the proportions of women with an outcome divided by the number of women) rather than, where available, adjusted data. Gordon explained that this was a reasonable approach in an RCT because of the steps taken to randomise between the comparative groups, but was not for non-randomised comparisons of interventions. He explained that the laparoscopic and hysteroscopic groups may differ in important respects and

1344 Ibid at 20 [100].
1345 Ibid at 20 [101].

that these differences may distort the results of a simple comparison of unadjusted data. He said that the results may be due to the unmeasured differences between the groups, rather than the difference between the two interventions.

1242 Gebski said he used the raw numbers 'because the numbers are what the numbers are'. He said that he did not want to use the results from the complex methods of adjustments in the studies because he did not know how they were performed.[1346] Gebski said that while propensity score matching was a reasonable method, it was still subject to debate.[1347]

Data overlap

1243 Gordon said there was considerable overlap in the data pooled by Gebski. The most significant overlap related to the Truven database used in Conover 2015, Perkins 2016 and Carney 2017. Gordon said:

> And it's a fundamental aspect of how studies should be pooled or meta-analysed, that you ought not to include duplicates in any sense of the same subjects from the same study. Now it's not necessarily always straightforward to deal with that, but efforts must be made to ensure that you're not getting, not duplicating the same result in some way. That's not just a matter of treating the outcome or defining the outcome differently. It goes to the whole issue of whether we're really getting new information because obviously in a meta-analysis we want to pool independent pieces of information, independent in the statistical but also the English sense of the word, distinct pieces of statistical evidence, and we don't want to give an impression, falsely or otherwise, that we're doing that when we repeat data from the same study. So it's - yeah, it's something that's fundamental to meta-analysis, I would say, and described as such in any of the standard ways that meta-analysis is discussed.[1348]

1244 In his pooled analysis of CPP, Gebski said there were 138,155 patients who underwent laparoscopic sterilisation and 142,031 patients who underwent hysteroscopic sterilisation. If the overlap between Conover 2015, Perkins 2016 and Carney 2017 was taken into account, these figures would be substantially reduced.

1245 Gebski said he did not specifically consider the data overlap but did not think it was a major problem. In cross-examination, Gebski agreed that the weight attributed to

1346 T3775 (TRA.500.037.0001_2 at 0092).
1347 T3823 (TRA.500.038.0001_2 at 0006).
1348 T3731 (TRA.500.037.0001_2 at 0048_23).

an outcome in a study largely drove his pooling calculation. Weight depended on the number of study participants who experienced that outcome. Gebski was asked the following questions about his pooled analysis of CPP:

> So if we look at [Carney 2017] and [Conover 2015] and [Perkins 2016]?---Yes.
>
> They are all studies which overlap, yes?---Yes.
>
> Take it from me that if I add all those weights together, that is those three studies that overlap, account for 96 per cent of the total weight. That's very significant, isn't it?---That would be, yes. Although Carney there, when you're saying the weight of, the overlap with Carney, I used just the women who had no prior pelvic pain and no prior bleeding, so in this case pelvic pain at the time, whereas I suspect that the Conover would use all of them.
>
> Sure, but that doesn't change the fact that of those three studies, the weights, which are the product of formulas, you've employed - - - ?---Yes.
>
> - - - add up to a very significant portion of the total weight, you agree with that?---Yes.
>
> So it is a material effect on the conclusion, this overlap?---Well the overlap would impact, yes.
>
> Not just an impact, but a material impact?---Probably, yeah, I agree.
>
> More than probably, it is?---Well I accept the 96 per cent, therefore it is, yeah.
>
> So that's material?---Yeah.[1349]

1246 The above line of questioning appears to overstate the effect of Gebski's failure to account for the overlap between Carney 2017, Perkins 2016 and Conover 2015 on his pooled analysis of CPP rates. The 96% refers to the combined contribution of those three studies to the denominator in Gebski's calculation of the pooled difference. Of course, those studies also contributed to the numerator in Gebski's calculation. The impact of failing to account for the overlap is uncertain. Removing the Carney 2017 and Perkins 2016 figures from Gebski's pooled CPP rate analysis set out at [1205] above appears to result in the pooled difference decreasing from 0.518% to about 0.289%. This simplistic calculation suggests that the data overlap will have had a material effect on Gebski's CPP pooled analysis. Neither Gebski nor Gordon

[1349] T3797-9 (TRA.500.037.0001_2 at 0115_26-0016_16).

explained how the data overlap could be properly accounted for. Gebski's AUB pooled analysis was not infected by data overlap.

No Essure RCT

1247 The experts agreed that RCTs are the highest level evidence upon which to assess the risk-benefit profile of a medical intervention.

1248 The main issues between the experts were the potential value and feasibility of an Essure RCT.

Value

1249 As the name suggests, an RCT involves a random process to allocate the interventions being compared to study participants. The randomisation of allocation is intended to remove the potentially distorting effect of both known and unknown confounding factors.[1350]

1250 Gordon said that generalisability is affected by RCT study population exclusions and inclusions that impact its typicality.[1351] There is a question about the utility of RCT outcomes to patients and doctors in the real world, given the characteristics of the study population. Gordon accepted that randomising involved a process of self-exclusion amongst the recruited population of an RCT, and this process could affect the generalisability of the study.[1352] He said that judgments about the generalisability of any study are always necessary given an RCT is conducted at a particular location, at a particular time, and by particular practitioners.[1353] Gordon said that the generalisability of an RCT is not a straightforward consideration. Judgments about administering treatments to populations unrepresented in the RCT are necessary. He said that in RCTs, 'conclusions are often generalised and extended to much wider

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1350 Gordon at 21 [61]-[62] (EXP.001.001.0418); T3613 (TRA.500.036.0001_2 at 0071); Kristy P Robledo and Val Gebski, 'Generalizability from well-designed RCTs underpin their scientific strength' (2019) 221(6) *American Journal of Obstetrics and Gynecology* 663, 663 (PUB.001.002.0226).

1351 T3586 (TRA.500.036.0001_2 at 0044_10).

1352 Generalisability being the applicability of study results across the population; T3856 (TRA.500.036.0001_2 at 0044).

1353 T3586-7 (TRA.500.036.0001_2 at 0044-5).

populations than those who were eligible for the trial'.[1354] He said something similar to a 'pragmatic RCT' with the broadest possible inclusion criteria would have been desirable for Essure to imitate real life as closely as possible.[1355]

1251 Gordon said that he had not turned his mind substantively to what protocol exclusions a properly conducted Essure RCT would require, if any.

1252 He accepted that he did not have a complete understanding of how the Essure procedure contraindications would affect the exclusions from an RCT. He said he had taken contraindications into account in his opinions about the feasibility of an RCT on the basis of the population size of actual studies conducted on women with Essure. He also referred to some limited information on contraindications in a 2005 study by Baxter et al ('Baxter 2005'),[1356] which was a prospective cohort trial to determine whether women would favour hysteroscopic sterilisation over laparoscopic sterilisation. However, he agreed his expertise was limited in interpreting this data. He said that he would not necessarily rule out women with particular conditions (for example bleeding) if it was feasible for them to receive either treatment.[1357]

1253 Gebski said that as a general rule, RCTs suffer from limited generalisability.[1358] He said:

> The proof of concept is already demonstrated in the device development and testing, and what remains is to evaluate the utility and safety of the device. Pragmatically, such evaluations can be determined from observational series with little extra to be gained from the requirement of a resource intensive RCTs which have been shown to have limited generalizability to the broader patient populations being the target of the intervention.[1359]

1254 In cross-examination, Gebski was taken to a letter to the editor he wrote in the *American Journal of Obstetrics and Gynaecology* titled 'Generalizability from well-

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1354 T3671 (TRA.500.036.0001_2 at 0129).
1355 T3587 (TRA.500.036.0001_2 at 0045).
1356 Niki Baxter et al, 'Hysteroscopic sterilisation: a study of women's attitudes to a novel procedure' (2005) 112(3) *BJOG: An International Journal of Obstetrics and Gynaecology* 360 (PUB.001.001.3724) ('Baxter 2005').
1357 T3588-90 (TRA.500.036.0001_2 at 0046-8).
1358 T3646 (TRA.500.036.0001_2 at 0104).
1359 Gebski at 15 [41] (EXP.001.002.0003).

designed RCTs underpin their scientific strength', in which he said:

> The design strength of randomization in a well-conducted clinical study ensures that all factors, both measured and unmeasured, are balanced among the groups being compared and guarantees that comparisons give unbiased and consistent estimates of the true underlying differences.[1360]

He explained that these comments referred to RCT design balancing the heterogeneity of surgical experience which strengthened its generalisability, but that this comment could not be extrapolated out to a statement that RCTs are broadly generalisable.[1361] He did not think that his opinions as set out in the published letter were inconsistent with his opinion in his primary report.[1362]

1255 Gebski said that a well-designed RCT will give consistent, unbiased estimates of the true underlying differences for a defined population, not the entire population.[1363] He said that once efficacy had been demonstrated on the study population, the intervention may then be offered to a broader population who were originally excluded from the RCT as part of a phase IV clinical trial involving randomisation.[1364] In summary, Gebski said that:

> … some randomised trials provide generalisability, other randomised trials or good well conducted randomised trials will provide a springboard, if you like, for generalisability because they're well conducted and they're consistent and you can use those results to try and extend to a broader population, but in general randomised trials do not - there's a big discourse between, or separation between the results of randomised trials and the results in the general population. That's been well documented.[1365]

1256 Gordon agreed that not every biomedical device like Essure had been subject to an RCT before receiving regulatory approval to go on the market.[1366] He said approval of a device to go on the market without requiring an RCT was a scientific failure by regulators. He accepted this was not a predominant view among regulators and was

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1360 Kristy P Robledo and Val Gebski, 'Generalizability from well-designed RCTs underpin their scientific strength' (2019) 221(6) *American Journal of Obstetrics and Gynecology* 663, 663 (PUB.001.002.0226).
1361 T3647 (TRA.500.036.0001_2 at 0105).
1362 T3653 (TRA.500.036.0001_2 at 0111).
1363 T3468 (TRA.500.036.0001_2 at 0126).
1364 T3650-1 (TRA.500.036.0001_2 at 0108-9).
1365 T3653 (TRA.500.036.0001_2 at 0111).
1366 T3573 (TRA.500.036.0001_2 at 0031_17).

not shared by the FDA at the time Essure was approved. He said that he disagreed with the approach of the FDA, but did not go so far as to say it was scientifically untenable.[1367]

Feasibility

1257 Brandwood was sceptical about the feasibility of an RCT of Essure.[1368] He said feasibility was driven by several factors:

> a) The size (number of patients and duration (years of follow up) of the trial necessary to be statistically valid for the selected outcome measures.
>
> b) The pool of patients available to be recruited into the trial[.]
>
> c) The size of the subset of patients (screened patients) from that pool who meet the trial inclusion criteria.
>
> d) The willingness of the screened patients to participate in the trial and particularly their willingness to accept that one of two very different treatments be chosen for them at random.[1369]

1258 Brandwood noted Gordon's evidence that an Essure RCT would require a minimum of 2,156 participants, Gebski's evidence that 18,266 participants would be required, and the agreed position that there should be a five-year follow-up period.[1370] He said that the clinical trial would need to recruit a far larger number of patients to achieve those minimums and that study period, given the patient losses that would occur at each stage. Brandwood described the losses as:

(a) first, from exclusion criteria, which in his experience typically reduced the pool by over 50%;

(b) second, the willingness of patients to accept randomisation, which he noted had been estimated at 8%; and

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1367 T3592 (TRA.500.036.0001_2 at 0050).
1368 Regulatory JER at 31 [156](e) (EXP.500.001.0003_2).
1369 Ibid at 31 [157].
1370 Ibid at 32 [161]–[162].

(c) third, the losses to follow-up, which he noted Gebski had estimated as likely to approach 50%.[1371]

He said this meant that a total of between 107,800 and 913,300 patients would need to be recruited into the study in order to achieve the final figures proposed by Gordon and Gebski.[1372]

1259 Brandwood accepted that in the Pivotal trial, screening had reduced an initial pool of 558 participants by only 7% to 518.[1373] He agreed that this was a much lower screening loss than he had suggested for an RCT, adding:

> … That's correct but we are talking about a different type of trial here. So whether the screening rates will be the same in this trial compared to a randomised control trial is an open question. I just wanted to qualify the response by saying that.
>
> Of course, it might not be 7, it might not be 50, it's anyone's guess at the end of the trial?---I suspect given randomised control trials tend to be far more rigorous in the selection criteria, I suspect the screening success rate would be lower. How much lower - I've estimated 50 per cent because that's what was assumed in the STOP protocol but, as I said, that's an estimate.[1374]

1260 Brandwood's randomisation reduction of 8% was based on Baxter 2005. Of the 96 trial participants, only eight expressed a willingness to be randomised. Of the 54 participants who expressed a preference for laparoscopic sterilisation, 52 gave 'wants to be asleep' as a reason.[1375] Turner submitted that the 'willing to be randomised' figure was obtained after telling survey participants that Essure would not require general anaesthesia, which was not consistent with how the Essure procedure was conducted in Australia. Brandwood explained that anaesthesia was only part of the patients' considerations. He agreed that one less consideration could change a patient's mind.[1376]

1371 Ibid at 33 [164].
1372 Ibid at 33 [166].
1373 T3660 (TRA.500.036.0001_2 at 0118).
1374 T3664 (TRA.500.036.0001_2 at 0122_5).
1375 Baxter 2005 (PUB.001.001.3724).
1376 T3657 (TRA.500.036.0001_2 at 0115).

1261 A further problem with Turner's submission is that it presumes that an RCT conducted in a jurisdiction such as Australia where the Essure procedure may involve general anaesthesia. Given the history of Essure and the need to recruit sufficient participants to a trial, it seems far more likely that any RCT would be attempted in the US, or across jurisdictions where the procedure does not involve general anaesthesia.

1262 It was put to Brandwood that in the Pivotal trial, only 12% of participants were lost to follow-up over five years.[1377] On that basis, Brandwood agreed that the loss to follow-up rate over five years would more likely be about 12% rather than the 50% he had used in his calculations.[1378]

1263 It is worth noting that of the 558 total participants in the Pivotal trial, 364 women completed the five-year follow-up. Forty women were subject to initial exclusion criteria, 65 women were lost to follow-up, and a further 89 women were subject to other events that occurred in the study period which prevented completion of the five-year follow-up. It is not clear whether some or all of the women in that final group of 89 would be treated as 'lost to follow-up' for the purposes of an RCT. This may mean that the loss to follow-up in an RCT would be significantly higher than 12%.

1264 Gordon said that participants lost to follow-up were not necessarily eradicated from the analysis for all purposes. He said that subjects lost to follow-up could be measured in many ways up to the point they are lost and included in the analysis.[1379]

1265 Gordon said a large target RCT sample size may necessitate longer recruitment and more clinical centres in order to achieve sufficient numbers.[1380] Gebski said that if the target sample size is not achieved, an RCT should not be abandoned and the recruited sample should be utilised.[1381] Gordon repeated that sample size is a secondary

1377 BAY-EDPA-0884277.
1378 T3660 (TRA.500.036.0001_2 at 0118).
1379 T3671 (TRA.500.036.0001_2 at 0129_8).
1380 T3605 (TRA.500.036.0001_2 at 0063).
1381 T3616 (TRA.500.036.0001_2 at 0074_4).

consideration to good study design quality.[1382]

1266 Gordon said that a long-term RCT was required given Essure was intended to be permanently implanted in a woman's body. He said that it was not practically feasible to complete such a long-term study before a device was used, but that this should have been done early in the history of Essure.[1383]

1267 Gebski said that an Essure RCT would have been almost impossible to conduct after clinical literature dealing with the comparative safety of the device became available because:

> … [t]here would only be a small number of physicians having the clinical equipoise required to participate in such [an] RCT making recruitment into any proposed study extremely challenging. The patient consent form would require full disclosure that (at the current time) there was little evidence of a difference in [adverse events] and a slightly lower risk of pregnancy with the Essure device [which] would further reduce the rate of accrual. The study would recruit a narrow group of patients of women who were undecided as to which device to accept.[1384]

Submissions on epidemiological evidence

Turner

RCT

1268 The Court cannot conclude, on the balance of probabilities, that there was a practical impediment to at least some form of long-term safety Essure RCT being conducted to produce meaningful results.[1385]

1269 Whether an RCT could (or even ought) to have been conducted is in many ways beside the point. The absence of any relevant RCT does not permit the defendants to claim that Essure is safe. Rather, its absence simply means that the Court does not have the best available evidence to enable it to accept a claim that Essure was safe. The defendants have invoked biostatistics in their pleaded defence as a method of

1382 T3565-6 (TRA.500.036.0001_2 at 0023–4); Regulatory JER at 8 (EXP.500.001.0003_2).
1383 Gordon at 55 [200] (EXP.001.001.0418).
1384 Regulatory JER at 28 [145] (EXP.500.001.0003_2).
1385 SBM.001.001.0004 at 176 [562].

demonstrating causation. The absence of any RCT raises the question of what general guidance in relation to causation, if any, can be robustly gleaned from the collection of non-RCT studies published in the academic literature.

522 study

1270 The 522 study is not conclusive but is the best study that exists in relation to Essure long-term safety.[1386] This is because the study specifically addresses safety outcomes and is prospective, giving it a better chance of controlling for known variables.

1271 While the 522 study is incomplete and only interim results are currently available, Gebski conceded that there was no persuasive reason why the interim nature of the results meant they should be given no weight at all. Further, the implication that the FDA would publish the interim results on its website if they were meaningless is not credible and should be rejected as a lawyer's construct.

1272 The 522 study states that it is not powered to detect statistical differences between the Essure and laparoscopic groups. As Gordon and Gebski agreed, just because a signal is not detected as statistically significant does not mean it does not exist in the whole population as a statistically significant difference —it just means that the sample size was not large enough to pick up the difference. But the corollary means that the results act as a 'floor' of sorts, because if something is detected as statistically significant even with a 'small' sample, then one knows there truly is a problem.

1273 The 2023 interim results do not paint a positive picture of Essure. Of the four key adverse events, Essure rates worse than laparoscopic tubal sterilisation in every interim analysis:[1387]

	Number of adverse events reported		
Event type	**2020**	**2021**	**2023**
Chronic lower abdominal and/or pelvic pain			

1386 Ibid at 182.
1387 Ibid at 184.

Essure	24	33	38
LTS	12	23	27
Abnormal uterine bleeding			
Essure	43	54	57
LTS	27	49	55
Gynecologic surgery			
Essure	52	55	63
LTS	8	12	20
Adjudicated allergy/hypersensitivity			
Essure	(not reported)	2	5
LTS	(not reported)	2	3

1274 The gynaecological surgery differences are statistically significant in the results from each year. Gynaecological surgery includes surgery for Essure removal and is therefore a proxy for the pleaded removal limitation.

1275 The 2023 interim results report the incidence of endometrial ablation as follows:[1388]

	Number of patients reported		
Event type	**2020**	**2021**	**2023**
Endometrial ablation			
Essure	27	29	32
LTS	6	9	17

Endometrial ablation is a recognised treatment for managing bleeding. The results are significant because they indicate increased AUB associated with Essure. The convergence in the reports of AUB between Essure and laparoscopic sterilisation by 2023 may be explained by the higher rate of successful treatment by ablation in the case of Essure patients.

1276 Similarly, women in the study who have undergone hysterectomy to remove Essure would no longer report severe pain or bleeding, again putting the apparent

[1388] Ibid at 185.

'convergence' of those adverse events over time into perspective.

Pivotal trial and Phase II study

1277 The results of these clinical trials are not a reliable guide to the safety of Essure. It is telling that Gebski was not asked by the defendants to give any opinion on the rigour or usefulness of either of these trials.[1389]

1278 The Phase II study was not a comparative study; had a very small sample size of 227; and was intended to measure the effectiveness of sterilisation at long-term follow up, not safety. This means that the drawing of any safety conclusions from it lacks rigour.[1390]

1279 There are four fundamental reasons why the Pivotal trial also cannot provide any reliable basis for drawing conclusions about the safety of Essure:

(a) Pivotal trials are typically at least comparative, if not also randomised. The lack of any comparator in the Pivotal trial meant that Conceptus disempowered itself from being able to make any reliable claim that adverse events were not caused by Essure.[1391]

(b) As Gebski explained, the Pivotal trial had poor generalisability as it 'sampled women in a way that [was] not representative of the general population of women who might use Essure'.[1392] Any attempt by Conceptus to adjust the demographic profile of the trial was done by reference to historical controls which is problematic.[1393]

(c) Judgments about causation were intrinsic to the conduct of the Pivotal trial, despite the unknowns about women's reproductive health and possible biases in the collection of data. This problem is exposed by the incongruity within the

1389 SBM.001.001.0004 at 177 [567].
1390 Ibid at 178-9 [568]-[573].
1391 Ibid at 179 [575], 181 [582].
1392 Ibid at 179 [576]; T3800 (TRA.500.037.0001_2 at 0117).
1393 SBM.001.001.0004 at 179 [577].

trial data, including participants who described their 'comfort' with Essure as 'good' despite also reporting moderate to severe pain. The only way to reconcile these reports is that these participants, or the investigator, failed to draw a causal connection (also meaning that investigators may have been incorrect when classifying adverse events as 'unrelated' to Essure).[1394]

(d) Like the Phase II study, the Pivotal trial was not designed to examine safety. Gebski accepted that the trial was 'not powered for safety outcomes' which 'has an implication for the robustness of any conclusion that could be drawn from [it] about safety'.[1395]

Gebski's pooled analysis and the Essure comparative studies

1280 Neither Gebski's pooled analysis nor the individual Essure comparative studies are sufficiently reliable to support a positive finding to make out the defence that laparoscopic sterilisation had 'equal or greater risk' than Essure.[1396]

1281 Gebski's opinion that 'there is little or no evidence of any additional harm' associated with Essure compared to laparoscopic sterilisation[1397] based on his pooled analysis should be rejected for the following reasons. First, it is based on a selective analysis of adverse events. Gebski analysed seven adverse events in accordance with an undisclosed list provided by the defendants' lawyers. The failure to disclose that list and other instructions should leave the Court with little confidence that there has been full disclosure of matters that contributed to the formation of Gebski's opinions, and the independence of his evidence.

1282 Gebski did not undertake an analysis of re-operation, which was among the adverse events discussed in the studies in the pooled analysis and which he conceded in cross-examination was a matter relevant to the risk-benefit profile of Essure. The best real world evidence comparing Essure with laparoscopic sterilisation reveals that about

1394 Ibid at 180 [578]-[581].
1395 Ibid at 181 [584]; T3832 (TRA.500.038.0001_2 at 0015).
1396 Ibid at 145 [451].
1397 Gebski at 36 (EXP.001.002.0003).

10% of women will need to undergo re-operation around two years after Essure insertion.[1398] Essure wearers in Australia were therefore exposed to the risks associated with general anaesthesia twice, when the device was inserted and again at the time of re-operation.

1283 Second, Gebski's pooled analysis and the defendants' submissions in relation to the individual comparative studies rely on the false premise that, in relation to sample size, 'bigger is better'. As Gordon explained, there is 'no coherent reason why increasing sample size might correct the potential biases, and in [his] opinion that is because there is no such reason. It is not consistent with basic statistical principles'.[1399]

1284 Third, Gebski had no regard for the limitations of the comparative studies. Gebski conceded that the studies were affected by deficiencies including:

(a) the limitations of reliance on insurance databases, such as:

(i) using data collected for the purpose of processing insurance claims as the basis for epidemiological research;

(ii) the different codes used in the insurance databases resulting in heterogeneity of measured outcomes across the different comparative studies, and the use of crude proxies because of the material difference between that insurance code data and a measured outcome of interest;

(iii) the probable underreporting in the databases of AUB and CPP;

(iv) the inability to distinguish between different severities of conditions; and

(v) that the databases are not representative of the general population.

1398 Gordon at 39 (EXP.001.001.0418).
1399 Gordon at 22 (EXP.001.002.0014).

(b) Gebski's failure to account for overlap in the pooled analysis resulting in double counting and overstatement of the total subjects covered;

(c) Gebski's failure to consider publication bias, conflicts of interest and the effect of the 'scientific marketing' program engaged in by the defendants. Gebski agreed that studies with statistically significant results were more likely to be published than those with non-significant results, but failed to take that matter into account in his pooled analysis. Gebski accepted that 'trials funded by a drug or device company were more likely to have positive conclusions and statistically significant results'.[1400] Eighteen of the 24 studies Gebski relied on in his pooled analysis had authors disclose some form of funding or employment link to Conceptus or Bayer. Despite this, he failed to address the issue of conflict. Gebski said that how conflict affects a study is not always obvious because the details may be opaque or not published at all.[1401] Five of the studies in Gebski's pooled analysis that were not connected to Conceptus or Bayer reported something adverse to Essure. What Gebski described as 'scientific marketing' was a conscientious, persistent and sophisticated strategy undertaken by Bayer from no later than mid-2014 to attempt to paint Essure in a positive light using apparently independent literature. Steward 2018 is an example. No Bayer witness gave evidence explaining this. These matters affect the reliability of the Essure comparative studies and Gebski's pooled analysis.

(d) Poor generalisability, which affects the weight to be given to the individual comparative studies and infects Gebski's pooled analysis.

(e) Failure of some of the comparative studies to adjust for known biases. Because the studies involved a retrospective non-randomised comparison, there could be no adjustment for unknown biases. This problem was compounded in Gebski's pooled analysis because he used the raw unadjusted figures.

1400 T3773 (TRA.500.037.0001_2 at 0090).
1401 T3775 (TRA.500.037.0001_2 at 0092).

1285 Gebski's failure to take into account problems that affect the quality of the Essure comparative studies fundamentally undermines the evidentiary value of his pooled analysis. The process of pooling becomes one of 'garbage in, garbage out'. Further, Gebski accepted that choices made in his pooling calculations, such as whether to use a fixed or random effects analysis, can impact whether there is a conclusion of statistical significance.[1402] A pooled analysis that is so sensitive to different choices is unstable to the point that the Court should give it little weight.

1286 Because of the problems with the individual comparative studies, an attempt to qualitatively glean something from collective consideration is not very useful.

1287 The net effect of the biostatistics evidence is that the defendants have failed to establish their defence that Essure had a risk-benefit profile that was better, or at least no worse, than laparoscopic sterilisation, or defeat the clear scientific evidence of the biological likelihood of causation.

Defendants

RCT

1288 The number of people screened for an RCT would need to be a multiple of the number of people who ultimately participate in the trial to its conclusion. While Brandwood was cross-examined on his theoretical calculations and conceded he could not be precise about the numbers, this does not detract from the proposition that a meaningful RCT would require the screening of a large number of people. As Gebski said, the recruitment difficulty would have been magnified after Essure became available on the market.

1289 The purpose of Turner's theorised RCT has never been made clear. An important but unexpressed premise of this part of Turner's case is that an RCT would have disclosed a safety issue with Essure compared to laparoscopic tubal ligation. The basis for this premise is not apparent, particularly in circumstances where the existing comparative

1402 T3754 (TRA.500.037.0001_2 at 0071–2).

studies that involved hundreds of thousands of women over extended periods in different jurisdictions, individually and collectively lead to the conclusion that Essure does not cause CPP or AUB.

522 study

1290 The 522 study is of minimal utility because the FDA has said that conclusions should not be made based on the published interim results. This is confirmed by the evidence of Carney and As-Sanie. Carney said that the interim results may provide misleading information because they were never designed to be relied upon.[1403] As-Sanie said that the interim study results are not published or peer-reviewed, do not contain an understanding of the clinical characteristics of participants and therefore do not control for confounders.[1404]

1291 The 522 study is descriptive and is not powered to detect statistical differences. This means that the study design and sample size are insufficient to detect statistically significant differences in outcomes between Essure and laparoscopic sterilisation.

1292 The study status is 'progress inadequate'. The 'progress of the study is not consistent with the study plan' because of the loss to follow-up rates in both the Essure and laparoscopic groups.[1405] This casts further doubt on the reliability of the interim results.

1293 The data of a significant proportion of participants in each group has not been included to allow for propensity score matching. That, logically, has a significant risk of skewing the data.

Gebski's pooled analysis and the Essure comparative studies

1294 The comparative studies show that there is no appreciable difference between the incidence of CPP or AUB associated with Essure and laparoscopic tubal ligation. That proposition is fortified by consideration of the totality of the comparative evidence,

1403 T2363 (TRA.500.024.0001_2 at 0042).
1404 T2606 (TRA.500.028.0001_2 at 0069).
1405 MSC.001.002.0001 at 2.

and is consistent with As-Sanie's extensive clinical experience.[1406] In light of the fact that laparoscopic tubal ligation does not cause CPP or AUB, the evidence shows that Essure also does not cause either of these conditions.[1407]

1295 The number of participants in the Essure comparative studies is a relevant consideration. In aggregate, the responses of over 200,000 women were analysed. Any limitations arising in respect of a particular study (for example, the use of opioids/analgesics as a CPP proxy in Conover 2015 and Bouillon 2018) are mitigated when another study reaches a similar conclusion.

1296 Turner's criticisms of the comparative studies should not lead to the conclusion that they do not have probative value. Studies that are retrospective and lower on the hierarchy than RCTs should not be discarded or ignored. As As-Sanie said, retrospective reviews that make inferences using diagnostic codes are widely used and supported in medical science, have the unique advantage of their large sample size, and have been found to be relatively accurate and reflective of what is found in clinical practice.[1408] As-Sanie noted that any limitation from the use of diagnostic codes for pain did not apply with the same force to the codes for AUB, which are more specific and provide a more definitive diagnosis.[1409]

1297 Turner sought to cast doubt on some of these studies because they analysed hysteroscopic devices in general, which meant that the Adiana device was included in those analyses. While the inclusion of the Adiana device is a limitation of those studies, the sample size of Adiana was so small that its inclusion could not have influenced the confidence intervals and is not likely to have changed interpretation of the data. It is not unreasonable to conclude that the hysteroscopic cohorts described in these studies would have been largely composed of Essure patients.[1410]

1406 Gynaecology JER at 13 [44] (EXP.500.001.0001); T2529 (TRA.500.027.0001_2 at 0087_18).
1407 SBM.500.001.0003_2 at 413 [3.8].
1408 T2574 (TRA.500.028.0001_2 at 0037).
1409 SBM.500.001.0003_2 at 440 [4.7].
1410 Carney 2017 at 10 (PUB.500.001.0020); BAY-ESSURE-0086934 at 26; BAY-ESSURE-0087834 at 51.

1298 Turner's allegations of publication bias and conflicts of interest go nowhere. Any affiliation with or funding contribution by Bayer was openly disclosed. There is no suggestion by Turner that the results of those studies were in some way biased or affected by the funding. The comparative studies where Bayer provided funding were peer-reviewed, used sound statistical analyses, and used publicly available databases. Strikingly, Gordon did not suggest that these studies should be discounted due to funding by Bayer or because they were authored by a person affiliated with Bayer.[1411]

1299 The best available data and the clinical experience of those familiar with the device and the conditions under consideration, demonstrate that there is no causal link between Essure and those conditions. Despite bearing the onus of proof, Turner has not adduced any competing epidemiological data suggesting to the contrary.

1300 Turner's attempt to make a case involving an increased risk of 're-operation' resulting from Essure should be rejected. That case is not pleaded, and there is nothing in the evidence of Gordon or other relevant experts to suggest that 're-operation' is an outcome of interest. Further, the Court should have no regard to the attempted pooled analysis in Turner's aide memoire (reproduced in Schedule 2) of studies in relation to the 're-operation' outcome. The aide memoire involves inappropriate comparisons between datasets and outcomes, and omits other relevant data sets without explanation.

1301 Gordon did not say that the Essure comparative studies were inherently unreliable or that they should be entirely disregarded.

1302 There is significant quality in the Essure comparative studies. Analysed individually or collectively, they lead to the conclusion that Essure does not cause CPP or AUB.

1303 The combined effect of the extensive testing conducted before and after Essure was placed on the market and the epidemiological evidence supports the following

1411 SBM.500.001.0003_2 at 416 [3.15].

propositions:

(a) There was no test or study that demonstrated an association, let alone a causal link, between Essure and CPP or AUB.

(b) No clinician gave evidence that they saw or treated patients who suffered from CPP or AUB which they positively determined to be caused by Essure. In particular, As-Sanie, who has extensive experience treating patients with CPP and saw Essure patients with CPP, had not seen any individual whose pain could not be explained by another cause.[1412]

(c) Viewed individually and collectively, the studies demonstrate that there was a similar, if not lower, rate of CPP reported by persons who underwent hysteroscopic sterilisation (principally by use of Essure) compared to persons who underwent laparoscopic tubal ligation.

(d) Similarly, viewed individually and collectively, the studies demonstrate that there was a similar, if not lower, rate of AUB reported by persons who underwent hysteroscopic sterilisation (principally by use of Essure) compared to persons who underwent laparoscopic tubal ligation.

(e) The expert clinicians agree that laparoscopic tubal ligation is not associated with CPP or AUB.

(f) It follows that Essure does not cause CPP or AUB.[1413]

1304 As-Sanie summarised her view of the acceptable risk-benefit profile of Essure as follows:

> … the use of the Essure device presents an acceptable risk to women who desire permanent sterilization. In her review of the studies that have been performed there is no significant difference in any long-term outcome, including pain and abnormal uterine bleeding, between the use of the Essure device and laparoscopic sterilization. As both methods have similar long-term

1412 T2529-30 (TRA.500.027.0001_2 at 0087_29-0088_5).
1413 SBM.500.001.0003_2 at 472 [11.1].

> outcomes and are highly effective methods of permanent contraception, both are acceptable options in her opinion. The Essure device, when it was available, provided a choice to clients and some preferred it because it did not require abdominal incisions and therefore there were fewer surgical risks and faster [recovery]. She says some patients are at higher risk for laparoscopic surgery than others, and the Essure device offered a safer alternative for permanent contraception for these patients (e.g. women who have extensive pelvic adhesions, who are morbidly obese, and for whom general anaesthesia is not safe due to medical comorbidities.)[1414]

Analysis

RCT

1305 Gordon and Gebski agreed that an Essure RCT examining adverse events as the primary outcome would need to have a non-inferiority design. Gebski explained that '[i]n line with clinical practice of "first do no harm", a non-inferiority design would seek to establish that even if the Essure device has a "slightly" higher rate than laparoscopic tubal ligation for a particular [adverse event], this rate is considered an acceptable rate by clinicians and patients alike'.[1415]

1306 The experts agreed that the sample size was dependent on the parameters set for the study. The relevant parameters are power, significance level and non-inferiority margin. The experts agreed that the higher the power, the lower the significance level and/or the smaller the non-inferiority margin, the larger the corresponding sample size.[1416]

1307 Gebski said that a study design aimed at ensuring patient safety would require a sufficiently large sample size to ensure the probability of making an incorrect decision was low. He said that an appropriate study design would adopt a power of at least 90%, a significance level of at most 2.5%, and a small non-inferiority margin.[1417] He said that adopting those parameters and a 1% non-inferiority margin, RCT testing for AUB as an adverse outcome would require a minimum of 14,200 patients. He said that the effect of also testing for other adverse outcomes, such as CPP and perforation,

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1414 Ibid at 473 [11.2]; Gynaecology JER at 21 [78] (EXP.500.001.0001).
1415 Regulatory JER at 9 [38](b) (EXP.500.001.0003_2).
1416 Ibid at 10.
1417 Ibid.

would lead to an adjustment of the significance level and a corresponding increase in the total sample size to 18,266 patients. Gebski said that it would be problematic to consent patients to evaluate non-inferiority for adverse events between Essure and laparoscopic tubal ligation without first reassuring the patients that there was no increase in pregnancies for the Essure device. He estimated that the sample size required for such a study would be in the order of 80,000 patients.

1308 Gordon adjusted the parameters of a hypothetical Essure RCT by decreasing the power to 80%, increasing the significance margin to 5%, and considering a non-inferiority margin up to 1.5%. These adjustments decreased the required patient numbers to a minimum of 2,156 when measuring a single outcome.

1309 I accept Gebski's evidence on the following points. First, an RCT designed with a higher power, lower significance level and smaller non-inferiority margin will have greater efficacy in determining the comparative risk profile associated with Essure. Second, the effect of adding further outcomes of interest will be to increase the required sample size of the RCT. Third, further complexities may need to be addressed before commencing an RCT, such as providing evidence to reassure patients that there was no increase in pregnancy rates associated with Essure.

1310 Gordon suggested that the long-term follow-up for an RCT should be in the range of five to 10 years. Gebski described some of the practical difficulties of conducting such a trial as follows:

> While the accrual rate for a hypothetical trial is unknown, if the rate of accrual was 2000 patients per year (approximately 5 per day) it would take at least 9–12 years to complete accrual. With a further 3-5 years of follow-up, a total study duration of at least 12 years would be required to provide unbiased estimates of safety, assuming no patient withdrawal or discontinuation.[1418]

I accept Gebski's evidence about the difficulties that may be experienced with enrolling sufficient patients to satisfy the RCT study design.

[1418] Ibid at 12 [55].

1311 I accept Brandwood's evidence that a substantial increase in the number of enrolled patients would be required in order to address relevant exclusion criteria, the lack of willingness to be randomised, and the loss to follow-up during a lengthy study period. While Turner challenged the degree of increase for these factors proposed by Brandwood, she did not suggest that the necessary increase was insignificant.

1312 Gordon's evidence 'that a total sample size of the order of several thousand would be appropriate for a non-inferiority study of long-term safety' of Essure understates the number of patients that would need to be enrolled in the study and does not grapple with the practical difficulties.[1419]

1313 Gordon said that it was appropriate to conduct one or more RCTs on Essure, and that sample size was a secondary matter. I accept Gebski's evidence that a more limited RCT conducted on a narrow patient cohort will have reduced generalisability to the broader patient population.

1314 Gordon said that a long-term RCT should have been done early in the period after Essure came on the market. I accept Gebski's evidence that the task of enrolling patients into an RCT would have been more difficult at that time.

1315 An Essure RCT was not required by the FDA as part of the PMA process or subsequently. No other regulator that approved Essure for commercial supply required that an RCT be conducted. While Gordon clearly did not agree with that approach, he did not say it was scientifically untenable. The evidence of Brandwood and Gebski was to the effect that an RCT of Essure was unlikely to have added significantly to safety information about the device, and was unnecessary.

1316 Turner spent considerable time and resources on the RCT issue. I accept the defendants' criticism that the relevance of the theorised RCT was never made entirely clear. Turner criticised the defendants for not conducting an RCT, and submitted that the testing and studies that were undertaken were deficient. Turner submitted the

[1419] Ibid at 8 [28].

defendants ought to have informed themselves about the pleaded defects and adverse events by conducting an RCT, and that their failure to do so was therefore relevant to their constructed knowledge of those matters.[1420]

1317 I conclude that there were real impediments to the feasibility of conducting Essure RCTs. Further, there were real issues about the efficacy of any RCT that was attempted. I am not satisfied that it was feasible to conduct an Essure RCT, or that the outcomes of a trial that was attempted would have added significantly to the available safety information about the device.

1318 There is no evidence that would allow me to conclude that had the theorised Essure RCTs been conducted, they would have disclosed a relevant safety issue with Essure compared to laparoscopic tubal ligation. Even on Turner's case, the margin of any increase in adverse outcomes such as CPP or AUB associated with Essure by comparison laparoscopic sterilisation was completely uncertain. It is speculative to suggest that an Essure RCT would have shown an increase in relevant adverse outcomes that was statistically significant.

Gebski's pooled analysis

1319 Gebski's pooled CPP analysis was fundamentally flawed because of his failure to account for the overlap in data between Conover 2015, Perkins 2016 and Carney 2017. The admittedly rudimentary calculation at [1246] above demonstrates that the double counting may have materially impacted the outcome of Gebski's CPP rate analysis. The failure to account for the overlap is a sufficient reason to place no weight on that aspect of Gebski's analysis.

1320 I accept Gordon's criticism that Gebski's CPP analysis is further undermined because he has attempted to pool heterogeneous outcomes. The very substantial variation in outcomes between studies reflects, at least in part, two differences in approach. First, there are significant differences in what is measured as a surrogate for CPP. Second,

1420 SBM.001.001.0004 at 193 [64]-[65].

the outcomes are counted in different units. I accept Gordon's criticism that the variation in the rates of CPP between the comparative studies indicates that different things are being measured, such that the outcomes cannot be readily pooled.

1321 I accept that by using a fixed effect analysis, Gebski has made no attempt to account for the heterogeneity between studies. I accept Gordon's criticism that a random effects analysis should have been used.

1322 Gebski used the raw data from each comparative study, rather than the data that was adjusted for known variables. As a result, Gebski's pooled analysis may be affected by bias resulting from the failure to take account of known variables that may have a different impact on the outcomes of interest between the hysteroscopic and laparoscopic groups. I accept Gordon's criticism that Gebski's pooled analysis should have taken into account the known variables and the adjusted data.

1323 The pooling exercise conducted by Gebski is not a comprehensive meta-analysis. I accept Gordon's criticism that there can be no half measures when conducting a meta-analysis, because data that is excluded may have a significant impact on the outcome.

1324 I reject Gordon's criticism of Gebski's decision not to include data of adverse events in the first three months following the sterilisation procedure, and where there were pre-existing symptoms of CPP or AUB. I accept Gebski's explanation that excluding the first three months of data means the results will not be confounded by the acute impact of the hysteroscopic or laparoscopic procedure. Further, Turner's case is that CPP and AUB were caused by an ongoing chronic inflammatory response that extended beyond three months. The exclusion of early data better reflects that case.

1325 I accept Gebski's explanation that inclusion of data from patient groups with a pre-sterilisation history of CPP or AUB would create difficulties with attribution of any change in adverse events that occurred post-implantation.

1326 I reject Turner's criticism that Gebski's analysis of adverse events was somehow

improperly selective and inappropriately driven by the defendants' lawyers. Gebski analysed the adverse outcomes of greatest interest in the proceeding, including CPP and AUB. It was not inappropriate for Gebski to receive direction from the defendants' lawyers about adverse events that were relevant on the pleadings, and on that basis should be part of his analysis.

1327 The only further adverse event that Turner said should have been included by Gebski in his pooled analysis was re-operation. The comparative incidence of re-operation between laparoscopic sterilisation and Essure may well be relevant to the risk-benefit profile of the device. However, re-operation is not part of Turner's pleaded case. It was only in some brief cross-examination of Gebski and in final submissions that Turner attempted to introduce re-operation as a relevant issue, in part on the basis of her argument that it was an inexact proxy for the pleaded removal limitation, or that it may be somehow relevant to the observed rates of pleaded adverse events. The experts were not asked to consider in their evidence in chief the biostatistical evidence as to re-operation, or whether re-operation was relevant to any fact in issue in the proceeding and, if so, how. I place no weight on Turner's attempted biostatistical analysis and I reject her last-minute attempt to introduce re-operation as an outcome of interest.

1328 The criticisms of Gebski's pooled analysis are more relevant to CPP than AUB. While I would not entirely dismiss Gebski's pooled comparative AUB analysis, I would accord it less weight than As-Sanie's evidence based on her review of relevant studies.

522 study

1329 For the following reasons, the interim results of the 522 study do not assist Turner in relation to the issue of general causation.

1330 First, Gordon and Gebski agreed that the 2023 interim results did not show any statistically significant difference between Essure and laparoscopic sterilisation for the outcomes of CPP and AUB. I reject Turner's attempts in final submissions to attribute meaning to the 522 study data that her own expert said was not statistically significant.

1331 Second, I accept Gebski's evidence about the limitations that should apply to consideration of the 2023 interim results set out at [1166] above. Further, I accept the evidence of Carney and As-Sanie warning about the risks of relying on interim results that have not been published, peer-reviewed or designed to be relied upon. The most recent clinical investigation report includes the following commentary:

> A Data Monitoring Committee (DMC) data review was conducted on 27 MAR 2020. The Committee recommended that the study continue according to the current integrated protocol. On 5 MAY 2021, the DMC recommended termination of the study due to futility, noting that "through no fault of Bayer, the actual numbers of enrolled study subjects (285 and 705 for Essure and control, respectively) are far below the originally planned sample sizes. Therefore, the study results will not provide any meaningful interpretation, statistically or clinically, regarding the Essure device or procedure's safety." The FDA has asked Bayer to continue the study, and Bayer has agreed to do so.
>
> This report presents the study results of the third interim analysis, which was done after the closing of the 3-year follow-up visit window for all subjects, as of the release date of the clinical database (10 MAR 2023). ...
>
> As recognized by the FDA, this study is descriptive; therefore, it is not designed or powered to detect statistical differences between the Essure and LTS groups. This study is ongoing, and results reported here arc interim and subject to change. Final conclusions should not be made until the study is completed and final adjudication of the data is performed. Accordingly, physicians and study subjects should base clinical decisions regarding patient care on the totality of scientific evidence regarding Essure's safety and effectiveness, not on these interim results.[1421]

1332 The 522 study was originally planned to have 1,400 women per arm. That enrolment was not achieved, with only 340 patients in the Essure group and 790 patients in the laparoscopic tubal sterilisation group. At the time of the most recent report, 175 patients from the Essure group and 380 patients from the laparoscopic group had discontinued from the study. As a consequence, the FDA changed the study status to 'progress inadequate' in 2022. I accept the defendants' submission that this casts further doubt on the reliability of the 2023 interim results.

Essure comparative studies

1333 The parties agreed that laparoscopic tubal ligation does not cause CPP or AUB, and

[1421] BAG.001.003.9013 at 9.

that it is the appropriate comparator against which to test the risk-benefit profile of Essure.

1334 I reject Turner's submissions which attempted to place the onus on the defendants to establish that the biostatistical evidence shows Essure has a risk-benefit profile that is no worse than laparoscopic tubal ligation. The onus of proving general causation rested with Turner.

1335 The outcomes of the comparative studies indicate that there is no statistically significant difference in the incidence of CPP or AUB associated with Essure and laparoscopic tubal ligation. Therefore, the comparative studies weigh against Turner's case that Essure can cause CPP and AUB. For the following reasons, I conclude that significant weight should be attached to the comparative studies.

1336 First, each of the studies appears to have adopted rigorous and appropriate statistical methods. This includes attempting to identify, measure and account for potentially confounding variables, including by use of propensity score matching, and checking outcomes by conducting sensitivity analyses. Gordon criticised the studies because they are lower on the hierarchy of biostatistical evidence and therefore did not control for unknown variables, in some cases included in the hysteroscopic group, that issues might arise as a result of reliance on registry data, and that some outcomes measured were not of assistance. However, Gordon did not criticise the statistical methods used in the studies. He accepted that serious attempts had been made to identify and control for potentially confounding variables. I accept the defendants' submissions that there is significant quality in the Essure comparative studies.

1337 Second, study size is a relevant consideration. Each of the comparative studies considered tens of thousands of women. I accept the evidence of As-Sanie and Gebski that the size of the populations in the comparative studies was a considerable strength. That proposition was accepted by Gordon, subject to a caveat about study quality.

1338 Third, relatedly, the comparative studies were based on data from different broad

population groups. Conover 2015, Perkins 2016 and Carney 2017 each analysed the Truven database which includes a large proportion of women across the US who are covered by industry medical insurance. Bouillon 2018 captured most of the French female population. Steward 2018 and Gariepy 2022 relied on data from the Medicaid database of public health insurance for American women. The consistency in outcomes across these broad populations adds to the strength and generalisability of the study outcomes. It is unlikely that large well-conducted retrospective comparative studies of differing populations would consistently fail to identify an increased association between Essure and the adverse outcomes of interest by comparison to laparoscopic tubal ligation.

1339 Fourth, I accept Gebski's evidence, supported by the studies he referenced, about the relative strengths of well-conducted large retrospective comparative studies.

1340 Fifth, As-Sanie conducted what was in effect a systematic review of the available studies. She considered relevant criteria including study quality and sample size. As-Sanie's analysis was consistent with the approach suggested by Gordon, and was of value.

1341 Sixth, Gordon focused in his evidence on the hierarchy of epidemiological evidence, the lack of highest quality evidence in the form of RCTs, and on some reasons why the comparative studies should be dismissed. Gordon concentrated on the negative, and did not positively consider what weight could be attached to the comparative studies and what conclusions they supported. This became apparent in cross-examination when Gordon accepted propositions about study quality, and that the outcomes of some studies were in favour of there being no difference between Essure and laparoscopic tubal ligation in terms of pelvic pain or AUB. In cross-examination Gordon gave evidence to the following effect:

(a) Decision-making about efficacy and safety has been made for decades on the basis of studies that were not RCTs.[1422]

(b) Such decisions are still being made today on the same basis.[1423]

(c) Such decision making is not irresponsible.[1424]

(d) Conover 2015 indicates the possibility that there is no difference between the rates of CPP associated with Essure and laparoscopic tubal ligation.[1425]

(e) Perkins 2016 does not indicate a difference in the rates of pelvic pain experienced by those with Essure implanted and those who underwent laparoscopic tubal ligation.[1426]

(f) Steward 2018 indicates there is no adverse difference in relation to CPP and AUB (for a 24-month period after the procedure) between Essure and laparoscopic tubal ligation.[1427]

(g) Bouillon 2018, in relation to AUB, is in favour of hysteroscopic sterilisation (including Essure) over laparoscopic tubal ligation.[1428]

1342 Seventh, I accept the evidence of As-Sanie and Gebski that the studies which did not differentiate the hysteroscopic sterilisation group to specifically identify Essure patients should not be disregarded. I accept that Adiana patients were a very small proportion of the hysteroscopic sterilisation groups in those studies. Gordon accepted, at least in respect of the outcomes of Gariepy 2022 and somewhat reluctantly, that the outcome of a study group that included Adiana was relevant to a consideration of the safety of Essure.

1422 T3713 (TRA.500.037.0001_2 at 0030_27–30).
1423 T3713-4 (TRA.500.037.0001_2 at 0030_30–0031_1).
1424 T3714 (TRA.500.037.0001_2 at 0031_2–3).
1425 T3726 (TRA.500.037.0001_2 at 0043_1–2).
1426 T3730 (TRA.500.037.0001_2 at 0047_3–25).
1427 T3737 (TRA.500.037.0001_2 at 0054_8–20).
1428 T3739-40 (TRA.500.037.0001_2 at 0056_24-0057_6).

1343 Eighth, I accept As-Sanie's evidence that data from insurance registries can properly be used for biostatistical measurement of intervention outcomes. As-Sanie agreed that some limitations were imposed by the use of registry data. However, I accept her evidence that registry databases are widely used in medical science to assess the health outcomes of interventions, and that studies supported the accuracy of the data. I accept that subject to consideration of study quality, the large sample sizes available by use of registry data was a substantial strength of the comparative studies. I accept the statement in Perkins 2016 that problems of misclassification in registry data are likely to be non-differential between the two study groups.

1344 Ninth, I accept the evidence of As-Sanie and Gebski that the outcome of Bouillon 2018 in relation to CPP should not be dismissed entirely because of the imprecise measurement proxy that was used.

1345 Tenth, I largely reject Turner's complaints about conflict of interest and bias. The two comparative studies that Turner said were impacted by this issue are Carney 2017 and Steward 2018. Carney 2017 considered the relevance of a pre-implantation history of CPP and AUB to the reporting of those adverse events after implantation. The study did not directly consider comparative outcomes between the hysteroscopic and laparoscopic sterilisation groups. Accordingly, it is less relevant to the outcomes of interest in this case. The interaction between Steward and Bayer does suggest a potential conflict of interest. However, Turner did not identify how that conflict of interest played out and impacted the study results.

XVI. CAUSATION STUDIES

1346 Robertson principally based her conclusion that Essure causes CPP and AUB in some women on the Essure histological studies, and her own evidence as to the biological plausibility of certain mechanisms that she said explained the development of persistent chronic inflammation and resulted in those adverse outcomes. However, Robertson also referred to the findings from clinical studies that she said were

consistent with symptoms of CPP and AUB occurring more commonly in women with Essure devices. She argued that the clinical findings from those studies aligned with and corroborated her opinions as to causation.

1347 Robertson identified a number of clinical studies that she said investigated 'the co-occurrence of chronic inflammation and chronic pain in women with Essure devices'. She said that:

> These studies do not demonstrate causality, but by showing that the two symptoms, pain and chronic inflammation, can and do coexist in some women, the data support the interpretation of a causal relationship.[1429]

In the immunology JER, Robertson added that '[this] clinical evidence includes several studies where pain is resolved after removal of devices by salpingectomy or hysterectomy'.[1430]

1348 The further studies identified by Robertson are 'case series'. They represent the lowest level of evidence on the NHMRC hierarchy of evidence agreed by Gordon and Gebski. Gordon, As-Sanie and Gebski were not asked to consider the strengths or weaknesses of these studies. Turner placed little reliance on the causation studies in her final submissions. For completeness, I address these further causation studies below.

Pelvic pain

Chene 2019

1349 The purpose of the 2019 study by Chene et al ('Chene 2019') was to assess changes in quality of life after laparoscopic removal of Essure.[1431]

1350 Of the 80 women involved in the study, 13 had a history of pain syndromes. Pre-operative ultrasonic findings included adenomyosis with heavy bleeding and/or cyclic pain in 28 women, non-symptomatic adenomyosis in five women, fibroids with

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1429 Robertson at 175 [727] (EXP.001.001.0127_2).

1430 Immunology JER at 18 (EXP.500.001.0004).

1431 Gautier Chene et al, 'Quality of life after laparoscopic removal of Essure® sterilisation devices' (2019) 3 (July) *European Journal of Obstetrics and Gynecology and Reproductive Biology: X* (PUB.001.001.3703) ('Chene 2019').

heavy bleeding and/or cyclic pain in five women, and non-symptomatic fibroids in five women. Further, 33 of the women underwent other uterine procedures in addition to Essure removal: 23 had endometrial ablations, five had laparoscopic myomectomies, and five had laparoscopic hysterectomies. Pain levels were measured prior to surgical removal and at the one-month, three-month and six-month points post-surgery. The baseline mean pain score of '3.6' before surgery reduced to '1.5' at one month, '0.8' at three months, and '1.5' at six months post-surgery. There was greater variation in responses at the six-month mark than at either earlier stage.

1351 I make the following observations about this study. First, there appears to have been a relatively limited consideration of participants' history of other gynaecological causes of pain, or the history of how that pain developed. The extent to which other possible causes of pain were identified and treated was not fully examined. Second, post-surgery follow-up was limited to six months. In that period, the mean pain score increased from the three-month low and showed greater variability between participants. Possible reasons for this increase and variability were not examined. Third, there was no control group examining the pain response of women without Essure devices following salpingectomy or hysterectomy.

1352 Six devices fractured in the process of surgical explantation by a tubal incision and traction approach.

1353 I conclude that Chene 2019 is of little utility to the consideration of causation.

Francini 2021

1354 A study by Francini et al ('Francini 2021') is a retrospective observational case series conducted at two academic tertiary care centres in France between February 2017 and March 2018. [1432] During the study period, 97 patients underwent surgical removal of Essure by salpingectomy, salpingectomy with cornuectomy, or hysterectomy.

[1432] Sarah Francini et al, 'Essure removal for device-attributed symptoms: Quality of life evaluation before and after surgical removal' (2021) 50(2) *Journal of Gynecology, Obstetrics and Human Reproduction* (PUB.001.001.3811) ('Francini 2021').

1355 The stated purpose of the study was to assess the quality of life of patients who were requesting surgical removal of Essure due to adverse effects attributed to the device.[1433] Health-related quality of life was measured before surgery and again at three months post-operatively using self-scored patient questionnaires. The study concluded that prior to surgical removal, the participating patients had a lower quality of life compared to the general population of women in the same age group; and that at three months post-surgery, the quality of life score had improved to a level similar to the general population.

1356 Francini 2021 noted that while there had been increased complaints about alleged adverse effects due to Essure in recent years, no causal association between the device and reported symptoms had been established. The study said:

> The women who believe their quality of life (QoL) has been negatively impacted by their Essure inserts often request surgical removal. Even if it appears that the withdrawal of the devices resolves symptoms for many patients, there is a lack of data regarding postoperative outcomes and accurate QoL measurement.[1434]

1357 The study recorded that 56 patients complained of pelvic pain pre-operatively and seven complained post-operatively. I note that there was a similar magnitude of reduction for a range of systemic complaints, including asthenia which reduced from 77 pre-operative complaints to eight post-operative; ENT disorders reduced from 35 to five; memory disorders from 33 to five; visual impairment from 33 to seven, cardiologic disorders from 18 to one; and weight increase from 18 to three.

1358 The study did not examine associations between pre-operative and post-operative scores for physical and mental health, age, type of symptoms, type of procedure or length of Essure placement.

1359 The study did not include a control group. The authors said:

> It is reasonable to assume that surgical Essure removal effects were associated with a placebo effect. However, this placebo effect is difficult to estimate given

1433 Ibid at 2.
1434 Ibid.

the lack of data in a similar context.[1435]

1360 There appears to have been no consideration in the study of the history of other diagnosed gynaecological conditions that were possible alternate causes of participants' pelvic pain. Further, the three-month follow-up of patients was even shorter than in Chene 2019.

1361 I conclude that Francini is also of little utility to the consideration of causation.

Eychenne 2021

1362 A study by Eychenne et al ('Eychenne 2021') involved patients seeking removal of Essure who had suffered persistent and treatment-resistant gynaecologic and non-gynaecologic complaints since implantation.[1436] The study focused on the assessment of reported symptoms, symptom evolution, and patients' satisfaction at six months following laparoscopic cornuectomy for Essure removal.

1363 Of the 130 patients identified in the study cohort, 20 were excluded because removal was performed by hysterectomy or salpingectomy alone, and a further six because Essure removal was not related to any adverse effects.

1364 The study said:

> Our findings, in line with other studies, support device removal in patients with complications attributed to the implants. The very low rate of concomitant pathology that could explain the symptoms supports this recommendation further. Regarding chronic pelvic pain for instance, only 3 patients underwent concomitant excision of endometriotic lesions. In contrast, the 76.9 % baseline rate dropped to 15.4 % at the time of postoperative visit.[1437]

The reference to concomitant pathology is to pathology that was identified on cornuectomy surgery.

1365 Of the 104 women included in the study, 80 had a history of CPP and 39 had a history

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1435 Ibid at 4.

1436 Camille Eychenne et al, 'Patients' satisfaction following laparoscopic cornuectomy for removal of hysteroscopic sterilization devices' (2021) 50(3) *Journal of Gynecology, Obstetrics and Human Reproduction* (PUB.001.001.3800) ('Eychenne 2021').

1437 Ibid at 3.

of prior abdominal surgery. No further detail of the prior surgery or outcomes was provided.

1366 The authors noted some limitations of the study:

> Firstly, its retrospective design carries the risk of missing data. Then, the measurement of several endpoints might be questionable. Indeed, symptom resolution was evaluated in a binary way (Yes/No), while a more precise evaluation, based on validated scoring systems, would have provided more reliable data. Nevertheless, our results originated from on a relatively large sample-sized and homogeneous population since all patients underwent the same surgical procedure. We have thus provided additional data on the feasibility and efficacy of laparoscopic cornuectomy for [Essure] removal in patients with complaints related to the devices. Beyond these findings, our study supports the causality between symptoms and the devices. However, more studies are required to clearly identify the underlying mechanisms involved in symptoms pathogenesis.[1438]

1367 Eychenne 2021 had further limitations in common with previous studies. No attention was paid to the history of CPP, prior abdominal surgery or other relevant gynaecological conditions. The study did not include a control group. There was no consideration of the possibility of a placebo effect. The period of follow-up was only six months.

1368 For the above reasons, I conclude that no significant weight should be attributed to Eychenne 2021.

Chauhan 2021

1369 In her primary report, Robertson relied on studies including one by Chauhan et al ('Chauhan 2021')[1439] to say that she expected women who had a persistent chronic inflammatory response to Essure to have symptoms including pain and AUB.[1440] She said that she would also expect symptoms as part of a 'maladaptive' immune response, especially an autoimmune or auto-inflammatory response. She said:

> While the science is still evolving, there is a biological rationale to support the

1438 Ibid at 4.

1439 Utkarsh Chauhan, Brett Cassidy and Jan Willem Cohen Tervaert, 'ASIA (Shoenfeld's syndrome) due to hysteroscopic Essure sterilization' (2021) 20(12) *Autoimmunity Reviews* (PUB.001.001.3761) ('Chauhan 2021').

1440 Robertson at 37 [119] (EXP.001.001.0127_2).

> view that disseminated inflammation and aberrant innate immune memory can cause increased allergic responses to food or environmental triggers, disposition to autoimmune diseases, and/or impaired capacity to detect and kill cancer cells.[1441]

1370 Robertson said:

> There are findings from clinical studies that are consistent with these symptoms occurring more commonly in women with Essure Devices, and being in part caused by their Essure Device. I am referring to studies that link removal of Essure Devices by salpingectomy surgery can cause symptoms of chronic pain and quality of life to improve. These clinical findings align with and corroborate the scientific opinions I have formed on the basis of my experience and knowledge of the cellular and physiological mechanisms.[1442]

1371 Chauhan 2021 was a retrospective study of 33 patients who elected to undergo Essure removal. The study described systemic manifestations in these patients and hypothesised that they were a consequence of an adjuvant effect of the device, which in turn suggested that the patients suffered from Autoimmune/autoinflammatory Syndrome Induced by Adjuvants ('ASIA') due to the implantation of a foreign body.[1443] Robertson gave further detail of her reliance on Chauhan 2021 later in her report:

> There is likely to be disposition to inflammatory and immune disorders in a subset of women. In this subgroup, contact with noxious agents such as a metal implant acts as an 'adjuvant' that stimulates an abnormal immune response. This condition has been termed "autoimmune/inflammatory syndrome caused by adjuvants (ASIA)". ASIA patients exhibit a constellation of symptoms that can include fatigue, cognitive impairment, and arthralgias. There is growing evidence that ASIA is triggered in women by implantation of foreign material such as breast implants and mesh for hernia repair.
>
> The Essure intervention has been evaluated as an intervention that has potential to provoke ASIA in some women. A retrospective cohort of 33 patients undergoing elective surgical removal of an Essure Device were examined. Their symptoms of pelvic pain and systemic symptoms were considered consistent with an ASIA diagnosis. These clinical findings align with and corroborate the scientific opinions I have formed on the basis of my experience and knowledge of the cellular and physiological mechanisms.[1444]

1372 Sokol challenged Robertson about her reliance on Chauhan 2021 in the immunology

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1441 Ibid at 40 [138].
1442 Ibid at 41 [144].
1443 Chauhan 2021 at 1 (PUB.001.001.3761).
1444 Robertson at 150 [620]-[621] (EXP.001.001.0127_2).

concurrent evidence. The following exchange occurred:

> SOKOL: One of those papers was a paper about ASIA, right?
>
> ROBERTSON: I think ASIA may be mentioned in one of those papers, I can't recall exactly.
>
> SOKOL: I think it was in the title. Are you aware that ASIA is completely not recognised by biologic societies and it's not a recognised or accepted diagnosis?
>
> ROBERTSON: I don't think I've referred to ASIA and if I have done it's only in a very minor way. Really it's just a term that describes a collection of allergy symptoms and autoimmune actions and links it to a range of causes including medical devices as being one driver. But, you know, I accept - I know the origin of it and, you know, that it's a term that's, like often happens in biomedical science, you know, it's sort of used to guide or, you know, stimulate research and then, you know, the evidence builds or doesn't build.
>
> Right?---I'm not particularly engaged with that concept.
>
> SOKOL: No, it's not recognised at all in the medical field amongst any serious practitioners or any national societies, and it's because the criteria that were raised for it everyone can have that criteria, everyone can meet that criteria.
>
> ROBERTSON: But I don't think that negates the value of the paper in terms of – that's certainly not why I cited it. I cited because if it was the Chauhan papers it's evaluating pain before and after the presence of a device and then the removal of a device and that would have been why I cited it. I don't think it negates the interpretations of the data.[1445]

Robertson said that while the study may have invoked the ASIA concept, she did not think it was a significant part of the paper.[1446]

1373 Chauhan 2021 describes ASIA as follows:

> The condition called Autoimmune/autoinflammatory Syndrome Induced by Adjuvants (ASIA) was introduced in 2011 to describe a spectrum of immune-mediated conditions triggered by exposure to an adjuvant [9,10]. The diagnostic criteria are outlined in Table 1. A diagnosis of ASIA requires fulfilment of two major criteria or one major and two minor criteria. Typical symptoms include fatigue, arthralgia, myalgia, pyrexia, "fibrofog", and sicca. Adjuvants, widely used in vaccines, are compounds that enhance the immune response to antigens. Several studies provide compelling evidence that implanted foreign body materials may act as adjuvants as well [10]. Literature demonstrates post-operative systemic and autoimmune-like symptoms among patients receiving breast implants, implantation of polypropylene mesh for

1445 T4279 (TRA.500.042.0001_2 at 0057_25).
1446 T4281 (TRA.500.042.0001_2 at 0059_10).

hernia repair, and after arthroplasty.[1447]

1374 Thirty-two of the women in the study underwent microscopic hysterectomy with bilateral salpingectomy to remove the devices. Chronic pain was documented as the primary complaint leading to removal.

1375 The median time between surgery and post-operative evaluation was 13 days. Pre-operative complaints included CPP (in 31/33 patients), arthralgias (in 21/33), irritable bowel syndrome (in 17/33), chronic fatigue (in 13/33), cognitive impairment (in 14/33), hair loss (in 11/33) and migraines (in 8/33). The study does not contain any further detail of the pre-operative complaints or the history of any gynaecological or other health complaints that may be relevant to the patients' symptoms.

1376 Chauhan 2021 records the results of the study as follows:

> Following explantation, patients underwent a post-operative evaluation at two weeks repeated monthly as needed. Most symptoms resolved within six weeks of follow-up. 100% of patients experienced complete resolution of their severe fatigue, cognitive impairment, menorrhagia, hair loss, bloating, and migraines. Only 5 of 31 patients at follow-up (16%) reported residual pelvic pain, two patients reported residual joint pain (6%), and a single patient continued to experience IBS symptoms following the procedure.[1448]

The study does not contain details of any histological analysis undertaken following hysterectomy and salpingectomy. No consideration of other possible causes of patients' symptoms is recorded. No detail is provided of the length of follow-up. Most of the paper is taken up with setting out a rationale for why implantation of Essure may trigger ASIA.

1377 I accept Sokol's evidence that ASIA is not recognised by medical societies or clinically accepted in the medical field by serious practitioners. Robertson clearly adopted and relied on the Chauhan 2021 ASIA rationale in an uncritical way in her reports. She stepped back from that position when challenged by Sokol during the immunology concurrent evidence session.

1447 Chauhan 2021 at 1 (PUB.001.001.3761).
1448 Ibid at 3.

1378 I conclude that no weight should be placed on Chauhan 2021.

Beckwith 2008

1379 Beckwith 2008 is a case study of a woman with no significant history of CPP who underwent uncomplicated implantation of Essure.[1449] She reported right-sided cramping pain two days after the procedure, which developed into fairly constant bilateral pelvic pain after 20 days. Conservative treatment failed. Evaluation via laparoscopy at ten weeks revealed no pathology or abnormality, at which point the Essure devices were removed by salpingectomy. The study recorded that '[f]inal tissue pathology showed no diagnostic abnormality and grossly unremarkable microinsert devices'.[1450]

1380 Beckwith 2008 did note that the Essure device in the right fallopian tube had no visible trailing coils into the uterus after placement. The Essure PTM states that: '[i]deally, 3 to 8 expanded outer coils should be trailing into the uterus'.[1451] It is unclear whether there is any relationship between the placement of the right Essure device and the patient's first complaints of right-sided pain.

1381 Robertson cited Beckwith 2008 as a study relevant to the high incidence of chronic pain after Essure implantation, and as ultimately supporting the causal relationship between inflammation and CPP. Even assuming that the causal connection between implantation of Essure and the pain complained of by the patient in Beckwith 2008 is established, it is difficult to see how the study offers any real support for Robertson's contentions. The pain was reported two days after the implantation procedure. Salpingectomies to remove the devices were performed ten weeks later. In other words, all of this occurred within the timeframe for normal wound healing and resolution of a foreign body response, and before the timeframe for development of chronic pathological inflammation and CPP.

1449 Andrew W Beckwith, 'Persistent Pain After Hysteroscopic Sterilization with Microinserts' (2008) 111(2) *American College of Obstetricians and Gynecologists* 511 (PUB.001.001.3747) ('Beckwith 2008').

1450 Ibid at 1.

1451 AMS.001.001.0010 at 33.

1382 For these reasons, I conclude that no weight should be placed on Beckwith 2008.

Clark 2017

1383 Clark 2017 is a study of 52 women who underwent Essure removal between September 2012 and July 2016.[1452] The reasons for removal were adverse effects suspected to be caused by the device. The most common reason for Essure removal was pelvic pain (reported by 50 of the 52 women).

1384 Surgical or pathological findings relevant to pelvic pain included three women with evidence of salpingitis; one with an Essure coil perforating through the myometrium; nine with endometriosis; eight with adenomyosis; and eight with adhesions.

1385 Thirty-two of the women responded to an eight question survey regarding symptom resolution and quality of life which was distributed one month after surgical removal. Surgical removal involved hysterectomy for 23 of those respondents. Seventeen women who completed the survey reported total improvement or almost total improvement of their pelvic pain. Ten women reported ongoing or worse symptoms in general following removal.

1386 The study authors concluded:

> Essure removal may be an effective treatment for most women with symptoms attributed to the device. It is important to counsel women that some symptoms may persist or even worsen following Essure removal. Future studies are needed to further define the adverse effects of Essure and the benefit of Essure removal in treating these adverse effects.[1453]

1387 Robertson described Clark 2017 as showing 'improved pain outcomes after Essure removal'.[1454]

1388 Clark 2017 offers no real support of Robertson's contentions. The analysis of patient symptoms depended entirely on patient responses to a questionnaire provided shortly

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1452 Nisse V Clark et al, 'Essure Removal for the Treatment of Device-Attributed Symptoms: An Expanded Case Series and Follow-up Survey' (2017) 24(6) *Journal of Minimally Invasive Gynecology* 971. (PUB.001.001.3767) ('Clark 2017').

1453 Ibid at 5.

1454 Robertson at 175 [726] (EXP.001.001.0127_2).

after surgical removal; alternate causes for pelvic pain were identified but not eliminated; there was only limited history taken of conditions that may be relevant to the participants' experience of pain; and there was no control group.

Casey 2016

1389 Casey 2016 is a study of 29 patients who underwent laparoscopic removal of Essure after experiencing pelvic pain following implantation.[1455] The Essure devices were removed by bilateral salpingectomy. Intra-operative findings included additional or misplaced Essure devices in three patients, endometriosis requiring surgical treatment in five patients, and adhesions in three patients.

1390 There was a significant time range for the onset of pelvic pain following Essure placement, from zero to 85 months. Thirteen out of the 26 patients who completed follow-up reported pelvic pain within one month of Essure placement, five reported the onset between one and 12 months, and eight reported the onset after 12 months.

1391 Twenty-three patients reported significant relief of pelvic pain symptoms at their post-operative visit; three reported persistent pelvic pain; and three were lost to follow-up.

1392 For the following reasons, I conclude that no weight can be placed on Casey 2016. First, there is little detail in the study of patients' gynaecological history and the onset of symptoms. Second, no attempt was made to consider the relevance of potential alternate causes of pelvic pain to the reported resolution of symptoms. Third, there was no follow-up of patients beyond the post-operative visit, and no consideration of whether resolution of symptoms was maintained. Fourth, there is no indication in the study that there was a consideration of recorded clinical histories before and after surgical removal. There is no detail given of what was meant by 'reported significant relief of pelvic pain symptoms'. Fifth, there was no consideration of the relevance of the timing of onset of pain symptoms. For reasons stated above in relation to Beckwith 2008, it is unclear how resolution of symptoms that commenced within one month of

1455 James Casey, Francisco Aguirre and Amanda Yunker, 'Outcomes of laparoscopic removal of the Essure sterilization device for pelvic pain: a case series' (2016) 94(2) *Contraception* 190 (PUB.001.001.3756).

Essure implantation are relevant to Robertson's contentions and Turner's case in relation to chronic inflammation and CPP. Sixth, the study did not include a control group.

Van Limburg Stirum 2020

1393 Van Limburg Stirum 2020 is a retrospective cohort study 'to determine whether any subject or procedural characteristics are associated with negative patient experience after Essure sterilisation'.[1456] Two hundred and eighty-four patients who had Essure devices implanted between 2002 and 2017 at two related hospitals in the US were asked to participate in a survey regarding symptoms and satisfaction with Essure. One hundred and twenty women responded to the survey. Only seven of the survey respondents had actually undergone surgical removal of Essure at the time of the survey.

1394 Thirty-eight respondents attributed pelvic pain to Essure.[1457]

1395 Respondents were categorised into two groups, the first being patients who had a negative experience of Essure (57 patients), and the second being patients that had no negative experience (61 patients). Patient characteristics were then compared between the two groups. Those characteristics included a history of gynaecologic medical conditions (26 patients in both groups), pain syndromes (37 in the first group and 23 in the second), psychiatric disease (33 and 20), both Essure devices inserted according to manufacturer's instructions (27 and 34), and social media use (22 and 8).

1396 In their discussion, the authors said:

> We observed that symptom prevalence after Essure is common (40.7% of respondents reported current symptoms), although it is far from certain that all symptoms attributed to Essure have a direct causal relation with the device. Interestingly, 34 of these respondents (70.8%) used hormonal contraception prior to the Essure procedure, which may mask at least some preexisting symptoms. It has been reported that a pain-generating gynecologic condition

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1456 Emilie V J van Limburg Stirum et al, 'Factors Associated with Negative Patient Experiences with Essure Sterilization' (2020) 24(1) *Journal of the Society of Laparoscopic & Robotic Surgeons* (PUB.001.001.4055) ('Van Limburg Stirum 2020').

1457 Ibid at 4.

> is diagnosed in 44%–50% of women based on surgical findings and pathology after removal of the device. Although in our study no significant association was found between negative Essure experience and history of gynecologic conditions, a comparable percentage (41.7%) of our respondents with symptoms reported having endometriosis, adenomyosis, fibroids, uterine polyps, ovarian cysts, a sexually transmitted infection, or pelvic inflammatory disease.[1458]

1397 The authors commented as follows on the relevance of social media use:

> Our results show a significant difference in participation in social media groups reporting problems related to Essure between women who had a negative experience versus those who did not (P = .003). The role of social media in procedure satisfaction deserves further investigation, especially in women who are planning removal of the device to optimize expectations.[1459]

1398 The authors also reflected on the relevance of socioeconomic factors:

> In addition, the impact of socioeconomic factors on our patient satisfaction rate should be noted. Respondents with a negative experience were more likely to have a low education level or income. This is in line with previous literature describing the role of socioeconomic factors on health care in the United States.[1460]

1399 The authors observed that factors associated with negative patient experience of Essure may be relevant to counselling women who want to undergo device removal:

> It is conceivable that women with these risk factors are more satisfied after Essure removal because they had a higher risk of being dissatisfied with Essure a priori.[1461]

1400 The authors noted that limitation of the study population to one academic medical centre may impact generalisability. They further observed, in relation to potential limitations of the study:

> Because of the retrospective study design and the use of a questionnaire, the results are subject to potential recall and response bias. In addition, most of the data reflect subjective assessments. Self-selection bias could not have been excluded. Overestimation of negative experience with Essure is conceivable because dissatisfaction with Essure may stimulate participation; however, it is reassuring that the nonrespondents did not differ from respondents in terms of baseline characteristics. Additionally, because our questionnaire was not

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1458 Ibid at 7.
1459 Ibid.
1460 Ibid.
1461 Ibid.

formally validated, results must be interpreted with due caution.[1462]

1401 Van Limburg Stirum 2020 was not directed to examination of a correlation or causal connection between CPP or other symptoms and Essure placement. The objective of the study was to consider how patient or procedural characteristics might be relevant to patients' experience and desire for surgical removal. The identified medical conditions and the improper device placement identified in a significant proportion of cases are sufficient alone or in combination to make any finding of correlation or causation between CPP and the placement of Essure impossible.

1402 Issues discussed by the authors of van Limburg Stirum 2020 point to reasons why limited or no reliance should be placed on the other studies relied on by Robertson as supporting a causal connection between Essure and CPP. These include:

(a) prior use of hormonal contraception masking symptoms that pre-existed Essure device implantation;

(b) the relevance of unrelated pain-generating gynaecological conditions;

(c) the relevance of social media participation;

(d) socioeconomic factors;

(e) the use of questionnaires, subjective assessments of symptoms, and self-selection bias to participate in a review or to seek surgical removal of Essure devices.

1403 I conclude that the results of van Limburg Stirum 2020 do not provide any support for Robertson's contentions.

Maassen 2018

1404 Robertson cited Maassen 2018 as evidence consistent with CPP 'occurring more commonly in women with Essure devices, and being in part caused by their Essure

1462 Ibid.

device'.[1463]

1405 The reported symptoms by patients in Maassen 2018 included abdominal pain in 69.9% of cases, and back pain in 31.2% of cases. Following surgical Essure removal, persistent complaints of abdominal pain reduced to 11% and back pain to 5%.

1406 There is an obvious difficulty faced by Turner in seeking to establish a relationship between persistent chronic inflammation and CPP based on the Maassen 2018 results. In the study, chronic inflammatory infiltrate was only noted on pathological assessment in six cases (6.5%). In other words, in many cases where reduction or resolution of pain was reported, pathological assessment of tissue showed normal anatomy. Further, there was no correlation in the study between device wear time and cases where chronic inflammatory infiltrate was identified. It is possible that in those six cases the Essure wear time was less than three months.

1407 It was reported in 23.7% of patients that symptoms occurred immediately after Essure placement. For reasons stated above, it is not possible to understand how those complaints could be related to persistent pathological chronic inflammation that developed after the normal time for resolution of the foreign body response.

1408 For many of the patients in Maassen 2018, Essure device removal involved a hysterectomy. The study does not include a comprehensive assessment of other gynaecological conditions that may have caused or contributed to patients' complaints of pain. There was no comparison between symptoms complained of, or the resolution of symptoms, against the type of removal surgery. The possible contribution of unrelated gynaecological conditions to pain was therefore not addressed. Robertson said:

> So I guess we're left thinking about whether there's any likelihood that the different surgical approaches could have had a bearing on the residual symptoms.[1464]

1463 Maassen 2018 (PUB.001.001.3857); Robertson at 41 [144] (EXP.001.001.0127_2).
1464 T4252 (TRA.500.042.0001_2 at 0030_10-13).

1409 There was no attempt in Maassen 2018 to match patients' complaints of symptoms and reported resolution of symptoms with a history of unrelated pre-existing conditions or comorbidities. Potentially relevant histories and comorbidities of patients in the study include a history of prior abdominal surgery in 38 patients, findings of paratubal cysts in 19 patients, and of endometriosis in eight patients.

1410 Other limitations of the study include:

(a) the absence of a control group;

(b) a short follow-up period of three months;

(c) a possible placebo effect of the removal procedure;

(d) an assumption that the reported symptoms were not caused by incorrect positioning of the Essure devices;

(e) possible bias as a result of the manner in which information for description and categorisation of symptoms was obtained; and

(f) the possible effect of increased public attention on the reporting of symptoms.

1411 I conclude that no weight should be placed on Maassen 2018 in relation to the question of causation of CPP by Essure.

Banet 2020

1412 Robertson relied on Banet 2020 as evidence that pain and chronic inflammation caused by Essure do co-exist in some women, and that 'the data support[s] the interpretation of a causal relationship'.[1465]

1413 Banet 2020 considered a patient group who underwent Essure removal, regardless of the stated reason for surgery.

1414 Findings on pathological examination unrelated to Essure included six patients with

[1465] Banet 2020 (PUB.500.001.0264); Robertson at 175 [727]-[728] (EXP.001.001.0127_2).

paratubal adhesions and 41 with paratubal cysts; 18 findings of non-fallopian tube adhesions and in the hysterectomy group; 24 of uterine adenomyosis; 20 of uterine leiomyma; two of endosalpingiosis of the uterine serosa; four of endometrial polyp; and one myometrial andenomatoid tumour. The study did not investigate possibly relevant uterine pathology in those cases where hysterectomy was not performed.

1415 Banet 2020 did not consider the symptoms complained of or the degree of resolution post removal, by reference to the surgery type or gynaecological findings unrelated to Essure.

1416 The authors noted that the study cohort is not representative of the general population of those with Essure devices, and that there was no control population available for comparison, as a limitation of the study.[1466]

1417 I conclude that Banet 2020 does not support Robertson's contention that the Essure device is a cause of CPP.

Rubin 2020

1418 The purpose of Rubin 2020 was to examine the assumption that pain in long-term wearers of Essure is related to the device.[1467] The study said:

> We reasoned that if Essure caused pain via tissue injury, then characteristic acute or chronic inflammatory changes would be seen at the site of Essure implantation. To explore this hypothesis, we examined hysterectomy specimens from patients with pelvic pain after long-term Essure use, and compared these to control patients with pain but without history of Essure.[1468]

1419 The study authors said:

> All patients, including cases and controls, did have findings that have been described as causes of pain in the medical literature, including adenomyosis, leiomyomas (some very small), endometriosis, adhesions, and acute salpingitis (this patient was not an Essure user). It would appear arbitrary to ascribe the pain to Essure in cases, but to other causes in controls.[1469]

1466 Banet 2020 at 5 (PUB.500.001.0264).
1467 Rubin 2020 (PUB.500.001.0247).
1468 Ibid at 1.
1469 Ibid at 4.

1420 The study authors concluded:

> The findings of this report may not be generalizable. This is an initial report intended to communicate the generally bland nature of the findings in a small number of cases.[1470]

1421 Rubin 2020 is one of the clinical studies that Robertson cited as being 'consistent with the symptoms occurring more commonly in women with Essure devices, and being in part caused by their Essure device'.[1471] In fact, it is clear the conclusions in Rubin 2020 are directly inconsistent with both of Robertson's contentions.

Catinon 2022

1422 The stated purpose of Catinon 2022 was to examine associations between local and systemic symptoms, and corrosion of the solder joint of Essure implants.[1472]

1423 Pathological analysis of tissue post-surgical removal identified uterine adenomyosis in 14 patients, non-specific inflammatory signs in 10 patients, and foreign bodies in seven patients. The authors also observed other cysts and myomas that were not further specified. It is not clear what is meant in the study by 'non-specific inflammatory signs' or 'foreign bodies'. The extent to which uterine tissue was examined is also unclear, leaving the possibility that further comorbidities may have been found by a more comprehensive examination.

1424 The study said:

> Adenomyosis, observed in the myometrium, was an associated condition in 15/18 cases. This pathology, easily identified by Magnetic Resonance Imagery and linked to a uterine traumatism could have been induced by the Essure implants.[1473]

The finding of 15 cases of adenomyosis recorded in this paragraph appears inconsistent with the earlier report of 14 cases. There was no explanation for the hypothesised causal connection between Essure and adenomyosis.

1470 Ibid.
1471 Robertson at 41 [144] (EXP.001.001.0127_2).
1472 Catinon 2022 at 2 (PUB.500.001.0299).
1473 Ibid at 4.

1425 The study reported a reduction in pelvic pain following surgical removal of Essure, with the total pain intensity score for all participants reducing from '84' to '32'. However, there was no attempt to correlate this reduction with other possible gynaecological causes of pelvic pain. Further, no long-term history of pain or other conditions was recorded in this study.

1426 There was no control group in the study.

1427 I have previously commented on the question of reliability of the Catinon 2020 and Catinon 2022 studies, given the failure by the authors to report relevant conflict and funding issues.[1474]

1428 I conclude that no weight should be accorded to Catinon 2022 on the question of causation.

Abnormal uterine bleeding

1429 In her primary report, Robertson said that clinical studies had 'linked altered numbers and function of uterine immune cells with uterine bleeding disorders'.[1475] She said:

> Several clinical studies have investigated the incidence of abnormal uterine bleeding (or surrogate measures thereof) after Essure placement. The study outcomes are somewhat contradictory and there is no clear consensus conclusion.[1476]

Robertson said, discussing Eychenne 2021, Chene 2019 and Francini 2021:

> Despite the limited size and quality of these studies, the clinical findings do not disagree with the scientific opinions I have formed on the basis of my experience and knowledge of the cellular and physiological mechanisms.[1477]

1430 In Chene 2019, there were no significant changes in menstrual bleeding reported following Essure removal.[1478]

1431 Robertson said that in the 64 women in Francini 2021 who had uterus preserving

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1474 See Chapter XIII.
1475 Robertson at 179 [743] (EXP.001.001.0127_2).
1476 Ibid at 179 [744].
1477 Ibid at 179 [745].
1478 Chene 2019 at 4 (PUB.001.001.3703).

surgery to remove Essure, 'the incidence of abnormal uterine bleeding was reduced from 55% before surgery to 10% at three months after surgery'.[1479] There were 95 patients in Francini 2021, 31 of whom had hysterectomy surgery. The type of surgery depended on 'Essure device position, associated clinical conditions and patients' choice'.[1480] Pre-operative complaints of abnormal menstrual bleeding were reported by 52 patients. It is possible that women with complaints of AUB tended towards hysterectomy surgery as a means of resolving those complaints. If that was so, it would reduce the number of non-hysterectomy surgery patients with pre-removal complaints of AUB. The experts agree that AUB is resolved by hysterectomy. That means that the eight patients who complained of persistent AUB were from the non-hysterectomy surgery group. Further uncertainty is introduced because 25 patients were lost to post-operative follow-up.

1432 Robertson's evidence about reduction in the incidence of AUB is simply not made out by the study data in Francini 2021. It is not possible to say whether there was any post-operative reduction in complaints of AUB among non-hysterectomy patients. Further, the study did not examine or eliminate other possible causes of AUB.

1433 In Eychenne 2021, complaints of AUB reduced from 40% of patients before surgery to 3% after surgery. For the reasons identified at [1366]-[1367] above, I conclude that little weight should be placed on the finding of a decreased rate in AUB complaints.

1434 Robertson also discussed two of the comparative studies, Steward 2018 and Gariepy 2022.[1481] Robertson said that the results of Steward 2018 showed that AUB was worse at six months and 12 months after hysteroscopic sterilisation versus laparoscopic sterilisation, but no different at 24 months.[1482] She said that in Gariepy 2022, insurance treatment claims for AUB were more common after hysteroscopic than laparoscopic sterilisation up to 12 months post-procedure, but that there was no significant

1479 Robertson at 179 [745] (EXP.001.001.0127_2).
1480 Francini 2021 at 2 (PUB.001.001.3811).
1481 Steward 2018 (PUB.001.001.3895); Gariepy 2022 (PUB.500.002.0010).
1482 Robertson at 179 [746] (EXP.001.001.0127_2).

difference beyond that time.[1483] Robertson said:

> There is good quality evidence that tubal sterilization (by laparoscopy or laparotomy) causes increased abnormal uterine bleeding. Therefore, comparing abnormal uterine bleeding in women with tubal ligation, is not the same as comparing to women in the broader community. Indeed, the lack of difference between the two sterilization groups in [Gariepy 2022] indicates that women with Essure devices are likely to have a higher level of abnormal uterine bleeding than women without sterilization interventions.
>
> Therefore, I do not find these clinical findings persuasive and do not consider them to disagree with the scientific opinions I have formed on the basis of my experience and knowledge of the cellular and physiological mechanisms.[1484]

1435 The premise of Robertson's reasoning based on Steward 2018 and Gariepy 2022 was that laparoscopic tubal sterilisation is associated with increased rates of AUB.[1485] Robertson reasoned that a finding that the rates of AUB following Essure device implantation were comparable with rates following laparoscopic surgery, supported a conclusion that Essure was a cause of increased rates of AUB.

1436 It was put to Robertson that while there had been controversy in the 1980s and 1990s about whether laparoscopic surgery resulted in increased rates of AUB, specialist gynaecologists now accepted based on epidemiology, literature and clinical experience that laparoscopic tubal ligation did not cause an increase in AUB. It was put to her:

> [Y]ou wouldn't contest that [experienced gynaecologists are] in a more specialist expert area in which to make that assessment?---No, actually I don't agree with that because in my business I have met many clinicians who are not fully abreast of the latest data and the synthesis of information in their fields. I don't want to sound disrespectful to clinicians, because they're really important people for all of us, but unless they're research clinicians who have a direct research interest in that specific topic, quite often they're not actually fully abreast of the latest science in that area. …
>
> Do you agree that what - you might not know because you haven't looked at it carefully, but what the epidemiological surveys show that the increase that occurred was attributable to cessation of oral contraception which had given rise to the observation of increases in abnormal bleeding after the sterilisation? Did you know that or you've not looked at the study?-

1483 Ibid at 180 [747].
1484 Ibid at 180 [748]–[749] (end notes omitted).
1485 T4380 (TRA.500.043.0001_2 at 0098).

> --It's not an area, this specific area, that I have a detailed understanding of. I have an understanding of it.
>
> Yes?---And actually I'm much more persuaded by the experts who work on exactly this topic, the clinical experts who are clinician researchers, for example, Professor Hilary Critchley, who's the senior author on the paper of [Jain] et al. that was published last year, that says there is an impact of prior surgical interventions, for example, tubal ligation, on bleeding. So I'm more persuaded by reading a paper written by a person who I know is an expert by virtue of their research expertise and focus, and in that case is a clinician, as well as a scientist, than I am by your assertion that some random gynaecologist has given an opinion.[1486]

1437 I make two observations about Robertson's evidence. First, while the paper referred to by Robertson does consider factors affecting AUB, contrary to Robertson's evidence, it does not identify tubal ligation surgery as one of those factors.[1487]

1438 Second, it is not in issue between the parties that laparoscopic tubal sterilisation does not cause increased rates of AUB. That is the unchallenged evidence of Korda and As-Sanie. Turner accepted that as a result, women who have undergone tubal sterilisation are an appropriate comparative group in epidemiological studies designed to test the relationship between Essure and increased rates of AUB.

1439 I reject Robertson's contention that the outcomes of Steward 2018 and Gariepy 2022 indicate that Essure is likely to be associated with an increased rate of AUB.

1440 I conclude that the case studies are of very significantly lower quality than the comparative studies considered in Chapter XV. It is evident, for reasons set out in that chapter, that the case studies would be accorded little if any weight by epidemiologists. The case studies provide no material support for Robertson's contentions that in some women Essure is a cause of CPP and AUB. For the above reasons, and for the reasons in Chapter XV, little to no weight should be attributed to the case studies in relation to general causation.

1486 T4378-9 (TRA.500.043.0001_2 at 0096_16-0097_11).

1487 Varsha Jain et al, 'Uterine bleeding: how understanding endometrial physiology underpins menstrual health' (2022) 18 (May) *Nature Reviews Endocrinology* 290, 303 (PUB.001.001.3838 at 14).

XVII. CLINICAL EXPERIENCE

1441 In his primary report, Korda expressed the following opinion:

> In summary it is my opinion that the Essure device often causes increased pain, increased or worsened heavy menstrual bleeding, increased or worsened dysmenorrhoea and damage to internal organs as a result of the inherent design of the device, as it is inserted into the Fallopian tube to set up an inflammatory response to effect tubal occlusion. As stated above such a response, in my experience can result in the symptoms of pain, abnormal bleeding and painful menstrual periods.[1488]

In the gynaecology JER, Korda said he had treated patients with pelvic pain that he considered was associated with Essure.[1489]

1442 Korda was asked in cross-examination about chronic inflammation following Essure implantation. The following exchange occurred:

> So your opinions are based on your general understanding of the process of inflammation and your own experience in your own practice?---Yes.
>
> And in your own practice how many women have you seen who have had the Essure procedure and consulted you in respect of symptoms?---In my own practice I've only seen women who have problems with it, the Essure Device. I've seen women who have actually had bleeding and pain.
>
> And you've only seen women who have had both bleeding and pain?---Either bleeding or pain or both.
>
> And how many have you seen?---I would have seen about half a dozen.
>
> And in respect of those half dozen, how many have you performed surgery on?---I would have performed surgery on all of them.
>
> In respect of all of them, over what time period is that?---Oh, I haven't kept a record, I have no idea. It's over a period of time I've seen such women. A period of a large - - -
>
> Ten to 15 years?---Probably.
>
> Half a dozen over ten to 15 years?---Probably.
>
> In each of those cases you performed a hysterectomy?---By the time I saw them

1488 Korda at 30 [6.3.16] (EXP.001.001.0025).
1489 Gynaecology JER at 9 [20] (EXP.500.001.0001).

they wanted a hysterectomy because of the problems they had.

So they attributed it to the device and you similarly, based on the fact that they'd had the device and they had the symptoms, accepted the association?---As long as all other possible causes had been excluded.

In each instance you performed a hysterectomy?---In each instance I performed a hysterectomy.

So that any other cause that was related to - and a salpingectomy?---As far as I know.

So that anything that was a cause of their symptoms that was in the fallopian tube or the uterus would have been removed?---Yes.[1490]

1443 Korda, As-Sanie and White agreed that histories of CPP and AUB in reproductive-aged women were common, and that in some women who experience symptoms of CPP and AUB no pathological cause for the symptoms is found following hysterectomy and histological examination. Korda said it is often the case that a cause is not identified for CPP. In the circumstances, the foundation for Korda attributing symptoms to the device in the cases of his six patients is insubstantial.

1444 As-Sanie said that in her medical practice she sees patients presenting with new or exacerbated pain following both implantation of Essure and laparoscopic sterilisation. She said:

> I would say in general my clinical experience is consistent with that patients that present with pelvic pain and/or abnormal uterine bleeding can have multiple etiologies to their pain and I've not found in my clinical practice that in those patients that I've seen, for example with Essure, that there are not other causes that I've identified and successfully treated outside of the Essure Device to alleviate their symptoms.[1491]

1445 As-Sanie said approximately half her time was devoted to clinical practice treating patients with gynaecological disorders including CPP and AUB.[1492] As-Sanie said:

> Among the many conditions I treat in my specialized, referral-based practice, I routinely evaluate and treat women who have had Essure sterilization and are requesting evaluation for chronic pelvic pain or abnormal bleeding.[1493]

1490 T2502 (TRA.500.027.0001_2 at 0060_10).
1491 T2529 (TRA.500.027.0001_2 at 0087_29).
1492 As-Sanie at 9 [27], 10 [28] (EXP.001.002.0005).
1493 Ibid at 10 [28].

As-Sanie said that after taking a detailed history, conducting a physical examination and obtaining relevant laboratory and imaging results, she offers evidence-based treatment options that may include pharmacologic, behavioural, and surgical therapies. As-Sanie said that when treating CPP, she begins by recommending the least invasive treatments with the lowest risk of side effects or complications, and only considers more invasive options when less invasive treatments are not appropriate or have not been effective.[1494] She said she only offers hysterectomy for the treatment of pelvic pain as a last resort.[1495] As-Sanie said she had removed 'a limited number, probably less than 20' devices in her own practice.[1496] As-Sanie said she had performed a hysterectomy on most of those patients.

1446 As-Sanie relied on her considerable clinical experience to conclude that there was no relationship between Essure and CPP or AUB.

1447 Rosen said that he had performed the Essure procedure on about 150 patients. He said that none of his patients had long-term issues that he linked to Essure.

1448 Rosen said that he had performed two hysterectomies and salpingectomies where Essure devices were removed. He said the first patient began to experience heavier periods after she stopped taking the OCP. He could not recall why the second patient required a hysterectomy. He said he did not regard the symptoms or the need for hysterectomy in either case to be related to Essure.

1449 The evidence of clinical experience weighs against there being any causal link between Essure and CPP or AUB.

1450 In this context, it is worth noting that there is no evidence of the laboratory tests for chronic inflammation, described by Sokol and Badylak as being standard and reliable, having been undertaken for patients wearing Essure.

1494 Ibid at 18 [66].
1495 Ibid at 19 [68].
1496 T2468 (TRA.500.027.0001_2 at 0026_18).

XVIII. CAUSATION

Principles and authorities

1451 There are two causation issues to be determined in this case. First is the question of general causation: namely, whether in some women Essure causes injuries including CPP and AUB. The second question is whether Essure caused the gynaecological symptoms experienced by Turner.

1452 Causation is not established if the evidence does no more than prove the possibility of the requisite relationship between the intervention, in this case Essure, and the claimed injuries.[1497] It is necessary for the finder of fact to feel actual persuasion that the evidence is sufficient to 'justify an inference of probable connection'.[1498]

1453 Even in cases involving complex questions of medical science, causation is not simply determined by reference to scientific opinion.[1499] In *Seltsam,* Spigelman CJ said:

> In circumstances where the aetiology of a disease is uncertain, or subject to significant scientific dispute, the Courts are not thereby disenabled from making decisions as to causation on the balance of probabilities. As Herron CJ said in *EMI (Australia) Ltd v Bes* [1970] 2 NSWR 238 at 242:
>
> > "Medical science may say in individual cases that there is no possible connection between the events and the death, in which case, of course, if the facts stand outside an area in which common experience can be a touchstone, then the judge cannot act as if there were a connection. But if medical science is prepared to say that it is a possible view, then, in my opinion, the judge after examining the lay evidence may decide that it is probable. It is only when medical science denies that there is any such connection that the judge is not entitled in such a case to act on his own intuitive reasoning. It may be, and probably is, the case that medical science will find a possibility not good enough on which to base a scientific deduction, but courts are always concerned to reach a decision on probability and it is no answer, it seems to me that no medical witness states with certainty the very issue which the judge

1497 *Seltsam* at [80]–[83] (Spiegelman CJ).

1498 *Fernandez v Tubemakers of Australia Ltd* [1975] 2 NSWLR 190 ('*Tubemakers*') at 197; *NOM v Director of Public Prosecutions* (2012) 38 VR 618 at [124] (Redlich and Harper JJA and Curtain AJA); *GLJ v The Trustees of the Roman Catholic Church for the Diocese of Lismore* (2023) 414 ALR 635 at [60] (Kiefel CJ, Gageler and Jagot JJ).

1499 *Tubemakers*; *Seltsam*.

himself has to try." [1500]

1454 Spigelman CJ said that epidemiological evidence may be particularly important in cases where medical science cannot determine the existence of a causal relationship between an exposure and an injury.[1501]

1455 Factors relevant to assessing epidemiological evidence, often referred to as the 'Bradford-Hill criteria', were summarised by Spigelman CJ in *Seltsam*:

> There is widespread acceptance amongst epidemiologists of the principles or postulates which are applied to assess the evidence of a statistical correlation or association. In evidence in the present case, is the article by McLaughlin and Brookmeyer, which contains the following summary:
>
> > *Key Principles in Interpreting Epidemiological Studies*
> >
> > l. *Strength of the Association*. In general the higher the risk estimate, the less likely the finding is a result of confounding or bias. ...
> >
> > 2. *Dose Response Effect*. If the risk of the disease rises with increasing exposure, a causal interpretation of the association is more plausible. ...
> >
> > 3. *Time Sequence*. The exposure or risk factor must precede the disease. ....
> >
> > 4. *Consistency*. Results from other epidemiological studies of the exposure-disease association should be similar. If similar results are found in different populations using various study designs, the plausibility of a causal interpretation is increased. An alternative explanation of bias or confounding would have to apply to each of the different studies, a highly implausible explanation.
> >
> > 5. *Biological Coherence*. Does the exposure-disease association make biological sense given what is known of the natural history of the disease? Do animal experiments support the association? Do other types of collateral evidence support the association, such as secular trends of the exposure factor in the disease? Unfortunately, for many diseases little is known about their aetiologies, so the informational background by which to judge biological coherence is often limited. Thus, failure of this broad principle does not necessarily weaken the plausibility of a causal interpretation.
> >
> > The first three principles can be applied to an individual study and used to assist the findings. The last two principles referred to results outside their particular study and relate more to external issues of coherence or consistency. All of the criteria or principles should be viewed as guidelines. Except, perhaps, for time sequence, none is required for a

1500 *Seltsam* at [94].
1501 Ibid at [93].

causal interpretation.[1502]

1456 Spigelman CJ referred to the factors as 'uncomplicated statements of commonsense propositions', and continued:

> The postulates or criteria are all matters which a court can take into account in determining whether or not it should infer, on the balance of probabilities, that a particular exposure caused injury in the specific case before the court. The approach of epidemiologists with respect to the identification and application of the postulates may be of assistance to the court by force of their reasoning. They do not constitute a scientific opinion which a court is constrained to accept.
>
> When assessing expert evidence on causation, the legal concept of causation requires the court to approach the matter in a distinctively different manner from that which may be appropriate in either philosophy or science, including the science of epidemiology.
>
> The commonsense approach to causation at common law is quite different from a scientist's approach to causation[.] An inference of causation for purposes of the tort of negligence may well be drawn when a scientist, including an epidemiologist, would not draw such an inference.[1503]

1457 The plaintiff in *Seltsam* suffered from a renal cell carcinoma allegedly caused by exposure to inhalation of asbestos fibres. There were a number of other recognised risk factors for the plaintiff contracting that disease. There was no medical investigation, such as tissue biopsy, that could demonstrate the likelihood of asbestos exposure being the cause of the disease. In this context Spigelman CJ, with whom Davies AJA agreed, concluded that the epidemiological evidence went no further than establishing asbestos exposure as a *possible* cause, and did not justify, when considered with all of the evidence, an inference of causation on the balance of probabilities.[1504]

1458 The defendants rely on two cases to demonstrate what they argue is an 'insurmountable difficulty' faced by Turner in establishing causation. The first is the decision of the High Court in *Amaca Pty Ltd v Ellis*[1505] ('*Ellis*'), which concerned a claim on behalf of the deceased estate of Mr Cotton, a smoker who had been exposed to inhalation of asbestos fibres and who had died of lung cancer. The epidemiological

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1502 Ibid at [139].
1503 Ibid at [141]–[143].
1504 Ibid at [183].
1505 (2010) 240 CLR 111 ('*Ellis*').

evidence was to the effect that the risk of contracting lung cancer due to smoking was much greater than the risk due to exposure to asbestos. No medical examination or investigation differentiated between the possible causes for Cotton's lung cancer. The plaintiff relied on the epidemiological evidence to establish factual causation by the interdependent operation of the two carcinogens he was exposed to — tobacco smoke and respirable asbestos fibres.

1459 The Court rejected the plaintiff's argument. It concluded that the epidemiological evidence was that it was more probable than not that smoking was a cause of Cotton's cancer, and that the risks and probabilities associated with asbestos exposure, considered alone or in conjunction with smoking, were low and not sufficient to found an inference of causation.[1506]

1460 The Court responded as follows to the plaintiff's submission that it would be paradoxical not to find causation established when the evidence showed that exposure to asbestos was a cause of cancer in some cases:

> … As explained at the outset of these reasons, despite this uncertainty, the courts must, and do, "reduce to legal certainty [a question] to which no other conclusive answer can be given". The courts do that by asking whether it is more probable than not that X was a cause of Y. Saying only that exposure to asbestos *may* have been a cause of Mr Cotton's cancer is not a sufficient basis for attributing legal responsibility. Observing that a small percentage of cases of cancer were probably caused by exposure to asbestos does not identify whether an individual is one of that group. And given the small size of the percentage, the observation does not, without more, support the drawing of an inference in a particular case. The paradox, if there be one, arises from the limits of knowledge about what causes cancer.[1507]

1461 The second case relied on by the defendants is *Merck Sharp & Dohme (Australia) Pty Ltd v Peterson*[1508] ('*Merck*'). The lead plaintiff in *Merck*, Mr Peterson, alleged that his use of a prescription medication called 'Vioxx', manufactured by the defendants, was a cause of a myocardial infarction he suffered in December 2003. Peterson had other risk factors for myocardial infarction including hypertension, hyperlipidemia, obesity

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1506 Ibid at [64].
1507 Ibid at [70] (citation omitted).
1508 (2011) 196 FCR 145 ('*Merck*').

and the presence of left ventricular hypertrophy. As was the case in *Ellis*, no medical examination or investigation provided evidence that could assist in determining the aetiology of Peterson's heart attack. Peterson relied on two matters to establish causation at trial. First, there was epidemiological evidence of an increased risk of myocardial infarction associated with consumption of Vioxx for the category of persons to which he belonged. Second, while a biologically plausible explanation for that increased risk was not proved, there was a theory of an acute risk of thrombotic outcomes from the consumption of Vioxx, and thus a risk of myocardial infarction, which was accepted at trial as possibly valid. On the basis of these two factors, the trial judge was satisfied on the balance of probabilities that in Peterson's case Vioxx had contributed to the formation of a thrombus sufficiently large to occlude a blood vessel to the heart, resulting in myocardial infarction. While the trial judge was not satisfied that a thrombus of the necessary size would not have developed without consumption of Vioxx because of Peterson's unrelated risk factors, the trial judge ultimately found for Peterson.[1509]

1462 On appeal, the Court accepted that the primary judges express refusal to find that Peterson's heart attack would not have happened but for the taking of Vioxx meant that his case should have been dismissed because the essential finding of fact that it was more probable than not that the consumption of Vioxx caused or materially contributed to the occurrence of his heart attack had not been made.[1510] The Court observed that factual causation is not established by showing an increased risk of injury by reason of the defendant's conduct. The question to be determined is whether the increased risk eventuated.[1511] The Court said:

> [98] That is the effect of the authorities on the test for causation under the common law in Australia. The position was summarised recently in *Tabet v Gett* (2010) 240 CLR 537 at [111]-[113]. Kiefel J, with whom Hayne, Crennan and Bell JJ agreed, said:
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> The common law requires proof, by the person seeking compensation,

1509 *Peterson v Merck Sharpe & Dohme (Australia) Pty Ltd* (2010) 184 FCR 1 ('*Peterson*').
1510 *Merck* [93]-[94] (Keane CJ, Bennett and Gordon JJ).
1511 Ibid at [97].

> that the negligent act or omission caused the loss or injury constituting the damage. All that is necessary is that, according to the course of common experience, the more probable inference appearing from the evidence is that a defendant's negligence caused the injury or harm. "More probable" means no more than that, upon a balance of probabilities, such an inference might reasonably be considered to have some greater degree of likelihood; it does not require certainty.
>
> The "but for" test is regarded as having an important role in the resolution of the issue of causation, although more as a negative criterion than as a comprehensive test. The resolution of the question of causation has been said to involve the common sense idea of one matter being the cause of another. But it is also necessary to understand the purpose for making an inquiry about causation and that may require value judgments and policy choices.
>
> Once causation is proved to the general standard, the common law treats what is shown to have occurred as certain. The purpose of proof at law, unlike science or philosophy, is to apportion legal responsibility. That requires the courts, by a judgment, to "reduce to legal certainty questions to which no other conclusive answer can be given". The result of this approach is that when loss or damage is proved to have been caused by a defendant's act or omission, a plaintiff recovers the entire loss (the "all or nothing" rule).
>
> [99] The "but for" test serves, in this field of discourse, as a negative criterion. That is to say, unless the defendant's actionable conduct is shown to be a necessary condition of the plaintiff's injury, the plaintiff's claim will not succeed. Thus, in A*maca* at [11]–[12], it was accepted that a plaintiff must show on the balance of probabilities that the actionable conduct of the defendant was a necessary condition of the occurrence of the harm in respect of which the plaintiff claims damages. It is true, as counsel for Mr Peterson pointed out, that this rule was not the subject of argument in *Amaca*; but it is also true that this rule represents the law in Australia binding on all courts below the High Court.[1512]

1463 The Court observed that the strength of the trial judge's finding of an increased relative risk associated with consumption of Vioxx, based on epidemiological evidence, was undermined because of the other possible causes of Peterson's injury. The Court concluded:

> In this case, as has been seen, there was a clear basis for concluding that Mr Peterson does indeed stand apart from the ordinary case. His personal circumstances were such that they afford a ready explanation for the occurrence of his injury independent of the possible effects of Vioxx. The strength of the epidemiological evidence as a strand in the cable of circumstantial proof is seriously diminished by this consideration. The epidemiological studies do not provide assistance in resolving the question

1512 Ibid (footnotes omitted).

> whether it was the risk posed by Vioxx, either alone or in combination with the other candidates, which did eventuate in this case.[1513]

The Court noted the trial judge's reference to reasons for uncertainty about the validity of the biological plausibility theory, and said:

> In these circumstances, the primary judge's conclusion in [772] proceeded on the view most favourable to Mr Peterson reasonably open to him, in that this strand of Mr Peterson's case was no more than a plausible account of how Vioxx might possibly have contributed to the occurrence of his [myocardial infarction].[1514]

As to the effect of the epidemiological evidence, the Court concluded:

> Secondly, it is apparent that, so far as Professor Harper's opinion was concerned, he was invoking the rule of thumb derived from the relative risk of 2.0. A small absolute risk may be doubled without making it a likely source of injury. Doubling a very low absolute risk of an adverse result may produce an absolute risk which itself remains so low that a positive finding of causation on the balance of probabilities would itself be an affront to commonsense. In the APPROVe study the absolute event rates for [myocardial infarction] were 21 events or 0.69 events per 100 patient years for patients consuming Vioxx, and nine events or 0.27 events per 100 patient years for patients consuming a placebo.
>
> The epidemiological evidence meant that it was possible that Vioxx consumption was a cause of Mr Peterson's [myocardial infarction]. But there were other candidates as causes of his injury, and the claims of those candidates were strong. Shortly before Mr Peterson commenced taking Vioxx, he was, by reason of his age, gender, hypertension, hyperlipidemia, obesity, left ventricular hypertrophy and history of smoking, a member of a group within the community, 25% of whom were expected by the cardiologists to suffer a heart attack within five years. Mr Peterson may simply have been the unlucky one in four of this cohort to suffer a [myocardial infarction]. We are unable to see how it can be said that it is more probable than not that Vioxx, whether alone or in combination with Mr Peterson's personal risk factors, was a necessary condition of the occurrence of his heart attack.[1515]

1464 A further relevant decision is *Amaca v Booth*[1516] ('*Booth*') which concerned a retired motor mechanic who suffered from mesothelioma caused by exposure to respirable asbestos. Booth claimed that exposure to asbestos in brake linings on which he worked for over 30 years was a cause of his disease. The following findings by the

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1513 Ibid at [113].
1514 Ibid at [116].
1515 Ibid at [119]–[120].
1516 (2011) 246 CLR 36 ('*Booth*').

trial judge were either not in dispute, or were not able to be challenged on appeal:

> • Mr Booth's mesothelioma was caused by the inhalation of asbestos fibre;
>
> • chrysotile asbestos has the capacity to cause mesothelioma;
>
> • the brake linings manufactured by Amaca and Amaba contained chrysotile asbestos; and
>
> • Mr Booth inhaled chrysotile asbestos fibre liberated from Amaca and Amaba products.[1517]

The trial judge accepted expert evidence to the effect 'that all asbestos exposure, both recalled and unrecalled, will contribute causally towards the ultimate development of a mesothelioma'.[1518] French CJ said, in relation to the defendant's reliance on epidemiological evidence:

> Amaca and Amaba relied, in the Tribunal, upon nineteen epidemiological studies published in peer reviewed journals about the incidence of mesothelioma among automotive mechanics and three "meta-analyses" which had combined the results of several studies to produce what was said to be "a more precise estimate of the risk". Each of the meta-analyses concluded that the epidemiological data showed that automotive mechanics are not at a greater risk of developing mesothelioma. The primary judge observed that the studies relied upon by the meta-analyses covered "motor mechanics", "garage workers" and "vehicle mechanics". His Honour said that the average exposure of motor mechanics might have "little in common with the particular exposure of Mr Booth".[1519]

The trial judge's criticisms of the epidemiological evidence culminated in the following conclusion:

> I am not persuaded that the epidemiological evidence specific to automotive mechanics is adverse to the submission that causation has been proved in this particular case.[1520]

With respect to this conclusion, French CJ said:

> This may be taken as a finding that the epidemiological evidence did not displace the inference of factual causation which was open on the basis of Mr Booth's history and the medical evidence relating to the cumulative effects of

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1517 Ibid at [14] (French CJ).
1518 Ibid at [20].
1519 Ibid at [22] (citations omitted).
1520 Ibid at [23].

exposure to asbestos.[1521]

1465 The conclusion by the trial judge that causation was established was based in part on epidemiological evidence showing that chrysotile had the capacity to cause mesothelioma. Discussing the use to be made of epidemiological evidence, French CJ said:

> In a discussion of the application of the Bradford Hill criteria in the *Restatement Third, Torts*, it was said:
>
> > Whether an inference of causation based on an association is appropriate is a matter of informed judgment, not scientific methodology, as is a judgment whether a study that finds no association is exonerative or inconclusive. No algorithm exists for applying the Hill guidelines to determine whether an association truly reflects a causal relationship or is spurious. Because the inferential process involves assessing multiple unranked factors, some of which may be more or less appropriate with regard to a specific causal assessment, judgment is required.
>
> Applying the Bradford Hill factors in his report of March 2009, Professor Henderson said that the epidemiological data were inconclusive for brake lining workers specifically, but had also shown quite conclusively that chrysotile has the capacity to induce pleural malignant mesothelioma. A dose-response relationship had been demonstrated for non-brake chrysotile exposures, although not for brake lining exposures. The causal relationship was supported by experimental studies and also from the perspective of biological plausibility. Temporality was fulfilled, as was reasoning by analogy. On that basis Professor Henderson said:
>
> > This being so, it is my conclusion from pathobiological principles that substantial or protracted chrysotile (chrysotile-tremolite) exposure to dust derived from new (non heat-altered) brake linings probably does have the capacity to induce mesothelioma in dedicated brake mechanics. One of the problems with epidemiological studies on this issue is that they do not clearly distinguish between dedicated brake mechanics versus general automotive mechanics or garage mechanics.
>
> In answer to the question posed for his opinion — Does exposure to dust derived from brake linings that contain chrysotile asbestos have the capacity to induce mesothelioma? — he wrote:
>
> > Accordingly, my response … is cautiously in the affirmative, 'on the balance of probabilities'. This opinion is not given at a high order of confidence because of the controversy over this issue in the scientific literature at present. However, from surveying all of the evidence (*not only* the epidemiological evidence) and from first principles and from what is known about other chrysotile-only exposures, a causal-

[1521] Ibid.

contributory relationship follows.[1522]

(Emphasis in original.)

1466 French CJ summarised the position in *Booth* as follows:

> In summary, a finding that a defendant's conduct has increased the risk of injury to the plaintiff must rest upon more than a mere statistical correlation between that kind of conduct and that kind of injury. It requires the existence of a causal connection between the conduct and the injury, albeit other causative factors may be in play. As demonstrated by medical evidence in this case and in particular by Professor Henderson's evidence, a causal connection may be inferred by somebody expert in the relevant field considering the nature and incidents of the correlation. The Bradford Hill criteria provide a guide to the kind of considerations that lead to an inference of causal connection. As noted above, they may include reference to relative risk ratio as an indicator of the strength of the association. Where the existence of a causal connection is accepted it can support an inference, in the particular case, when injury has eventuated, that the defendant's conduct was a cause of the injury. Professor Henderson offered that inference of specific causation by reference to Mr Booth's exposure to the products of both Amaca and Amaba. Where such an inference is drawn, the probability that it is correct is not to be determined only by reference to epidemiologically based ex ante probabilities. In *Betts v Whittingslowe*, Dixon J employed apposite logic when he said:
>
> > [T]he breach of duty coupled with an accident of the kind *that might thereby be caused* is enough to justify an inference, in the absence of any sufficient reason to the contrary, that in fact the accident did occur owing to the act or omission amounting to the breach of statutory duty.
>
> (Emphasis added.) That logic encompasses the case of an ex ante probability, of accident given breach, supported by a causal explanation linking breach and accident. In this case an explanatory causal mechanism was proposed in the medical evidence.[1523]

1467 In their joint judgment, Gummow, Hayne and Crennan JJ noted that three of the experts gave evidence that they had each encountered cases of mesothelioma where the only identified exposure to asbestos was from working with brake linings. In relation to the epidemiological evidence, the majority concluded:

> It was open to the primary judge to decide that he was "not persuaded that the epidemiological evidence specific to automotive mechanics is adverse to the submission that causation has been proved in this particular case".
>
> The Court of Appeal, with respect, correctly concluded:
>
> Findings as to the cumulative effect of exposure to asbestos were

1522 Ibid at [45]–[46] (citation omitted).
1523 Ibid at [49] (citations omitted).

> undoubtedly open. [Mr Booth's] witnesses, including Professor Henderson and Dr Leigh, sought to reconcile that approach with the epidemiology which suggested there was no increased risk in the case of brake mechanics. It was open to his Honour to accept their evidence, as he did. The underlying proposition put forward by the appellants, that the epidemiology was conclusive, in accordance with the principles applicable to such evidence, did not give rise to a question of law, but to a question of fact, which his Honour resolved against the appellants.[1524]

1468 The decisions in *Seltsam*, *Ellis*, *Merck* and *Booth* serve to emphasise the importance of epidemiological evidence in cases where there is scientific uncertainty about whether a tortious exposure can and did cause injury.

1469 I note the following further matters. First, in *Booth*, the only identified cause of mesothelioma was exposure to respirable asbestos, whereas in each of *Seltsam*, *Ellis* and *Merck* there were other important risk factors for the disorder suffered by the injured plaintiff which required consideration. While epidemiological evidence did support a conclusion that the tortious exposure could cause the compensable injury, it did not elevate the risk posed by that exposure above other risk factors to show that it was the probable cause.

1470 Second, there was no evidence in *Seltsam*, *Ellis* or *Merck* of a clinical test outcome or other signal that distinguished between risk factors and weighed in favour of injury having been caused by the tortious exposure.

1471 Third, the trial judge in *Booth* accepted expert evidence, based on epidemiological data, that exposure to chrysotile asbestos had the capacity to induce mesothelioma. Further, the trial judge accepted expert opinion that all exposure to respirable asbestos was causative of mesothelioma in a particular case. This meant that biological plausibility generally, and specifically in the instance of Mr Booth himself, was established.

1472 Causation in Turner's negligence case is to be determined in accordance with s 51 of the *Wrongs Act*. Turner did not argue that the common law exception to the

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1524 Ibid at [90]–[91] (citation omitted).

application of the but for test that is reflected in s 51(2) of the *Wrongs Act* should apply. No issue arose in this case requiring particular consideration of s 51(1)(b). Section 51(1)(a) of the *Wrongs Act* is a statutory statement of the but for test.[1525] Accordingly, to succeed in her case, Turner must prove on the balance of probabilities that Essure was a necessary condition of her gynaecological symptoms.

Submissions

Turner

1473 In the biomaterials JER, Robertson, Chrzanowski and Badylak said:

> [If] the inflammatory phase of the wound healing process is not complete by 6-8 weeks, and at most by 3 months, it meets the definition of a chronic wound[.] We consider a wound to be a chronic wound when, at 3 months or more since injury, there is ongoing inflammation and immune response activity in the immediate vicinity of the wound[.] We consider that this time frame applies when wound responses include a foreign body response[.] We consider the matter of timing to be important as any analysis of tissue to determine whether chronic inflammation exists must be made in the context of the time since the wound was made[.]
>
> …
>
> We agree that in all women, the wound healing response to placement of an Essure Device involves a chronic inflammatory response phase. In most women, this phase will be short-lived and will be completely resolved within 6 weeks, and at most 3 months of Device placement. We agree that in many women, the Device undergoes complete healing with resolution of inflammation and extensive fibrotic tissue/scar formation.[1526]

1474 It follows from these agreed statements and the agreed definition of chronic inflammation that if ongoing chronic inflammation is present more than three months after implantation of Essure, then the foreign body response and the persisting chronic inflammatory response has failed to resolve and is pathological with adverse health consequences. The agreed position of the experts and the clear evidence in the Essure histological studies of ongoing chronic inflammation beyond three months is evidence of pathological chronic inflammation caused by Essure.[1527]

1525 *5 Boroughs NY Pty Ltd v State of Victoria* (2021) VSC 785 [167].
1526 Biomaterials JER at 25-6 (EXP.500.001.0006).
1527 SBM.001.001.0004 at 81 [232].

1475 Sokol's oral evidence that inflammation surrounding the device at three months or more was expected was inconsistent with the definition of chronic inflammation to which she agreed. Sokol's attempt to resile from the statement by distinguishing between a normal wound healing response and a foreign body response cannot be maintained given the statement expressly refers to Essure, rather than a general wound healing principle.[1528] In any event, Sokol's oral evidence that active chronic inflammation may continue for six months or more as part of the normal foreign body response to Essure cannot be accepted in circumstances where the evidence did not appear in any of her reports and was unsupported by any authority. Sokol's attempt to rely on Valle 2001 in support of her timeframe proposition demonstrated a flawed and obviously circuitous line of reasoning.

1476 Murdock's opinion that chronic inflammation was not pathological unless it amounted to a diagnosis of chronic salpingitis was not shared by any other witness and should be disregarded.

1477 The following features of Essure and the fallopian tube meant there was a risk of ongoing chronic inflammation in some women:

(a) Implantation of Essure causing permanent damage to the thin epithelial layer and underlying tissue of the fallopian tube. Turner submitted that implantation of a device into an epithelial surface was unique to Essure and made it more susceptible to causing ongoing injury;[1529]

(b) The vulnerability of the fallopian tube and uterus to incomplete healing and chronic wound formation due to:

(i) the peristaltic activity and movements of the fallopian tube during physical activity which increase the risk of trauma to tissues adjacent to

1528 SBM.001.001.0004 at 81 [234].
1529 Ibid at 43.

the device;[1530]

(ii) their specialised, robust and hypervigilant pro-inflammatory immune response to medical devices such as Essure;

(iii) the unusual and specialised form of scar-free wound healing in the uterus, shared by the SUTJ region of the fallopian tube, which results in regenerative healing without formation of fibrotic scar tissue; and

(iv) the characteristic hypoxic state of the fallopian tube and uterus, given that low oxygen content is a risk factor for poor wound healing and promotion of inflammation;

(c) The use of PET fibres in the device to promote chronic inflammation, which can result in the foreign body response lasting longer than the usual timeframe consistent with normal wound healing;

(d) Metal particles and ions continually leached from the device and provoke an ongoing inflammatory response which interfered with wound healing. The removal of the epithelial layer also promoted the transfer of ions directly to cells and tissue surrounding Essure, contributing to and prolonging the chronic inflammatory response;[1531] and

(e) The sharp edges of the nitinol outer coil of the device had the potential to cut into, erode, and cause ongoing tissue injury and inflammation in the event of movement. Essure deployment caused focal bleeding and damage to the internal lining of the isthmus and SUTJ regions of the fallopian tube and uterus. The outer coil's edges were at least sharp enough to cause bleeding and damage to the inner layers of those organs.

1530 Ibid.
1531 Ibid at 47.

CPP and dysmenorrhea

1478 No expert evidence was adduced by the defendants to challenge the biological mechanism posited by Turner that chronic inflammation elicited by Essure can cause or exacerbate pelvic pain, including dysmenorrhea.

1479 In the immunology JER, Robertson and Sokol agreed:

> We agree that inflammatory cytokines and other mediators released by immune cells can promote the activation of pain sensing neurons causing the sensation of pain. This process could be elevated in the setting of chronic inflammation through the direct priming of peripheral pain sensing neurons. This mechanism can directly lead to peripheral pain and indirectly lead to central pain. A chronic inflammatory response to the Essure Device could increase the risk of onset of pelvic or abdominal pain.
>
> … A chronic inflammatory response to the Essure device could exacerbate pelvic or abdominal pain.[1532]

In oral evidence, As-Sanie agreed that inflammation is an important mechanism in causing pain,[1533] and that it was biologically plausible that persistent inflammation in a person may well cause pain.[1534]

1480 On the basis of this evidence, the Court should find that if Essure causes an ongoing chronic inflammatory response, that ongoing chronic inflammatory response can cause and exacerbate pain including CPP and/or dysmenorrhea.[1535]

1481 Robertson's opinion that a persistent chronic inflammatory response to Essure devices would have 'a very high likelihood' of triggering CPP is underpinned by two broad forms of evidence. First are clinical studies that show an improvement of CPP symptoms after surgical removal of Essure devices. Robertson said that analysis of Bayer's MAUDE database revealed that pain was the most commonly reported complaint following Essure insertion. Robertson also identified that Banet 2020 and Rubin 2020 provided a link between chronic inflammation and pain in some women, and that other causation studies linked improvement in pain symptoms and quality

1532 Immunology JER at 17-8 (EXP.500.001.0004).
1533 T2561 (TRA.500.028.0001_2 at 0024_28).
1534 T2571 (TRA.500.028.0001_2 at 0034_17).
1535 SBM.001.001.0004 at 105 [292].

of life in some women with surgical removal of Essure devices. Robertson said that while the causation studies had limitations, the information they provide aligns with and corroborates her opinion that:

> On the basis of current biomedical understanding of the causal links between persistent chronic inflammation and pain, on the balance of probabilities I expect persistent chronic inflammation to an Essure Device to cause chronic pelvic pain in a not insignificant proportion of women.[1536]

1482 Second is the logical synthesis of the following facts:

> (1) that the Essure Device causes persistent chronic inflammation in the fallopian tubes of some women; (2) that chronic inflammation in other tissues in the body causes chronic pain, through both nociceptive and neuropathic (central) pathways, and (3) there is no reason to suggest that the fallopian tube and uterus are less likely than other sites to elicit a pain response — in fact they may be more susceptible by virtue of their location in the peritoneal cavity.[1537]

1483 Robertson's evidence is supported by Korda, who said that Essure was designed to cause an inflammatory response in the fallopian tubes, and that the general symptoms of inflammation include pain.[1538] Korda said that it was a matter of basic medicine that inflammation causes pain.[1539]

1484 While studies showing the link between Essure and pain are of some utility in understanding a causal connection between the two, the Court can and should also consider the likelihood of pain resulting from the device based on scientific principles and the opinions of leaders in their field on the likelihood of that connection. The question the Court is addressing is not one of scientific certainty, but of the balance of probabilities.[1540]

1485 Given that the defendants' experts agree that the mechanism by which Essure causes CPP is biologically plausible, and that they accept the Essure device *can* cause CPP, the Court should reject the conclusions of As-Sanie or Gebski based on their analysis of the epidemiological studies, and accept the opinions of Robertson and Korda that

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1536 Robertson at 177 [733] (EXP.001.001.0127_2).
1537 Robertson at 119-20 (EXP.001.002.0015_2).
1538 Ibid at 26.
1539 T2479, T2498 (TRA.500.027.0001_2 at 0037, 0056).
1540 SBM.001.001.0004 at 106 [296].

the Essure device will likely cause CPP in at least some women.[1541]

AUB

1486 The mechanisms by which Essure causes AUB are summarised as follows:

(a) Menstruation resembles a tightly controlled, self-limited inflammatory response.

(b) During menstruation, macrophages progress from a pro-inflammatory to anti-inflammatory phenotype to give way to tissue repair, cessation of bleeding and endometrial proliferation.

(c) If the phenotype of uterine macrophages and uNK cells and other immune cells are not correctly controlled or synchronised, this can contribute to heavy bleeding and bleeding at inappropriate stages of the cycle.

(d) An immune response in the fallopian tube adjacent to and draining into the uterus and in the lymph nodes serving the uterus will impact the uterus.

(e) An immune response to Essure will impact the immune cell populations that modulate tissue remodelling in the endometrium.

(f) Ongoing inflammation in the SUTJ and body of the uterus will cause changes to uterine physiology and immunology that impact regulation of tissue regeneration, bleeding and repair.

(g) The consequence is new or worsening menstrual bleeding disorders.

(h) Abnormal bleeding can increase the duration and intensity of pain and the dysregulation of the systemic immune response would amplify effects of AUB.

(i) Inflammation will cause changes to the regular monthly cycle of uterine tissue growth and vascular remodelling.

1541 Ibid at 110 [308].

(j) Irritation of the endometrium by the portion of the device that is still in the uterine cavity can cause endometritis.

1487 Robertson pointed out that analysis of Bayer's MAUDE database showed that abnormal bleeding was routinely reported among the top-ranked symptoms in relation to Essure. She said:

> On the basis of current biomedical understanding of the causal links between chronic inflammation and abnormal uterine bleeding, on the balance of probabilities I expect persistent chronic inflammation to an Essure Device to cause abnormal uterine bleeding in a not insignificant proportion of women.[1542]

1488 In circumstances where there was no real challenge by the defendants to the evidence on the biological mechanism issue, the Court should accept that Essure has the capacity to cause or exacerbate menstrual bleeding by those mechanisms.

1489 Given the flaws in the conclusions of As-Sanie and Gebski based on analysis of the epidemiological evidence, the Court should accept the opinions of Robertson and Korda that Essure will likely cause AUB in at least some women.

Defendants

1490 Turner's case, which was largely based on Robertson's evidence, asserted a range of theories to the effect that Essure was capable of causing the alleged harm. Robertson's theories were predicated on very limited direct evidence and, as a result, amounted to no more than hypotheses of what might happen. The Essure histological studies, and the studies involving metals testing conducted on either new or explanted devices, constituted the direct evidence,[1543] which should be given greater weight when determining whether Turner has discharged her burden of proving that Essure caused the alleged harm. Many of Robertson's hypotheses amounted to no more than 'brainstorming'.[1544]

1542 Ibid at 113 [319]; Robertson at 181 (EXP.001.001.0127_2).
1543 SBM.500.001.0003_2 at 476.
1544 Ibid at 700.

CPP and dysmenorrhea

1491 Ions that leach from Essure devices in vivo may trigger a DTHR. This was the only direct evidence that the device could cause a chronic inflammatory reaction. DTHR occurred at a vanishingly small rate, was the subject of a specific warning, and is a condition that can be readily treated.[1545]

1492 Women may experience pain during or immediately following the placement of Essure, including due to tubal spasm. This risk was the subject of an appropriate specific warning in the IFUs and PTMs, and accordingly it cannot be actionable.[1546]

1493 The mechanisms by which Turner alleges that Essure causes CPP and/or dysmenorrhea are all premised on the assumption that the device causes ongoing chronic inflammation, being a persistent pathological state of chronic inflammation. However, Turner has not established any of the specific hypotheses proposed by Robertson as to how Essure may cause ongoing chronic inflammation. Further, Turner's pathologic chronic inflammation case is simply not supported by the epidemiological data.[1547]

1494 In her written evidence, Robertson said repeatedly that the vast majority of women implanted with Essure would experience a successful wound healing response with no ongoing or persistent pathologic chronic inflammation.[1548] In the immunology JER and in cross-examination, Robertson gave evidence that was directly inconsistent with her reports when she said that in 'many women' there was evidence 'that the foreign body response to a device often fails to completely heal and becomes stalled in the inflammatory phase'.[1549] The identified inconsistency reflects adversely on the weight that can be placed on Robertson's evidence, and on her credibility as a witness. The written evidence in Robertson's first two reports is entirely consistent with the available epidemiological data concerning Essure. Her inconsistent evidence in the

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1545 Ibid at 699 [3.19].
1546 SBM.500.001.0003_2 at 783 [3.3]-[3.4].
1547 Ibid at 787 [3.15]-[3.17].
1548 Ibid at 788, [3.19].
1549 Immunology JER at 4 (EXP.500.001.0004_2); T4010–12 (TRA.500.040.0001_2 at 0020-2).

immunology JER came after she had, on her own admission, come to 'have greater conviction in [her] opinion' that there was an adverse impact often, and in many women.[1550] Robertson maintained this conclusion even after admitting that there was insufficient data available to quantify 'the distribution of adverse impact'.[1551]

1495 Robertson sought to justify her opinion by saying that in her view, at least 50% of the women involved in the histological studies exhibited evidence of an ongoing inflammatory response. While she accepted those studies were not 'broadly generalisable',[1552] she said that it would not be unreasonable to generalise that about the same proportion of women with similar clinical conditions would have similar pathology.[1553]

1496 Robertson's inability to quantify the rate at which she says Essure exerts the hypothesised adverse effects on women, ultimately reflects the fact that Turner has failed to prove that Essure has these effects at all. It was telling that Robertson's first attempt to quantify these effects was in the witness box when challenged with parts of her own written evidence.[1554]

1497 Unlike Korda and As-Sanie, Robertson is not a clinical gynaecologist. Korda and As-Sanie agreed that patients who undergo Essure placement could experience new pelvic pain or exacerbation of existing pelvic pain. However, they disagreed about the relationship between any such pain and Essure.[1555]

1498 Korda's opinion was that Essure causes chronic inflammation in some women, and that chronic inflammation causes pain. However, he also agreed that up to 25% of women may experience chronic pain during their reproductive lives, and that often a cause of the pain is not identified.[1556]

1550 T4015 (TRA.500.040.0001_2 at 0025).
1551 Ibid; SBM.500.001.0003_2 at 791 [3.20](b).
1552 T4006 (TRA.500.040.0001_2 at 0016).
1553 T4008 (TRA.500.040.0001_2 at 0018).
1554 SBM.500.001.0003_2 at 794 [3.29].
1555 Ibid at 795 [3.32].
1556 T2487 (TRA.500.027.0001_2 at 0045); Korda at 32 [103] (EXP.001.002.0011); SBM.500.001.0003_2 at 795.

1499 As-Sanie said that inflammation needs to be persistent and repetitive to be a cause of chronic pain, and that she did not see any evidence of that occurring with Essure. She did not accept that the presence of inflammation was either necessary or sufficient to result in pain. She said that while it was biologically plausible that persistent inflammation could cause pain, the available data did not show that there was an association between Essure and increased rates of CPP.[1557]

AUB

1500 The epidemiological evidence by itself should be enough to dispose of Turner's allegation that there is an increased incidence of AUB associated with Essure.

1501 Mechanisms by which it is alleged that Essure gives rise to a risk of AUB turn on the hypothesised capacity of the devices to cause persistent pathologic chronic inflammation and/or to affect uterine tissue. These allegations are theoretical in nature and are not supported by direct evidence.

1502 Korda's oral evidence concerning the mechanism or relationship between the Essure devices and new or increased menorrhagia or AUB was that it was not caused by inflammation in the fallopian tube. That evidence is directly inconsistent with parts of the causation mechanism alleged by Turner.

1503 Korda proposed what he described as two 'possible mechanism(s)' for why Essure devices were a cause of AUB: first, that the inflammatory process extends to the lining of the uterus causing endometritis; second, that the portion of the device protruding into the uterine cavity causes irritation of the lining of the uterus and an inflammatory response, resulting in bleeding. The only evidence Korda referred to as supporting these possibilities was the 522 study interim results, which he said showed a higher incidence of abnormal bleeding in women wearing Essure devices by comparison to those who had laparoscopic tubal ligation.

1504 There is no evidence that Essure causes endometrial inflammation or endometritis.

1557 SBM.500.001.0003_2 at 796 [3.35].

Further, as As-Sanie said, there was no evidence of which she was aware that suggested local inflammation in the site of a foreign body could spread like an infection caused by bacteria. For these reasons, Korda's evidence that AUB could be caused by insertion of Essure devices ought not be accepted.

Analysis

CPP and dysmenorrhea

1505 I conclude that Turner has not established that Essure can cause chronic inflammation resulting in CPP and dysmenorrhea by any of the mechanisms on which she relies.

1506 Most of my reasons for this conclusion are set out in the preceding Chapters. I further summarise those reasons as follows.

1507 First, for reasons set out in Chapter XV, the comparative studies weigh in favour of there being no increased risk of CPP and dysmenorrhea associated with Essure. That was the conclusion As-Sanie reached from her analysis of the comparative studies, supported by her own clinical experience. Gordon and Korda both accepted in cross-examination that the studies were of evidentiary value, and that they weighed in favour of Essure not causing an increased risk of pain. The epidemiological evidence was a very significant barrier to Turner's causation case succeeding.

1508 Application of the Bradford-Hill criteria does not assist Turner's causation case. The epidemiological evidence does not show an increased risk estimate associated with Essure above the accepted comparator, laparoscopic tubal ligation. There is no relevant dose response effect. Given how common pelvic pain and dysmenorrhea are among reproductive-aged women, it is of limited relevance to consider cases where symptoms commenced some time after Essure implantation. The comparative studies and As-Sanie's analysis show that outcomes consistently do not support causation.

1509 The plaintiffs in *Seltsam*, *Ellis* and *Merck* failed despite there being epidemiological evidence that supported a finding of general causation. That is because the evidence only established the possibility, and not the probability, of causation in circumstances

where no clinical test was available to distinguish between possible causes. The evidence in Turner's case is weaker. The epidemiology weighs against general causation. There were numerous other possible causes of the common diagnosis of CPP. There is no evidence of clinical test outcomes or some other objective signal that weighs heavily in favour of Essure being a cause of CPP and dysmenorrhea.

1510 The remaining evidence that Turner relied on to establish general causation is far from compelling. I note the final comments made by As-Sanie in the gynaecology concurrent evidence session dealing with CPP and dysmenorrhea:

> … there have been a lot of hypotheses presented in the various expert reports and I don't necessarily agree with all the hypotheses and haven't actually seen any data to support it … as a clinician who spends a lot of time talking to patients about potential causes of pain, part of my primary goal is to both validate their symptoms but not to provide misinformation … I think it's critically important to tell patients or other - you know, hypotheses should be investigated but there is a very negative impact of propagating misinformation that's not based on scientific data … that's where I base [my] assessment of the data.
>
> The six comparator studies?---Well in general whenever I make a decision or recommendation it's going to be based on the evidence and this was the evidence that I identified for this particular study and I guess I just wanted to bring up that hypotheses are good but we can't make clinical decisions or recommendations based on hypotheses that there aren't, that there's no data to support it.[1558]

1511 Second, the histological evidence does not weigh heavily in favour of causation. For the reasons set out in Chapters XI and XII the mere presence of inflammation reported in those studies provides only very limited support for the contention that Essure can cause pathologic, ongoing chronic inflammation in the fallopian tubes of some women.

1512 The third issue concerns the relationship between inflammation and pain. As-Sanie was cross-examined about her opinion regarding the causal relationship, if any, between Essure and persistent pain. She said that inflammation needed to be

[1558] T2613-4 (TRA.500.028.0001_2 at 0076_29–0077_18).

'persistent and repetitive' to be a cause of pain.[1559] As-Sanie was asked:

> I take it then you would agree that in the case of inflammation that is found to be persistent, it may well cause pain?---In some situations. I mean there are certainly situations where we see inflammation that patients have no symptoms at all, so I don't think it is necessary, nor sufficient.[1560]

As-Sanie was asked:

> In effect what you say is you need, in order for you to be satisfied, sufficient data to make the extra connection for you to draw the inference between causality and pain, if we're talking about the Essure Device?---Do I want data to guide my opinion? Is that what you're saying?
>
> Yes?---Yes, I would hope that all scientists would want data to guide their opinion.
>
> …
>
> But you agreed with my proposition before that if it was proven in some women to be persistent, then that may well be a cause of pain?---No, I don't see the data that would suggest that and, as I just said previously, if patients aren't experiencing persistent, a higher level of persistent pain, compared to those with tubal ligation, then I don't see the causal relationship.
>
> But as a matter of scientific principle you agreed before that if someone has persistent inflammation it may well cause pain, yes?---It is biologically plausible, yes.[1561]

As-Sanie was the preeminent expert at trial in relation to pain. I accept her evidence.

1513 Sokol gave evidence to the same effect from an immunologist's perspective. While she agreed that inflammation can cause pain, she added that there was a lack of evidence linking Essure with the chronic production of cytokines, and that the evidence in Rubin 2020 and Valle 2001 suggests there was no link between pelvic and abdominal pain and fallopian tube inflammation.

1514 A finding that ongoing chronic inflammation is present in some cases beyond the expected time for resolution of the foreign body response to Essure, or that it is biologically plausible for persistent ongoing chronic inflammation to cause or

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1559 T2571 (TRA.500.028.0001_2 at 0034_4).
1560 T2571 (TRA.500.028.0001_2 at 0034_9-14).
1561 T2571-2 (TRA.500.028.0001_2 at 0034_21–27, 0035_7–16).

exacerbate pelvic or abdominal pain, is not sufficient to establish that the inflammation in the fallopian tube will cause pain.

1515 Fourth, there is little if any evidence in the Essure histological studies, or from any other source, indicating that the observed chronic inflammation is pathologic and likely causing adverse health outcomes. As I have previously observed, there are no reported findings of chronic wounds, abscesses, tissue necrosis, rampant neovascularisation, swelling or fever. There is no evidence that the clinical tests for active chronic inflammation about which Sokol gave evidence have been administered, let alone with positive results.

1516 Fifth, it is possible that corrosion of metal ions and particles from Essure devices has caused or contributed to active chronic inflammation. Corrosion, in particular of tin particles from the solder joint, may be a feature of the device affecting the kinetics of the normal foreign body response. However, the possibility that corroded metal ions and particles from the device could cause or contribute to an active inflammatory response did not, without more, establish the likelihood that in some cases that response would be ongoing and pathologic.

1517 Sixth, I have concluded that there is no evidentiary substance in the other chronic inflammation mechanisms theorised by Robertson and Chrzanowski. There was no reason to suppose that any of the theorised mechanisms resulted in an increased risk that Essure would cause ongoing pathologic chronic inflammation in some women.

1518 Seventh, in support of her opinion that Essure is a cause of chronic inflammation resulting in CPP and dysmenorrhea in some women, Robertson has placed some weight on the causation studies and the MAUDE database on the basis that they 'align' with her opinion. Logically, it is difficult to see how that evidence lends any real support to Robertson's causation opinion. Given the prevalence of pelvic pain, dysmenorrhea and the conditions that may be a cause of those symptoms, a database record of complaints of new or increased pain following the Essure procedure, or

studies that show a reduction in reported symptoms following Essure removal by salpingectomy or hysterectomy, are not particularly meaningful unless other causes for symptoms have been identified and eliminated and a control group of non-Essure patients is included for comparison. The comparative studies that used appropriate biostatistical methods and made serious attempts to control for confounding factors did not demonstrate any material increase in risk of pelvic pain and dysmenorrhea associated with Essure by comparison to laparoscopic sterilisation. I have concluded that no significant weight should be attached to the causation studies in relation to this issue.

1519 Eighth, As-Sanie relied on her considerable clinical experience, that includes treating a significant number of women with Essure, to support her conclusion that there is no causal connection between the device and CPP and dysmenorrhea. Rosen's clinical experience also lends support to that conclusion. The limited evidence given by Korda about the six women with Essure he has treated gave no real support to Turner's causation case. I have concluded in Turner's case that her gynaecological symptoms were not caused by Essure. There is no clinical evidence of substance that the device causes CPP or dysmenorrhea.

1520 Ninth, it was necessary to determine causation in the context of an agreement by the experts that pelvic pain and dysmenorrhea are commonly experienced by women of reproductive age; that there are a broad range of conditions that may cause those symptoms, many of which are themselves common; and that it is not uncommon that a cause of a woman's pelvic pain will not be identified.

1521 Turner has not particularised the degree of any risk to women implanted with Essure that they would develop ongoing chronic inflammation resulting in CPP and/or dysmenorrhea. Robertson's evidence about the degree of risk women faced has varied. In her primary report, Robertson said that in the vast majority of women, the

foreign body response to Essure would resolve without complication.[1562]

1522 In the immunology JER, Robertson said:

> … that in the context of the Essure Device, the Device was designed to provoke inflammation, and there is evidence that the foreign body response to a Device often fails to completely heal and becomes stalled in the inflammatory phase. [I consider] there is compelling evidence of this in many women. [I consider] that in the case of the Essure Device, both host and Device factors affect the likelihood of the tissue response to the Device becoming stalled in the inflammatory phase.[1563]

1523 In cross-examination, Robertson said there was compelling evidence that in many women the foreign body response to Essure devices did not successfully complete. Robertson was challenged about her use of the words 'often' and 'many' in the immunology JER. She said:

> If you've put a device in 750,000 women and even 10 per cent of those women have an adverse response, that's 75,000 people, and in my mind that is perfectly adequate to be often and many.[1564]

Robertson then agreed that there was not enough data to say that 10% of women with Essure suffered adverse health outcomes. She said, however, that 50% of the women in the Essure histological studies showed evidence of being adversely impacted by the device, and that it would not be unreasonable to generalise that about the same proportion of women with similar clinical conditions might also be affected.[1565] The premise for Robertson's opinion about the degree of risk has not been established. There is no convincing evidence in the histological studies of women being adversely impacted by the device.

1524 I accept the defendants' submission that the lack of precision in this evidence is a further demonstration that Turner has failed to prove that Essure can cause CPP and dysmenorrhea.

1525 Considering all of the evidence, I am not satisfied that there is a risk of Essure causing

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1562 Robertson at 11-12 [3]-[7], 80 [300]-[301] (EXP.001.001.0127_2).
1563 Immunology JER at 4 (EXP.500.001.0004 at p 4).
1564 T4005 (TRA.500.040.0001_2 at 0015_27).
1565 T4007-8 (TRA.500.040.0001_2 at 0017_27-0018_11).

ongoing chronic inflammation resulting in new or increased CPP or dysmenorrhea.

AUB

1526 My reasons in relation to causation of CPP and dysmenorrhea are equally applicable to AUB. The following further matters are relevant.

1527 First, Bouillon 2018 found a lower incidence of AUB after hysteroscopic sterilisation compared to laparoscopic sterilisation. The study covered most of the French population for a four-year period. Gordon did not criticise the biostatistical methods used in Bouillon 2018 in relation to AUB. The outcomes of other comparative studies are not inconsistent with Bouillon 2018. If anything, the epidemiological evidence is an even more significant barrier to a finding of causation in relation to AUB.

1528 Second, the mechanisms proposed by Korda and Robertson are inconsistent. Korda proposed that coils of the device trailing into the uterus could irritate the endometrium causing endometritis resulting in AUB. Korda did not say that inflammation in the fallopian tube in response to implantation of the Essure devices was causally relevant to the development of AUB. The foundation of the mechanisms proposed by Robertson was local fallopian tube immune response to Essure.

1529 Third, there is no evidence of endometritis or other inflammatory signs in the uterus related to or caused by Essure. In this regard, Turner referred to a single case reported in the annual PMA reports as follows:

> **Pt. S2000-44-020**
> The patient had bilateral Essure placement on 7116/00. She reported heavy periods since 1/9/01. The hysterectomy was done on 10/16/02, making wearing time 27 months. The uterine specimen showed the cervix to be unremarkable. There was chronic endometritis with focal breakdown of the endometrium. The myometrium was unremarkable. Both fallopian tubes revealed dense fibrosis with near total to total occlusion. There was mild chronic inflammation and no acute inflammation. Severe disruption of the epithelium and lamina propria was present in both tubes.[1566]

The identification of endometritis in a woman with Essure devices, without more, says

[1566] BAY-ESSURE-0028999_R at 574.

nothing about whether there was a relationship between the two. The evidence of this histological analysis does not assist Turner's case.

1530 In oral evidence, Korda said that his AUB causation opinion was 'speculative' and 'based on what [he understood] about the way medicine works and pathology develops'.[1567] Korda accepted that his opinion was a hypothesis which had not been established by evidence.

1531 Fourth, as set out elsewhere in these reasons, AUB is 'a very common condition' affecting women of reproductive age.[1568] The experts agreed that there are multiple causes of menstrual bleeding conditions. In relation to this topic, Korda said:

> We know that there is a whole body of women who have what's called dysfunctional bleeding where no diagnosis is made and we don't know what causes the bleeding.[1569]

1532 Fifth, As-Sanie's clinical experience does not support any causal connection between Essure and an increased risk of AUB.

1533 Sixth, the experts called by Turner were completely unable to articulate in any cogent way the degree by which Essure leads to an increased risk of AUB. I accept the defendants' submission that in the context of the evidence in this case, this inability is relevant to whether the theorised risk exists.

1534 The evidence does not establish a risk that Essure can cause new, increased or worsened AUB.

Fatigue, breakage and fragmentation

1535 Turner submitted that two mechanisms led to the risk of the Essure device fatiguing and breaking in vivo. First, corrosion of the solder joint led to the risk of the Essure device coming apart. Second, multiaxial loading on the device meant that there was a risk of fatigue causing it to break. Turner argued there was a risk that a device that

1567 T2618 (TRA.500.028.0001_2 0081_20).
1568 Gynaecology JER at 15 [52] (EXP.500.001.0001).
1569 T2615 (TRA.500.028.0001_2 at 0078_21–24).

broke or fragmented would cause injury to internal organs and more disseminated chronic inflammation in the pelvic cavity, and may give rise to the need for surgical removal.

1536 Turner relied on data recorded in a Clinical Evaluation Update Report dated 28 September 2018, prepared by Bayer ('2018 CEUR'). The report contains a table of adverse event reports received by Bayer in 2017. One line item in the table is described as 'device breakage', with a total of 589 cases recorded.

1537 In his primary report, Chrzanowski said that while the fatigue characteristics of nitinol were relatively good, multiaxial loading present in the case of Essure raised the prospect of mechanical movements causing fatigue fracture. He said that '[s]ince the fracture of the device was reported, in [his] view the Essure device is adversely affected by fatigue'.[1570] In a supplementary report, Chrzanowski said that Goodwin 2023 'showed substantial corrosion of the solder that increases substantially the risk of the loss of the integrity of the Essure device'.[1571]

1538 Turner submitted that Eiselstein's evidence that reports of device breakage were 'more likely' to be the result of 'pulling the device apart' on removal, rather than being caused by fatigue and breakage in vivo, was speculative.[1572] Turner submitted that the reported instances of device breakage, including in the 2018 CEUR, were not attributed to device removal. She submitted that those reported incidents supported Chrzanowski's evidence that Essure is in fact susceptible to fatigue and eventual fatigue fracture, particularly having regard to it being implanted permanently in the fallopian tube.[1573]

1539 In his primary report, Eiselstein defined fatigue as 'the tendency of a material to break under repeated stresses'.[1574] He said that Chrzanowski had provided no evidence that

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1570 Chrzanowski (EXP.001.002.0012).
1571 Chrzanowski at 3 (EXP.001.002.0019).
1572 T4494-5 (TRA.500.045.0001_2 at 0064-5).
1573 SBM.001.001.0004 at 97-8.
1574 Eiselstein at 22 [4.6] (EXP.001.002.0004).

stainless steel or nitinol are subjected to cyclic stresses or strains at a level and/or frequency that could induce fatigue fracture.[1575] Eiselstein disagreed with the implication in Chrzanowski's report that Essure is adversely affected by fatigue. He noted that there had been no confirmed fatigue fractures with the Essure device, and that there was 'no indication that fatigue loading (multiaxial or not) [had] sufficient loading (stress or strain) amplitude and frequency to cause fatigue fractures'.[1576] Eiselstein said:

> I disagree with Dr Chrzanowski on fatigue. Indeed, this is a permanently implanted device; however, simply stating that since there is a likelihood of mechanical movement does not imply that fatigue fracture or failure will occur. Nor is "some possibility of fatigue fracture" very quantitative or concerning as many engineered products are subjected to alternating forces, strains, and stresses for the life of the product without experiencing fatigue failure. For fatigue failures to occur, there must be a sufficiently large amplitude force or strain/stress applied enough times (generally millions of cycles are required) to the device to initiate a fatigue failure[.] I have looked in the technical literature to see what biomechanical forces or strains might be exerted to the fallopian tubes and was not able to find any such information. Dr. Chrzanowski states that documentation was provided to him regarding fractures; however, he does not reference these documents. I have not seen any such documentation in which a device was fractured in situ versus broken upon removal. Although I think the likelihood of a fatigue failure is unlikely for the reasons I gave above, to distinguish the difference between fracture initiated upon removal versus in situ fatigue would at the least require a microscopic examination of the fracture surface, and I have not seen any such examination. Such examinations are typically done on fractures, as discussed by several studies.[1577]

1540 Chrzanowski and Eiselstein agreed that there was a need to review documents supporting the information contained in the 2018 CEUR table, to determine whether there was any evidence to support fracture or breakage prior to or during removal. They said that this could include radiography to determine whether there had been any loss of mechanical integrity of the Essure device.[1578] In the biomaterials JER, Eiselstein said that he had reviewed the table in the 2018 CEUR and had:

> … not seen any evidence of breakage, fragmentation or fracture of the device other than what occurs during insertion or removal. [I do] believe that the

1575 Ibid at 86 [10.3.2].
1576 Ibid at 88 [10.5.1].
1577 Ibid at 88 at [10.5.2].
1578 Biomaterials JER at 29 (EXP.500.001.0006).

> forces generated during improper insertion or removal are likely much higher than when properly inserted. Also, if removed after the device has been implanted for several weeks it is likely to be embedded in the fallopian tube requiring significant force to remove.[1579]

1541 Chrzanowski said:

> … that if the breakage occurs during the insertion or removal, it indicates that either (i) substantial forces that far exceed properties of the surrounding tissues act on the devices during these procedures, or (ii) the Essure Device has either metallurgical defects or substantially loses its mechanical properties properties during its use. [I agree] that micrographs or the inspection of the fractured Essure Device would be required to assess the mechanism of the fracture.[1580]

1542 In cross-examination on this issue, Eiselstein said that '[he had] seen no evidence of any fatigue or fracture or cracking, stress corrosion cracking, on any of these devices',[1581] and that the reported cases of device breakage were most likely the result of damage done when the device was being extracted from the fallopian tube. It was put to Eiselstein that his evidence was just speculation, and he said:

> It is based on my understanding of the fatigue of stainless steel and the fatigue of nitinol. I've done quite a bit of work in that area, and given that these devices are so thin, it's very difficult to think that you could possibly generate a sufficient amplitude and frequency of loading that would result in any sort of fatigue or fracture of this device.[1582]

1543 Chrzanowski expressed the risk of fatigue fracture and breakage of the Essure device as a possibility which has not been excluded. His evidence is not sufficient to establish that fracture or breakage of the nitinol or stainless steel components of Essure occurs in vivo. For the following further reasons, I conclude that Turner has not established a risk of fatigue, breakage or fragmentation of Essure resulting in organ damage or disseminated chronic inflammation.

1544 First, Chrzanowski and Eiselstein agreed that nitinol and stainless steel have good fatigue strength.

1545 Second, as Eiselstein observed, there is no evidence of the forces that would be

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1579 Ibid.
1580 Ibid.
1581 T4494 (TRA.500.045.0001_2 at 0064_2).
1582 T4495 (TRA.500.045.0001_2 at 0065_7).

necessary to result in fatigue failure or breakage. Further, there is no evidence that Essure is subject to forces of sufficient amplitude and cycles to result in fatigue failure when implanted in the fallopian tube. I accept Eiselstein's evidence that this is very unlikely to be the case.

1546 Third, Chrzanowski and Eiselstein agreed that the fractured components of a device would need to be examined in order to determine the reason for failure. There is no evidence that this occurred in the case of the reports of device breakage recorded in the 2018 CEUR, or on any other explanted Essure device.

1547 Fourth, I accept Eiselstein's evidence that, at least in some instances, significant force is likely to be applied to devices in the process of explantation. Korda, As-Sanie and Robertson all said that there was a risk of fracture and breakage of the device on surgical removal by salpingectomy.[1583] There is some confirmation of this in Goodwin 2023, where the stainless steel inner coil of the device was, in some cases, stretched or unwound during removal. Further, in Chene 2019, a number of devices were broken in the process of removal.

1548 Fifth, contrary to Turner's submission, the 2018 CEUR data appears to refer to breakage in the process of device insertion and on removal. I could not find any reference in the report to instances in which breakage occurred during the period of device wear.

1549 Finally, I conclude that the evidence has not established, as a matter of probability, that corrosion of the solder joint risks the components of the Essure device coming apart in vivo. There is no evidence of this having occurred. It is likely that tissue ingrowth and fibrosis would maintain the components of the device in position after the solder join was weakened by corrosion.

1550 Turner has not established that implanted Essure devices can cause injury as a result

1583 Gynaecology JER at 17 (EXP.500.001.0001); Robertson at 190 (EXP.001.001.0127_2).

of fatigue, breakage and fragmentation during the period of wear.

Migration and expulsion

1551 Turner submitted that the evidence showed there was a risk of migration of the Essure device. She submitted that this risk was supported by evidence of fallopian tube peristalsis, the lack of integration of the device with adjacent tissue, the risk of device breakage, and the possibility of incomplete fibrosis which impacts device fixation.

1552 In the biomaterials JER, the experts agreed:

> … that the term 'migration' refers to macro movements of the device of a few centimetres or more, within the tube, into the uterus, and/or through the wall of the tube into the peritoneal cavity. We agree that the medical literature reports compelling evidence of migration (macro movement) of the device, although this is not common and occurs in only a small subset of women.[1584]

1553 Robertson said:

> that an incomplete foreign body response is likely to promote the chances of migration, because the extent of anchoring in the surrounding tissue can be compromised if fibrosis is incomplete or a capsule forms[.] She also considers that the natural peristaltic activity of the fallopian tube would promote the likelihood of device migration[.][1585]

1554 Chrzanowski said that migration of the Essure device could be caused by multidirectional forces acting on the device and differences in stiffness between the device and surrounding tissues.[1586]

1555 Badylak gave three reasons for disagreeing with Robertson and Chrzanowski. First, he said that after the device is deployed, it is embedded within the wall of the fallopian tube which prevents macroscopic movement in either the proximal or distal direction. Second, the deposition of fibrotic tissue would then envelop and secure the device in place.[1587] Third, insertion of the Essure device would cause cessation of peristalsis in that section of the fallopian tube.

1584 Biomaterials JER at 29 (EXP.500.001.0006).
1585 Ibid.
1586 Ibid.
1587 Ibid at 30.

1556 In the gynaecology JER, Korda and As-Sanie agreed that relevant studies suggest the rate of migration of the Essure device is less than 0.5%,[1588] and that the rate of expulsion is between 0.05% to 2.9%.[1589] Korda and As-Sanie said:

> The experts agree that migration, expulsion, and perforation are all intrinsic risks associated with the placement of a foreign body into the human body and are not specific design failure of the Essure device. The experts agree that with increased surgeon skill and experience in placement of the Essure device, the risk of migration, expulsion and perforation are lower.[1590]

As-Sanie used 'migration' to describe the Essure device moving into the abdominal cavity, and 'expulsion' to refer to the device moving into the uterus and the cervix and out of the vagina to be 'expulsed' out of the body.[1591]

1557 In her primary report, As-Sanie summarised the results of studies that considered the frequency of Essure migration:[1592]

> The FDA similarly analyzed data on migration with Essure (2015 FDA Executive Summary, p. 60):

Article	Country	n	Migrations
Arjona[27]	Spain	1630	3 migrations to the abdominal cavity
Aparicio-Rodriguez-Minon[34]	Spain	517	1 case: migration of both devices into abdomen
Grosdemouge[41]	France	1061	8 migrations (location not specified)*
Panel[42]	France	382	5 migrations: 1 peritoneal cavity, others unspecified
Povedano[36]	Spain	4306	2 asymptomatic migrations into abdomen
Rios-Castillo[54]	Spain	1321	1 (location not specified)*
Thiel[56]	Canada	610	14 proximal or distal migrations noted on HSG*
Gerritse[78]	Netherlands	100	1 migration to the abdominal cavity

*May have included migration within the fallopian tube, or expulsion into the uterine cavity

> Additional studies published after FDA's 2015 assessment include the following:
>
> a. Kamencic (2016): In 1,430 patients who had Essure followed by a subsequent surgery, 8 appeared to have pain attributed to perforation or migration of the microinsert (0.5%).

1588 Gynaecology JER at 7 [7] (EXP.500.001.0001).
1589 Ibid at 7 [9].
1590 Ibid at 7 [10].
1591 T2466 (TRA.500.027.0001_2 at 0024_16-9).
1592 As-Sanie at 32 [112]-[113] (EXP.001.002.0005).

b. Franchini (2017): In 1,968 patient who had Essure, 4 perforations and 1 expulsion were detected by hysterosalpingography 3 months after the Essure placement.

1558 As-Sanie also tabulated the outcomes of studies into the rate of Essure expulsion:[1593]

The following clinical trials and large-scale observational studies investigate device expulsion:

Study Design	Study	Outcome
Essure Clinical Trials (FDA Executive Summary 2015, p. 16)	Phase II	0.5% (1/206) expulsion rate
	Pivotal Trial	2.9% (14/476) expulsion rate
	"TVU" Study	1.2% (7/597) could not rely on Essure at confirmation testing due to perforation, expulsion, distal placement, or proximal placement
Single-Arm Studies	Veersema (2011)	Of 1,145 subjects who received sterilization with Essure, there were two expulsions at HSG confirmation testing (0.17%).
	Povedano (2012)	In 4,108 women with Essure who completed 3 months of follow up, there were 19 expulsions (0.46%)
	Câmara (2017)	Out of 1,064 patients with Essure, there were four expulsions (0.39%), two of which were on the same day as insertion.
	Francini (2017)	Out of 1,968 patients with Essure, there was one expulsion (0.05%)

1559 Turner again relied on the 2018 CEUR, which she submitted showed numerous instances of device migration and dislocation. The table of adverse event reports in the report records 1,870 adverse event reports of device dislocation in 2017. Those numbers are further categorised in the following table from the report:[1594]

Table 4.7-8: Categorization of Unsatisfactory device location reports by PT

Preferred Term	Total number of cases
Device Expulsion	316
Uterine Perforation	424[a]
Fallopian tube perforation	315
Perforation	572
Embedded Device	147
Device Dislocation[b]	1870[b]
LLT Device Migration	1353

[a] Excluding 33 cases coded under LLT: uterine perforation post procedural, which are discussed in Section 4.7.1.8.
[b] Includes cases of device migration.

1593 Ibid at 33 [116].
1594 BAY-JCCP-1120549 at 114.

1560 Turner relied on the following explanation of terms set out in the 2018 CEUR:

> Device migration is defined as the movement of an Essure insert from what appears to be an appropriately placed location (i.e., spanning the interstitial portion of the fallopian tube) at the conclusion of the placement procedure to another anatomical location. It is not used to describe inserts that were placed in unsatisfactory devices locations such as within the abdominal or pelvic cavity. Many reporters use the terminology of migration without any knowledge of the original position of the insert. Bayer relies on the reporter's terminology and therefore codes for device migration based on the verbatim provided.
>
> Device dislocation is used for the remaining scenarios when an unsatisfactory device location is reported, for example, an unsatisfactory confirmation test, or tubal patency with no information regarding device location. Reports of device migration (LLT) code to device dislocation (PT) within MedDRA.[1595]

The report explained that the term 'device dislocation' is very broad and 'can be applied to any insert that is not documented to be in a satisfactory location according to the criteria in the IFU'.[1596]

1561 The adverse event reports in the 2018 CEUR come from various sources. The following further detail was given of the device dislocation numbers:

> There were 316 cases reporting device expulsion of which approximately 70% were non-medically confirmed and 64.87% were reported by lawyers. 77% of the device expulsion cases were classified as incidents. The reason for the relatively high number of these cases being reported as incidents is that an operative procedure for device removal was performed. Often this procedure was a hysterectomy or a salpingectomy, neither of which should be required for an expulsed device that typically can be removed via hysteroscopy.
>
> There were 1870 cases reported with the PT of device dislocation of which 144 (7.7%) were medically confirmed. 97.2% of the device dislocation cases were classified as incidents. A further breakdown of the 1870 events in which the preferred term of device dislocation was reported revealed 1353 events of device migration. The majority of these reports (96.15%) were legal cases in which the vague term "migration" of the Essure device was reported; in several of these cases a perforation was also reported. Only 28 out of the 1353 (2%) cases reporting device migration were medically confirmed.
>
> The overall reporting rate of unsatisfactory device location in the time period of this CEUR was 19.12% (based on worldwide sales of 15626 kits during 2017) which is higher than last year's rate, as sales (used as denominator in the calculation) declined considerably and at the same time the number of reports (numerator) rose mainly due to solicited reporting and legal claims received in

1595 Ibid at 113.
1596 Ibid at 114.

2017, many of them referring to events which occurred in previous years. Since calculating a rate based only on the sales for 2017 is not a valid representation of the rate of events reported, cumulative events divided by cumulative sales are also provided from the beginning of the product history through 31 DEC 2017 to provide an additional perspective to assist in the interpretation of the data (Table 4.7-9).

Table 4.7-9 Rates of Unsatisfactory device location for the time period of this CEUR and cumulative rates from the beginning of the product history through 31 DEC 2017 expressed as cases/sales.

Preferred Term	Interval reporting rate (%)[a]	Cumulative reporting rate (%)[b]
Device Expulsion	2.02	0.18
Uterine Perforation	2.71	0.14
Fallopian tube perforation	2.02	0.14
Perforation	3.66	0.06
Embedded Device	0.94	0.05
Device Dislocation	11.97	0.4
LLT Device Migration	8.66	0.17

[a] based on worldwide sales of 15626 kits during 2017

[b] based on worldwide cumulative sales of 11,41,598 kits.

It can be seen that the event rates for the time period covered in this CEUR are increased relative to the cumulative rates across all categories of unsatisfactory device location. This is related to the reporting of events from previous time periods and the decline in sales during the period covered by this CEUR.[1597]

1562 Most of the reports were not medically confirmed. Vagueness in the terms 'migration' and 'device dislocation', and the lack of medical detail, means there is significant uncertainty about what was being reported. The fact that most reports were from lawyers suggests an adversarial feature to the reporting. The unexplained difference to the cumulative reporting rates means there can be no confidence that the 2017 rates are accurate. Further, the rates are fundamentally inconsistent with the outcomes of the studies referred to by As-Sanie. I conclude the 2018 CEUR data for 2017 significantly overstates the rates of migration and expulsion. No conclusion can be reached about the rates of device migration or expulsion based on the data.

1563 Next, the defendant submitted that the evidence did not demonstrate that where migration or expulsion occurs, it leads to material harm (perforation, which may be

1597 Ibid.

associated with expulsion or migration, is dealt with later in these reasons).[1598]

1564 Korda said that the consequences of intraperitoneal migration of the Essure device was the prospect of an unplanned pregnancy, either intrauterine or ectopic, and the likely need for further gynaecological surgery.[1599] He said that, as Essure was designed to produce acute and chronic inflammation, upon expulsion or migration the device may damage the abdominal cavity or the site of migration.[1600] For example, if the device migrated and attached to the bowel, it may cause inflammation at that site which could theoretically cause obstruction or perforation of the bowel.[1601] Major surgery would then be required to remove the device.[1602]

1565 Korda said that by contrast, a Filshie clip is an inert device which is designed to occlude the fallopian tube externally and does not cause a significant inflammatory response.[1603] He said that while a Filshie clip may migrate, it is very rare for it to cause harm upon migration or cause any inflammation, pain or discomfort.[1604] Korda said that whether or not a clip requires removal is dependent on the location of the device.[1605] He said that major surgery is required if a clip migrates near the liver. However, the migrated clip does not usually cause any abnormalities or problems and can be left in situ.[1606]

1566 As-Sanie said that while there are a wide range of possible consequences associated with expulsion and migration, most patients experience limited consequences of those risks and no injury to other organs. She said that migration of an Essure device:

> … does have a risk of causing an inflammatory response and/or damage to those internal organs, but the reality is in both the literature, as well as my clinical experience, the vast majority of patients that experience it are actually asymptomatic and we found it incidentally, like at time of imaging or looking

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1598 SBM.500.001.0003_2 at 753.
1599 Korda at 17 [6.1.15] (EXP.001.001.0025).
1600 T2455 (TRA.500.027.0001_2 at 0013_7-11).
1601 T2456 (TRA.500.027.0001_2 at 0014_15-22).
1602 T2455 (TRA.500.027.0001_2 at 0013_26-29).
1603 T2456 (TRA.500.027.0001_2 at 0014_25-30.
1604 T2457 (TRA.500.027.0001_2 at 0015_7-8).
1605 T2457 (TRA.500.027.0001_2 at 0015_17-18).
1606 T2457 (TRA.500.027.0001_2 at 0015_24-28).

> for the device for another reason. So many patients don't have symptoms. Having a negative consequence like injury to the bowel, injury to the bladder is incredibly rare.[1607]

As-Sanie said if an Essure device is found to have migrated, surgical removal by laparoscopy is offered because '[u]nderstandably patients don't wish to have a device that is not in the correct spot'.[1608]

1567 I conclude that there is a low risk of migration or expulsion of Essure following implantation. I accept the evidence of Korda and As-Sanie as to the degree of that risk.

1568 I conclude that some recorded cases of migration or expulsion are likely to be the result of error by the physician in placement of the device in the fallopian tube. There is no evidence of the proportion of migration events that are the result of physician error. I accept Badylak's evidence that when the device is properly located it is embedded within the wall of the fallopian tube and becomes fixed in that position by the deposition of fibrotic tissue.

1569 I accept As-Sanie's evidence, based on her clinical experience and a review of the literature, that in most cases women experience few if any adverse consequences from device migration. Surgical removal by laparoscopy is likely to be offered if it is discovered that a device has migrated into the peritoneal cavity. As-Sanie and Korda agreed that if a device migrated into the peritoneal cavity it may become attached to another organ and require surgical removal. I accept that in such a case there is the potential for more serious health consequences. However, neither As-Sanie nor Korda was aware of such a case in their own practice or in the scientific literature. I was not taken to evidence of any reported cases of this occurring. I accept As-Sanie's evidence that such an outcome 'is incredibly rare'.

Perforation

1570 Turner's case is that the risk of perforation arose as a consequence of the risk of device

1607 T2464 (TRA.500.027.0001_2 at 0022_22-31).
1608 T2645 (TRA.500.027.0001_2 at 0023_4).

breakage, fragmentation and/or migration, as the device or its fragments can penetrate soft tissues of the organs with which they come into contact.[1609] Turner has not established a risk of breakage, fatigue failure or fragmentation of Essure during the period of wear. The only evidence of breakage of fragmentation is during device removal and possibly insertion. The risk of perforation of organs or tissues following breakage or fragmentation can otherwise be dismissed.

1571 Korda and As-Sanie agreed that perforation generally occurs at the time of insertion, and involves the Essure device perforating through the uterus or fallopian tube.[1610]

1572 The defendants' summarised the reported perforation events from the Conceptus/Bayer clinical trials in a table that is reproduced below:[1611]

Clinical Study	Reported perforation events
Peri-hysterectomy Study	Only 3 of the 99 participants (3%) experienced a perforation during the Essure Insert procedure. The first perforation occurred with the use of the Support Catheter (an additional external catheter used to create more column strength and more forward placement during the Essure Insert procedure) which was discontinued in 1999. The second perforation in a patient who had prior tubal ligation (which was an exclusion criterion for the protocol) and was suspected to be the cause of the perforation. No etiology could be identified in the third patient to experience a perforation.
Pre-hysterectomy Study	3 of 63 patients (4.76%) reported tubal peroration were reported, all without clinical sequela. The Support Catheter referred to in the row above was used during the device placement of two of those patients and has since been discontinued.
Phase II Study	7 women (3.1%) experienced a perforation. The since discontinued Support Catheter was used with 5 of the 7 women (71.4%) who experienced perforations in the Phase II Trial.
Pivotal Study	The perforation rate for the Pivotal Trial was 1.1%, accounting for 5 of the 464 who had bilateral placement of the Essure Insert.

1609 SBM.001.001.0004 at 100 [280].
1610 T2454 (TRA.500.027.0001_2 at 0012_19-21); T2463-2 (TRA.500.027.0001_2 at 0021_29-0022_2).
1611 SBM.500.001.0003_2 at 774-5 [4.85].

ESS305 Post-Approval (or newly trained physicians) Study	2 of 584 patients (0.34%) reported perforation events.
SUCCES II Clinical Trial	Perforations were reported to arise in 24 of the patients (0.9%), consisting of 14 fallopian tube perforations (0.5%), and 10 uterine perforations (0.4%).
TVU Clinical Trial	5 of 597 participants (0.83%) reported perforations which were definitely or probably related to the Essure Insert.

1573 In her report, As-Sanie included an FDA summary of the rates of perforation in the published literature, which includes a number of single arm studies:[1612]

Author	Country	N	Perforations (%)
Aparicio-Rodriguez-Minon	Spain	517	1 uterine (0.2%)
Grosdemouge	France	1061	2 (0.2%)
Gerritse	Netherlands	100	1 (1%)
Langenveld	Netherlands	149	3 (2%)
Legendre	France	311	1 uterine (0.3%)
Levie	U.S.	578	2 uterine* (0.3%)
Panel	France	382	1 (0.3%)**
Povedano	Spain	4306	1 (0.02%)
Sakinci	Turkey	30	1 uterine*** (3.3%)
Sinha	U.K.	112	1 (1%)
Thiel	Canada	610	22 (33.6%)
Veersema	Netherlands	1145	7 (0.6%)

* one during insertion of hysteroscope
** underwent concomitant endometrial ablation
*** asymptomatic, identified at HSG

1574 Korda and As-Sanie agreed that the perforation rate recorded in the relevant studies was between 1.1% and 3.1%.[1613]

1575 Turner again relied on data from the 2018 CEUR to establish the frequency of perforation. The description in the report following the table reproduced at [1559]

1612 As-Sanie at 31 [111] (EXP.001.002.0005).
1613 Gynaecology JER at 7 [11] (EXP.500.001.0001).

above is as follows:

> There were 700 cases of uterine/fallopian tube perforation (39 cases with both fallopian tube and uterine perforation events); approximately 85% of these cases were non-medically confirmed legal reports. In addition 572 cases had unspecified perforations (e.g., Perforation of organs, perforation not otherwise specified-NOS) coded to the MedDRA PT: Perforation; the vast majority of these cases (97.7%) were legal. All events of perforation are currently classified as Incidents.[1614]

The difference with the cumulative reporting rates suggests that the 2017 rate may not be reliable.

1576 Korda and As-Sanie agreed, as to the risks associated with perforation:

> The experts agree that damage to internal organs is theoretically possible as a result of perforation following insertion. The experts agree that damage to internal organs is a risk of all surgical procedures of the abdomen and pelvis. The experts are not aware of any documented case of damage to internal organs caused by an Essure device.[1615]

1577 Korda said that the likely consequences of tubal or uterine perforation included pain, bleeding and the necessity for further gynaecological surgery.[1616]

1578 As-Sanie said that the risk of perforation is not unique to the Essure device.[1617] She said in her primary report:

> It is also important to note that perforation of the uterus is a known risk of procedures that involve placing an instrument or device within the uterus, such as all hysteroscopic procedures as well as IUD placement. Agostini (2002) reported a 1.6% risk of perforation during hysteroscopic surgery generally. Based on my clinical training and experience, the uterus is known to be a resilient organ and typically heals following these procedures without issue. For example, IUD perforations are quite common (I have observed far more IUD perforations than Essure perforations in my practice). The vast majority of the time, patients with IUD perforations do not have pelvic pain and instead become aware of the perforation due to abnormal bleeding or missing IUD strings. In these cases, surgery to remove an IUD is typically not an emergency procedure and removals can be scheduled weeks out from the visit in which imaging initially detected a migration or perforation.[1618]

1614 BAY-JCCP-1120549, p114.
1615 Ibid at 11 [36].
1616 Korda at 17 [6.1.14] (EXP.001.001.0025).
1617 T2465, (TRA.500.027.0001_2 at 0023_15-20).
1618 As-Sanie at 32 [115] (EXP.001.002.0005).

As-Sanie said the uterus is a resilient organ that in her experience typically heals following perforation. She said that while there are a wide range of possible outcomes following perforation, in most patients there are only limited consequences.

1579 I conclude that:

(a) the risk of perforation of the uterus or fallopian tube associated with Essure is likely to be in the range agreed by Korda and As-Sanie;

(b) perforation is most likely to occur at the time of insertion of the device, as agreed by Korda and As-Sanie;

(c) there is no recorded case of perforation occurring weeks or months after implantation of an Essure device;

(d) the rate of perforations associated with insertion of Essure is similar to other hysteroscopic procedures and the placement of IUDs;

(e) in most cases, perforations of the uterus or fallopian tube will recover without serious consequences. There are no documented cases of damage to other internal organs caused by an Essure device following perforation of the fallopian tube or uterus.

Corrosion and allergic/hypersensitivity reaction

1580 It is agreed that nickel ions released from an Essure device can cause DTHR in some women. For the reasons in Chapter XIII, Turner has not established any other mechanism by which corrosion from Essure can cause harm.

1581 In the immunology JER, Robertson and Sokol agreed:

> [W]e consider that the Essure Device could cause chronic or persistent chronic inflammation by a mechanism/s separate from the foreign body response. We agree that chronic or persistent chronic inflammation could arise as a consequence of a hypersensitivity reaction to Essure and/or its components (for example, nickel).[1619]

[1619] Immunology JER at 16 (EXP.500.001.0004).

1582 As discussed above at [813], Robertson and Sokol agreed on the definition of nickel hypersensitivity, and Robertson, Badylak and Chrzanowski agreed that this type of reaction could be generated by metal ions leached from a biomedical device.

1583 Robertson and Sokol agreed that sensitisation to nickel is different to nickel hypersensitivity/DTHR. They explained that sensitisation is marked by a presence of immune cells specific to nickel in the absence of clinical reactivity. They agreed that skin patch testing is the most common test for sensitisation. DTHR will only occur in a proportion of cases where there is a positive patch test.

1584 Sokol said that systemic contact dermatitis is a central clinical manifestation of DTHRs to implanted devices. She said it is characterised by diffuse dermatitis that temporally correlates with and persists after device implantation, and requires confirmation by evidence of sensitisation to a component of the device using patch testing or another method.[1620] DTHR may also manifest in other tissues of the body, including mucosal surfaces.

1585 Sokol said that hypersensitivity reactions to Essure were rare and had been reported in only 0.01% of cases, referring to a study by Zurawin and Zurawin ('Zurawin 2011').[1621] She said that these reactions can be treated using a combination of oral antihistamines and topical or systemic steroids.[1622]

1586 Robertson made three points about the risk of hypersensitivity reactions to Essure. First, she said a hypersensitivity reaction in response to a biomedical device may not result in a positive patch test or in symptoms of contact dermatitis. She said that there was no readily available test for hypersensitivity to nickel that manifested in tissue other than the skin.[1623]

1620 Immunology JER at 24 (EXP.500.001.0004).

1621 Robert K Zurawin and Jonathan L Zurawin, 'Adverse Events Due to Suspected Nickel Hypersensitivity in Patients with Essure Micro-Inserts' (2011) 18(4) *Journal of Minimally Invasive Gynecology* 475 (PUB.500.001.0105) ('Kurawin 2011').

1622 Sokol at 25 (EXP.001.002.0001).

1623 Immunology JER at 24 (EXP.500.001.0004).

1587 Second, Robertson said that as a result, hypersensitivity reactions to Essure are likely to have been significantly under-reported. Robertson said:

> Evidence for different repertoires of T cells with T cell receptors that react to different nickel haptens is reported for T cells recovered from people with orthopaedic implant failures, compared to people with contact dermatitis. This provides a clear indication that priming and sensitization can occurs in the joint wound site, and that different T cells are primed from those primed in the skin. The authors [of Zurawin 2011] attribute this to "the different availability of self peptides in these two different tissues."
>
> In my opinion, the very low rate of nickel hypersensitivity reported in this study of women with Essure Devices is a major underestimation. In my opinion, hypersensitivity to nickel may not be identifiable based on dermatitis or patch testing, if priming to nickel occurs via the fallopian tube. It is highly biologically plausible to have a local hypersensitivity to nickel that is not evident or detectable in the skin.
>
> In my opinion, absence of a positive patch test result (in the skin) does not rule out nickel sensitivity primed by nickel exposure in the fallopian tube. I expect this to occur because T cells primed to nickel in the fallopian tube are responding to different nickel haptens formed by interactions with proteins found in that site, and/or that T cells primed in the reproductive tissues do not traffick into the skin, and/or because anti-inflammatory mediators or cells exist that suppress a DTH reaction in the skin but not in the fallopian tube. Importantly, existence in the skin of anti-inflammatory mediators or cells that suppress a DTH response in a sensitized person does not imply that those same anti-inflammatory mediators and cells exist in the fallopian tube.[1624]

1588 When Robertson was cross-examined about Zurawin 2011 she said:

> They are measuring it by virtue of whether there's an impact in the skin and one of the very strange findings that people are unable to explain is why, if anything, women with Essure Devices appear to have this extremely low level of delayed type hypersensitivity to nickel when we know that 8.5 per cent of Australian people and a similar number of American women should test positive. So that on its own suggests that something very curious is going on, that the Essure Device is changing the immune response to nickel in some way, and from a biological perspective the most logical hypothesis around that is that there is a reproductive tract delayed type hypersensitivity reaction going on that impacts its manifestation in the skin.[1625]

Robertson said that the authors of Zurawin 2011 noted that the rate of 0.01% was an underestimation, and that they found that number 'very hard to reconcile with their

1624 Robertson at 129 [348], 130 [351]-[352] (EXP.001.002.0015_2).
1625 T4200 (TRA.500.041.0001_2 at 0118_7-20).

understanding of the immunology'.[1626] When challenged, Robertson acknowledged that the figure of 8.5% referred to a positive patch test, not hypersensitivity.[1627]

1589 The results of Zurawin 2011 are set out as follows:

> [T]he incidence of reported nickel-related reactions or complications from the Essure micro-insert remains far below the range of 18% to 24% in women with contact nickel allergy. Of the 436 937 Essure kits sold since its commercial release, there have been only 63 reported cases in which nickel hypersensitivity was suspected, or 0.014%, and none in clinical trials. It is safe to assume that these 63 cases represent underreporting of suspected nickel allergy cases. Even if the reporting of adverse effects were to be underestimated by several orders of magnitude, the Essure data demonstrate an almost negligible occurrence of proved nickel-related reactions.[1628]

The authors expressed the following conclusion:

> Even considering the possibility of underreporting by several orders of magnitude, the reported incidence of adverse events suspected to be related to nickel hypersensitivity in patients with Essure micro-inserts is extremely small (0.01%). The incidence of confirmed nickel reactions is even smaller. This very low incidence of clinical reactions is consistent with data from other nickel-containing implantable devices and is reassuring, raising the question of whether nickel reactions are clinically relevant in the use of nitinol-containing micro-inserts for hysteroscopic sterilization.[1629]

When it was put to Robertson in cross-examination that the conclusion of Zurawin 2011 was inconsistent with her construction of the article, she said:

> Well, I don't agree because I mean it was some time ago that I read this but my recollection is that they are mystified and unable to explain why it is so low.[1630]

Robertson noted that the authors expected that approximately 72,000 to 96,000 patients implanted with Essure would exhibit nickel sensitivity, based on the reported positivity rate of 18% to 24%. She said that while the outcome of Zurawin 2011 might be reassuring, 'it doesn't provide a solution to the biological quandary of what has happened to those 72,000 patients that should have been showing signs of nickel

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1626 T4202 (TRA.500.041.0001_2 at 0120_25).
1627 T4201 (TRA.500.041.0001_2 at 0119_1).
1628 Zurawin 2011 at 7 (PUB.500.001.0105).
1629 Ibid at 1.
1630 T4203 (TRA.500.041.0001_2 at 0121_20).

sensitivity'.[1631]

1590 Robertson relied on an article by Kimber and Basketter ('Kimber 2021') to support her opinions.[1632] The conclusions of Kimber 2021 were summarised by the authors as follows:

> The conclusions reached are that (a) sensitization can potentially be acquired as the result of exposure to implants containing nickel, but is not a common occurrence; (b) sensitization to nickel and/or other metal allergens is very rarely a cause of adverse reactions to implants; and (c) routine preoperative patch testing for sensitization to nickel is unnecessary, unless there is a significant clinical history of nickel allergy.[1633]

The authors referred to studies which showed that confirmed hypersensitivity reactions associated with Essure were 'extremely low'.[1634] When these matters were put to Robertson in cross-examination, she said:

> Yeah, and it's similar to [Zurawin 2011] which is just weird. No one can understand why it is that low. But the key point of this paper, and the reason that I've cited it, is that it describes and collects a lot of information saying that even though these things may be rare, and especially when they're evaluated with a skin-based test… they can occur and they do occur[.][1635]

Robertson hypothesised again that the rational biological explanation was that, in the case of Essure, the immune response to nickel did not manifest in the skin in the usual way.[1636] In fact the Kimber 2021 hypothesis was that exposure to nickel from Essure served to downregulate nickel-specific immune responses.[1637]

1591 Robertson said that the most biologically plausible explanation for the low rate of nickel-related adverse events, which was supported by a study by Chen ('Chen 2021')[1638], was the possibility of a local hypersensitivity reaction to a biomedical device

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1631 T2404 TRA.500.041.0001_2 at 0122_25).

1632 Ian Kimber and David A Basketter, 'Allergic Sensitization to Nickel and Implanted Metal Devices: A Perspective' (2021) 33(6) *Dermatitis* 396 (PUB.001.001.3844) ('Kimber 2021').

1633 Ibid at 1.

1634 Ibid at 6.

1635 T4209-10 (TRA.500.041.0001_2 at 0127_24-0128_1).

1636 T4211 (TRA.500.041.0001_2 at 0129_16).

1637 Kimber 2021 at 6 (PUB.001.001.3844).

1638 Lan Chen et al, 'The T Cell Repertoires from Nickel Sensitized Joint Implant Failure Patients' (2021) 22(5) *International Journal of Molecular Sciences* 2428.

that does not manifest in dermatitis. She said that Zurawin 2011 did not evaluate that possibility.[1639] Sokol explained that in Chen 2021, two patients were selected on the basis of prosthetic joint failure and a positive nickel patch test. The study considered systemic circulating T cells from the blood, not from the site of joint failure. The patients did not express hypersensitivity in terms of systemic contact dermatitis and there was no evidence that their joint failure was due to hypersensitivity reactions. Sokol said the study found a high percentage of T cells with a specific protein on the surface for their receptor. She said:

> [The authors of Chen 2021] noted that those two receptor proteins are highly expressed in contact dermatitis patients, or patients that have nickel contact dermatitis, and so they said that this suggested that skin and joint sensitisation could share similar pathogenic T cells. I would argue that this is really the exact opposite of what Professor Robertson said, that she deduced that this paper really showed that there's a separate type of T cell, and really what they showed is that there is one type of T cell that can go potentially to multiple places, although again we do not know if this was actually going to the joint to cause any joint damage.[1640]

1592 Robertson responded as follows:

> … the point is that there were also some distinct types of T cells that were restricted to the different sites means that it's biologically plausible to have a T cell response in a joint replacement or an Essure Device that wouldn't necessarily manifest in the skin, and that was the point I was making, that it's biological feasible, based on that data, not necessarily that it would occur in the two patients that were in the study.[1641]

1593 Sokol answered:

> I would just state that you said just now that there were T cells with receptors that were specific to certain areas, and all of these T cells were taken from the same space, they were taken from the peripheral blood. We didn't have any T cells that were taken from the skin, we didn't have any T cells that were taken from the joint space, so all we know is that all of these T cells share at least one circulation space, which is the blood. There's no evidence that they are specific to any one place.[1642]

1594 Third, Robertson said that hypersensitivity reactions that manifested at the site of an

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1639 T4204 (TRA.500.041.0001_2 at 0122_20).
1640 T4243 (TRA.500.042.0001_2 at 0021_16-27).
1641 T4244 (TRA.500.042.0001_2 at 0022_11-19).
1642 T4244 (TRA.500.042.0001_2 at 0022_20-28).

implanted biomedical device could not be readily treated with topical corticosteroids as suggested by Sokol. Sokol said that she would use oral antihistamine therapy in addition to topical corticosteroids to treat dermatitis, and in some cases would use oral steroid therapy to treat internal manifestations. She said that oral steroids were used to give time for the immune response to develop tolerance 'because we know that the longer we keep the device in, the more likely we are to get to that tolerised state'.[1643]

1595 Sokol has considerable clinical, research and teaching experience and expertise in relation to allergies. She regularly evaluates and treats patients for allergic reactions and metal hypersensitivity, and treats patients for systemic allergic reactions to implanted metallic medical devices. Her evidence about the rarity of DTHR cases in response to Essure is consistent with the scientific literature. I conclude that DTHRs to metal ions leached from Essure are rare. I accept Sokol's evidence that cases of DTHR are amenable to treatment.

1596 I do not accept Robertson's evidence on this topic. Robertson appeared to confuse or conflate the relatively common sensitivity to nickel most commonly determined by patch testing in the absence of clinical reactivity, with the far less common cases in which a DTHR occurs. The scientific articles and studies did not support her opinions. On any reasonable reading, the studies either did not contain supportive evidence, or in fact supported a contrary position to that expressed by Robertson.

1597 The evidence does not establish that metal ions other than nitinol that leach from Essure can cause a DTHR.

Removal limitation

1598 Turner confirmed in final submissions that she did not rely on the removal limitation as a defect in and of itself. Rather, Turner relied on the limitation as being relevant to the magnitude of the risk of the adverse events, in particular CPP and AUB. In other

1643 T4245 (TRA.500.042.0001_2 at 0023_29).

words, Turner argued that a woman who experienced CPP, AUB or other adverse events that were caused by Essure may require surgical removal of the devices in order to resolve those symptoms.

1599 There was very little dispute among the experts about the removal limitation. Once implanted in accordance with the manufacturer's instructions, the Essure device was not designed to be removed.[1644] As-Sanie and Korda agreed that by about three months after placement, an Essure device could only be removed by a salpingectomy, cornuectomy, or hysterectomy. Usually removal was done by laparoscopy.[1645]

1600 The experts agreed that the surgical risks associated with Essure removal included the risks of anaesthesia, complications such as post-operative infection; development of thromboembolism (pulmonary embolus, deep veinous thrombosis); damage to abdominal organs such as the bladder, bowels, blood vessels, ureters and nerves; hernia and abdominal and pelvic adhesions; bowel obstruction; and new or persistent pain.[1646]

1601 The experts were also agreed about the long-term health risks associated with hysterectomy. I described those risks in Chapter XIX.

1602 Korda and As-Sanie agreed that hysterectomy is a last resort treatment for pelvic pain and AUB, and is recommended 'only when symptoms are life impacting and refractory to a trial of more conservative options (such as medications)'.[1647]

XIX. TURNER'S CASE

1603 Turner had Essure devices hysteroscopically inserted into her fallopian tubes in September 2013 to achieve permanent sterilisation. Sometime later, Turner developed gradually worsening symptoms including dysmenorrhea, menorrhagia, dyspareunia

1644 SBM.500.001.0003_2 at 806 [6.4].
1645 Gynaecology JER at 17 [EXP.500.001.0001].
1646 Ibid at 17–8; Robertson at 45 (EXP.001.001.0127_2).
1647 Gynaecology JER at 18 [68] (EXP.500.001.0001).

and CPP. In June 2018 Turner was referred to a gynaecologist, Dr Russell Dalton, who recommended and performed hysterectomy surgery. The surgery was successful and led to the resolution of her symptoms.

1604 Turner alleges that Essure was a cause of the dysmenorrhea, menorrhagia, dyspareunia and CPP she suffered, and of the need for hysterectomy surgery.

History, tests and treatment

1605 Turner was born in 1986 and was aged 37 years at the time of trial. She has three children who were born in October 2005, January 2009 and June 2013.[1648]

1606 Turner is a physically active person and generally enjoys good health. She developed eczema as a child and has been occasionally symptomatic as an adult.[1649] She suffered from depression and anxiety at different times throughout her life, and took the antidepressant medication Prozac episodically between December 2011 and February 2016.[1650]

1607 Turner described her menstrual cycle as follows:

> I never really experienced period pain before having Essure inserted. I would just get a bit of niggly period pain for a day or so around the start of my period. I would only take painkillers to manage this pain on the odd occasion. My periods were irregular. It was not unusual for me to have 6 weeks between periods. When I had my period, I would bleed for around 3 to 7 days but it was not heavy. I used regular tampons during the day and regular pads at night.[1651]

1608 Lam said that the most likely cause of Turner's described pain and irregular menstrual cycle was endometriosis and/or adenomyosis. He said that PCOS was a likely cause of the irregular menstrual cycle. White said the pain that Turner described was not abnormal, and that there was insufficient information about Turner's menstrual pattern to indicate that the irregularity had a pathological cause.[1652]

1648 Turner at 1 (LAY.001.001.0001_R).
1649 Ibid at 3.
1650 Ibid at 3 [21].
1651 Ibid at 3–4 [23].
1652 Plaintiff JER at 3 (EXP.500.001.0005).

1609 Turner suffered a miscarriage in mid-2004 before becoming pregnant with her first child. She struggled to conceive her second child in 2007-2008. In March 2008, Turner attended with a gynaecologist who recorded a history of irregular periods with 'the last one being some six weeks from the first', and concluded that 'she may well be anovulatory'.[1653]

1610 In November 2011, Turner was referred by her GP to a gynaecologist to discuss permanent sterilisation.[1654] The specialist clinical notes that have been tendered commence in June 2013 and do not disclose whether Turner acted on the referral and consulted with a specialist in 2011.[1655] Turner said that she recalled being told at the time that tubal ligation was not an option due to her age. She could not recall whether this advice was given to her by a GP or by the gynaecologist.[1656]

1611 Clinical notes from before and after the Essure procedure show occasions when Turner was prescribed the OCP. Notes record complaints by Turner about some side effects of the OCP. Turner said she could not recall what the side effects were, but that the OCP 'did not agree with her'.[1657] Turner said that on some occasions she did not take the OCP when it was prescribed and on other occasions could not recall whether or not she took it. The clinical notes are consistent with there being significant periods of time during which the OCP was not prescribed to Turner. I conclude that Turner seldom used the OCP.

1612 The first antenatal notes relevant to Turner's pregnancy with her third child include a history that the length of her menstrual cycle varied between four to five weeks and was irregular.[1658]

1613 Turner said that she consulted with gynaecologist Dr Colin Weatherill throughout the pregnancy with her third child, and recalled a discussion with him about permanent

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1653 TUR.001.001.0309_R at 15.
1654 Ibid at 2.
1655 Ibid; TUR.001.001.0087_R at 22.
1656 Turner at 4 [27] (LAY.001.001.0001_R).
1657 Ibid at 10 [79].
1658 TUR.001.001.0087_R at 28.

contraception and Essure. However, the clinical notes do not disclose that Turner had an antenatal consultation with Weatherill. I conclude that Turner's memory of this aspect of her history is inaccurate.

1614 Turner's third child was born on 25 June 2013.

1615 On 8 August 2013 Turner attended with Dr Vamsee Thalluri, a registrar at Weatherill's clinic, 'for discussion of ESSURE'. The clinical notes include: 'detailed alternative options for patient, but patient sure she wants a permanent sterilisation procedure.' Turner signed an operative consent form for the Essure procedure with the alternative of tubal ligation if required.[1659]

1616 Turner gave the following evidence about her consultation with Thalluri:

> I recall being told by Dr Thalluri that Essure was a permanent device, and I understood that it couldn't be reversed. I knew that tubal ligation could be reversed, but also that it was expensive and difficult to do. I also understood from the conversations with my doctors that Essure was a day procedure, and so was a less intrusive and significant a procedure than tubal ligation and with a faster recovery time. I understood that there was around a 6-week recovery time with tubal ligation.
>
> I do not recall being given any documents, brochures or other written material about Essure prior to having the devices inserted.
>
> The only risk of the Essure device that I recall being told about by Dr Thalluri was that if the implants couldn't be placed successfully then they wouldn't be effective to block the fallopian tubes, so the devices would remain in place and I would have to have a tubal ligation procedure for permanent contraception. As this was the procedure I originally wanted to have, I didn't see this as a real downside. I also did not take this warning to mean that Essure was a particularly high risk device. I don't recall the specific wording given to me by Dr Thalluri but I got the sense that it was safe and uncontroversial and that it didn't involve any more risk than tubal ligation.
>
> I do not recall being told that there were risks that having the device inserted may result in pelvic pain or heavy menstrual bleeding.
>
> I do not recall being told about the materials the Essure coils were made of. I believe that if I had been told that nickel was in the device I would have asked more questions about it. I have experienced skin reactions to nickel jewellery in the past and I believe that if I had been made aware that I was having a

1659 Ibid at 2; TUR.001.001.0001_R at 22.

> device involving nickel implanted I would have thought more about whether this was a good idea for me.
>
> I recall being shown a picture of an Essure coil by Dr Thalluri or Dr Weatherill in its 'contracted' state prior to having the devices inserted. I can't recall whether the image was on a page or on a computer screen, but I do recall that it was a picture of a contracted coil that gave a sense of its scale. I do not recall when I was shown this picture or by whom.[1660]

1617 Turner said that she did some internet searches to find out more about Essure before her implantation operation. She said that she could not recall seeing anything from these searches that raised concerns or made her think there were particular risks or dangers associated with Essure.[1661]

1618 The Essure implantation procedure was performed by Weatherill on 25 September 2013.[1662] There were no complications and Turner recovered quickly.

1619 Clinical notes record Turner attending her GP clinic on three occasions in 2013 after the Essure procedure. The first two attendances related to a continuation of treatment for eczema. The third attendance, on 21 November 2013, was with a registered nurse for a pap smear. The notes of that attendance include:

> Contraception = Oral contraception
>
> Signs or symptoms of Intermittent bleeding – nil[.][1663]

1620 Turner said that in 2014–2015 her menstrual periods began to change, with the bleeding becoming much heavier than before the Essure devices were implanted. She said that around the same time she began to experience regular sharp and severe pains in her pelvic and abdominal areas. Turner said that these pains lasted between five minutes and an hour and were debilitating. She said that she experienced these pains often and at random times, not just around the time of her period or ovulation. Turner said that she also began to experience a constant level of internal dull pain and a

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1660 Turner at 4-5 (LAY.001.001.0001_R).
1661 Ibid at 5 [38].
1662 Ibid at 5 [44]; SBM.001.001.0004 at 20.
1663 TUR.001.001.0262 at 10.

feeling of 'heaviness' around her pelvis and lower back, and that she became very tired, fatigued and lacking in energy.[1664]

1621 During 2014 and 2015 Turner's marriage broke down. Her final separation from her husband occurred in late 2015 when she left the family home with her children. She lived with her mother for some months before obtaining rental accommodation.[1665]

1622 The GP clinical notes record six attendances by Turner during 2014 for complaints including conjunctivitis, hay fever and eczema. The notes of the attendance on 30 September 2014 record that Turner was to cease taking Prozac.[1666]

1623 Turner attended with her GP on 2 February 2015.[1667] The clinical notes of that attendance record Turner complaining of feeling tired and of 'upper [gastrointestinal] pain'. The GP referred Turner to have blood tests and a pelvic x-ray. In evidence in chief, Turner said that this was the first time she could recall attending a GP about pelvic and abdominal pain and fatigue.[1668] In her oral evidence, Turner said she could not recall what symptoms she had when she attended the GP on that occasion, and that she could not recall ever having pain from her chest upwards. Turner could not remember the outcome of the pelvic x-ray.

1624 Turner's mother, Lorraine Shields, said at times when she visited Turner before Turner separated from her husband, she observed Turner lying on the couch in pain with a heat pack on her stomach, complaining of severe abdominal and back pain. Shields could not say how many times this occurred.[1669] Shields said she was aware that Turner was having 'bad days' from about mid-2015 onwards.[1670] After Turner came to live with her in late 2015, Shields encouraged her to go to a doctor to seek advice about the problem.

1664 Turner at 6 (LAY.001.001.0001_R).
1665 Ibid at 8.
1666 TUR.001.001.0262 at 8.
1667 TUR.001.001.0262_R at 8.
1668 Turner at 7 [53] (LAY.001.001.0001_R).
1669 T1016 (TRA.500.011.0001_2 at 0053_19-27).
1670 T1011 (TRA.500.011.0001_2 at 0048_11-2).

1625 There were only three further GP attendances in 2015, the first two of which were for unrelated matters. At the third appointment on 26 August 2015, Turner was re-prescribed Prozac for her increased anxiety related to the marriage breakdown.[1671]

1626 In late 2015, Turner commenced a relationship with Jason Smith who lived in Ballarat. Turner continued to reside in Mount Gambier with her children and travelled to and from Ballarat to spend time with Smith throughout 2016. In a statement made as evidence in chief, Smith said:

> At the start of our relationship, Patrice did not speak much about the menstrual bleeding issues that she was experiencing. She kept a lot of this private at the start of our relationship but opened up about it more as time went on. We did discuss the pain quite early on, although I do not recall the specific date.[1672]

In cross-examination, Smith clarified that he became aware Turner was suffering from pain and menstrual problems 'from basically the start [of when they] started talking' and '[t]hings got worse over time'.[1673] Smith said he could not recall the first occasion Turner mentioned that she was experiencing pain and menstrual problems. He said it was early on in the relationship, but he could not be precise.

1627 Turner attended with her GP on 13 January 2016. The note of that attendance records:

> Hist and tx for depression noted
> Did not tolerate [sic] ceasing medication last year
> Is currently well
> Prescriebd [sic]
> May consider a 2nd trial to cease this year or next[.][1674]

On that occasion, Turner was again prescribed Prozac. The defendants submitted that the note 'Is currently well' is inconsistent with Turner's evidence that she commenced suffering pelvic pain and AUB in 2014 or 2015. I reject that submission. The note clearly relates to Turner's mental health and not her physical health.

1628 Turner attended her GP clinic for a pap smear on 16 February 2016. The notes of that

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1671 TUR.001.001.0262 at 7.
1672 Smith at 2 [7] (LAY.001.001.0014).
1673 T1020 (TRA.500.011.0001_2 at 0057_12).
1674 TUR.001.001.0262 at 7.

attendance include:

> LMP [last menstrual period] = Irregular at present 2.2.16.[1675]

1629 On 12 April 2016, Turner attended with her GP and was referred for a pelvic ultrasound.[1676] The radiologist's report records that a transvaginal ultrasound was performed with a clinical note of 'tender right lower quadrant'.[1677] The radiologist reported that Turner's uterus measured 84 x 46 x 52 mm, that the endometrial thickness was normal, and that both ovaries displayed multiple small peripheral follicles raising the possibility of PCOS. Turner reattended with her GP the following day. The clinical notes of that attendance include: 'pain RIF [right iliac fossa] getting worse'.[1678] Turner was referred to the emergency department of the local hospital. The emergency department was full and no beds were available, so after waiting for an hour Turner left without receiving treatment.[1679]

1630 Turner next attended with her GP on 28 July 2016. The clinical notes of that attendance include:

> Reports menometorrhagia [sic]
> Onset 6 months ago
> Menarche at 15 yrs
> Menstruation been fine & regular until January this year
> Now heavy menstrual loss, lasting longer than usual
> Reports dyspareunia
> Stopped OCPs 3 yrs ago
> Both tubes clipped, normal on USS 3 months ago
> Pap smear normal in Feb 2016
> Nil family h/o cancers/bleeding disorders
> Nil h/o bleeding disorder[1680]

1631 Turner reattended with her GP on 2 August 2016 to discuss the possible causes of her symptoms and treatment options. She was prescribed the OCP, which she said she

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1675 Ibid at 6.
1676 TUR.001.001.0262_R at 5.
1677 Ibid at 37.
1678 Ibid at 5.
1679 Turner at 7 [54] (LAY.001.001.0001_R).
1680 TUR.001.001.0262 at 5.

does not recall taking.[1681]

1632 Turner attended with her GP for unrelated reasons on two further occasions in 2016.

1633 Turner relocated from Mount Gambier to Ballarat in early 2017. Turner first attended a new GP clinic on 2 February 2017. The clinical notes of that attendance include: 'menorrhagia since years' and 'pain as well'. The notes also record Turner complaining of fatigue and lethargy, and of 'bleeding associated with clots'.[1682]

1634 Turner was referred for a pelvic ultrasound on 7 February 2017. The radiologist reported:

> A very bulky retroverted uterus has been demonstrated with a volume of 200cc. It has a uniform endometrial thickness of 12mm.
>
> Bilateral Essure coils have been demonstrated extending from the uterine fundus into the tubal regions.
>
> Ovaries appear of normal size, the right measuring 13cc and the left 7cc with numerous small follicles demonstrated on both left and right side with a dominant follicle on the right measuring 2cm. A number of follicles appear to be peripheral and subserosal in position suggestive of PCOS though on strict follicular number criteria, the patient does not fit this diagnosis.[1683]
>
> The uterus dimensions were recorded on ultrasound images as length 9.80cm; height 6.07cm and width 6.41cm.[1684]

Turner reattended with her GP on 9 February 2017. The history noted by the GP includes that all results were normal and the 'bleeding [had] stopped'.[1685]

1635 Turner attended a new GP clinic in Ballarat on 30 January 2018. The notes of that attendance include:

> Pelvic pain
>
> coils in tubes 4 yrs ago
> Has had increasing pelvic pain[.][1686]

1681 T985 (TRA.500.011.0001_2 at 0022_3).
1682 TUR.001.001.0359_R at 3.
1683 Ibid at 3–4.
1684 Lam (EXP.001.002.0006).
1685 TUR.001.001.0359_R at 3.
1686 TUR.001.001.0138_R at 3.

Turner was referred for another pelvic ultrasound which was performed on 16 February 2018. There were some restrictions in the ultrasound because of Turner's menstrual status at the time. The radiologist reported a bulky uterus, measuring 7.5 x 5.5 x 7.3 cm with a volume of 157cc, and a normal number of ovarian follicles.[1687] The GP clinical notes of Turner's reattendance on 20 February 2018 record that the ultrasound result was: 'OK … bulky uterus & ovaries/ nil specific'.[1688]

1636 On 2 May 2018, Turner attended with a different GP at the same clinic who recorded the following history:

> pelvic pain
>
> pelvic pain long standing
> investigation recently
> nad
> coil tubal since then symptoms last 4-5 years
> done at mount gambler
> wants referral for removal.[1689]

1637 Clinical records dated 12 June 2018 read:

> pelvic pain
>
> has had tubal coils for contraception about 4 yrs ago
> ongoing pelvic pain
> has h/o endometriosis as well
> needs to see someone with experience in tubal coils
> spoke to Dr Mongafor advice, happy to see her
> will call and find out if Mr Dalton is happy to see her
> will let me know for referral
> long consult
> discussed bt results[.][1690]

1638 In June 2018, Turner was referred to gynaecologist Dr Russell Dalton. Dalton performed a transvaginal ultrasound that he reported showed '55mm eccentric myometrial thickening' and 'normal' ovaries. Dalton commented: 'myometrial changes consistent with adenomyosis. No hard evidence of endometriosis'.[1691] He

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1687 Ibid at 12.
1688 Ibid at 3.
1689 Ibid at 2.
1690 Ibid.
1691 Ibid at 8.

also recorded the following examination findings: 'Bimanual examination revealed left fornix tenderness and a bulky uterus'. Dalton's diagnosis was adenomyosis.

1639 Dalton performed a laparoscopic hysterectomy on 25 June 2018. In the operation record, Dalton noted a finding on examination under anaesthetic that Turner's uterus was 'enlarged and mobile', and recorded a post-operative diagnosis of adenomyosis.[1692]

1640 A histopathology report was prepared on 27 June 2018. The pathologist recorded the uterus size as 100 x 70 x 52 mm and weighing 158 g. Microscopy examination was performed on three blocks of the anterior cervix/endometrium, three blocks of the posterior cervix/endometrium, and two blocks of the fallopian tubes. The pathologist recorded the following conclusion: 'Total hysterectomy and bilateral salpingectomy: Late secretory endometrium and small intramural leiomyoma'.[1693] The pathologist reported that no endometritis was seen. The pathologist made no reference to adenomyosis or to signs of inflammation.[1694]

1641 Turner was reviewed by Dalton post-surgery on 7 August 2018. In a letter to Turner's GP, Dalton recorded that the histology from the operative specimen was benign. Under 'Diagnosis', Dalton recorded: 'post-operative check — normal findings'. [1695]

1642 Turner recovered well following surgery and reported that her symptoms of dysmenorrhea, menorrhagia, dyspareunia and CPP had resolved.

Expert evidence on Turner's diagnosis

1643 The expert gynaecologists White and Lam agreed that the possible causes of Turner's combination of symptoms included PCOS, endometriosis, adenomyosis, and PID.

1644 There was no history of abnormal vaginal discharge or fever, evidence of a positive cervical swab nor abnormality seen on histological examination of Turner's uterus and

1692 TUR.001.001.0181_R at 16.
1693 Ibid at 23.
1694 Ibid at 23.
1695 Ibid at 13.

fallopian tubes following hysterectomy. The experts agreed on this basis that there was no evidence supporting a diagnosis of PID or endometritis.

1645 No evidence of endometriosis was found by Dalton during surgery or by the pathologist on histological examination. Accordingly, endometriosis can also be dismissed as a diagnosis.

Adenomyosis

1646 Adenomyosis involves infiltration of endometrial tissue, composed of glands and stroma, into the myometrium. The displaced glands incite 'spiral vessel angiogenesis and smooth muscle hyperplasia and hypertrophy, leading to thickening of the junctional zone, and cause diffuse uterine enlargement when severe'.[1696] Endometrial tissue may invade the myometrium either diffusely or in focalised areas.[1697]

1647 Adenomyosis generally only affects women in their reproductive years and tends to affect older women, more commonly those in their forties.[1698] Prevalence is uncertain, 'with diagnosis rates varying from 10–80 per cent depending on the subjects examined and the stringency with which it is sought'.[1699] The causes and mechanisms of adenomyosis are unclear.

1648 The symptoms of adenomyosis are variable. They commonly include heavy and/or prolonged menstrual bleeding, dysmenorrhea, dyspareunia and pelvic pain. Women are asymptomatic in about one-third of cases. A clinical history of a progression of symptoms over time is consistent with adenomyosis. However, symptoms may be stable.[1700]

1649 Abdominal tenderness on palpation, and an examination finding indicating a bulky uterus, are consistent with a diagnosis of adenomyosis.

1696 Plaintiff JER at 5 (EXP.500.001.0005).
1697 T1742 (TRA.500.018.0001_2 at 0008_12)
1698 T1742 (TRA.500.018.0001_2 at 0008_19).
1699 Plaintiff JER at 4 (EXP.500.001.0005).
1700 T1747 (TRA.500.018.0001_2 at 0013_7).

1650 The experts agreed that since adenomyosis is a condition defined on the basis of histological findings, the diagnosis can ultimately only be confirmed by histological examination of uterine tissue. However, they were at odds about the diagnosis in Turner's case.

1651 The examining pathologist did not report any signs consistent with adenomyosis on examination of tissue following hysterectomy. On that basis, White concluded that it was unlikely Turner suffered from adenomyosis.

1652 Lam said that because adenomyosis is characterised by infiltration of endometrial tissue into the myometrium, it is not a condition that can be identified by examination of the outer surface of the uterus. He said that diagnosing adenomyosis requires gynaecologists:

> …to rely first and foremost on a set of symptoms that are variable but, over time, often progress, as commonly is the case as the disease infiltrates more extensively[.][1701]

Lam said that imaging testing, in this case transvaginal ultrasound, has become more important in the suspicion and diagnosis of adenomyosis. Guidelines have been set for examining radiologists because of the subjective nature of ultrasound examination.[1702] Lam said that if he received ultrasound reports of a bulky uterus with an increase in uterine size over time, he would request the radiologist to re-examine and provide a more detailed report looking at the myometrium in order to confirm a diagnosis of adenomyosis. He said that if he was still unsure about the diagnosis, he might then recommend a more expensive MRI test.[1703]

1653 Lam concluded, for the following reasons, that adenomyosis was the most likely diagnosis and cause of Turner's symptoms. First, the pain symptoms reported by Turner were consistent with adenomyosis.[1704] Second, the reported signs on ultrasound examination, being the bulky uterus that became more enlarged over time

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1701 T1760 (TRA.500.018.0001_2 at 0026_27-30).
1702 T1762 (TRA.500.018.0001_2 at 0028_1).
1703 T1763 (TRA.500.018.0001_2 at 0029).
1704 Lam at 17 (EXP.001.002.0006).

and the eccentric thickening of the myometrium reported by Dalton, were consistent with adenomyosis. Third, there is a high level of under-diagnosis of adenomyosis following histological examination of uterine tissue. Lam said that the lack of reference to adenomyosis by the examining pathologist did not weigh heavily against the diagnosis of the disorder. Fourth, Lam said that on his examination of a number of still images from the ultrasound performed in 2017, there were clear signs consistent with adenomyosis that were not reported by the radiologist. Fifth, Lam said that on his examination of images taken at the time of hysterectomy surgery, there were signs consistent with adenomyosis that were not reported by Dalton or the examining pathologist. Sixth, 'Turner's uterine weight was 158g, which is heavy, consistent with the ultrasound, laparoscopic and pathologic findings of a bulky, enlarged uterus, as seen in adenomyosis'.[1705]

Symptoms

1654 White said that Turner's history before implantation of the Essure device of 'niggly' pain at the beginning of her period was not abnormal.[1706] She said that neither Turner's statement nor clinical history clarified when the irregular periods occurred. Turner had no particular difficulty conceiving, which a woman with infrequent periods may have. White said there was nothing that strongly suggested a pathological cause for Turner's irregular menstrual cycle.[1707]

1655 Lam agreed that Turner's statement that she 'never really experienced' period pain before Essure supported an inference that she did not find the period pain she experienced to be impactful. He agreed that this history was crucial when considering whether any period pain experienced by Turner pre-Essure had a pathological basis.[1708]

1705 Ibid at 33 [2.6].
1706 T1781 (TRA.500.018.0001_2 at 0047_18).
1707 T1782 (TRA.500.018.0001_2 at 0048).
1708 T1803 (TRA.500.018.0001_2 at 0069).

1656 Lam said that the increasing severity of symptoms corresponded with the increasing infiltration of the adenomyotic process into the myometrium.[1709] He noted that Turner reported her symptoms of AUB and pain increasing in severity over time. He attributed Turner's symptoms to adenomyosis because they were consistent with the disorder and because of the development of her symptoms.[1710]

1657 Lam said that heavy menstruation is the most common symptom of adenomyosis and is more common in women with deep foci of adenomyotic tissue. He said that dysmenorrhea is the second most common symptom, and has been found to be associated both with the amount of adenomyotic foci and the depth of invasion.[1711]

1658 White agreed that Turner's symptoms were those often seen in women with adenomyosis.[1712] White made a distinction between a finding that certain symptoms are consistent with a diagnosis, versus a finding that a diagnosis is consistent with symptoms. She said that a woman may present with a range of symptoms which could suggest a number of differential diagnoses. Depending on the certain set of symptoms, it may be possible to say that those symptoms are consistent with a diagnosis of adenomyosis. However, one cannot reason backwards to say that a diagnosis of adenomyosis is consistent with the symptoms, as this does not acknowledge the range of diagnoses that could explain the woman's presenting features. She said that Turner's presenting symptoms were common for women, though usually in a slightly older demographic.

Reported signs on ultrasound examination

1659 The experts agreed that features consistent with adenomyosis that may be identified on ultrasound examination include uterine enlargement; uterine asymmetry, particularly between the anterior and posterior walls; changes in the appearance of

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1709 Lam at 17 [2.3.4] (EXP.001.002.0006).
1710 Ibid at 17.
1711 Ibid at 18 [2.3.4](f).
1712 White at 5 [1.3](a) (EXP.001.002.0010).

the myometrium, including heterogeneity; and sometimes the presence of cysts within the myometrium.[1713]

1660 Lam said the dimensions of the uterine corpus and cervix change with age and parity. Lam noted the World Health Organisation manual of diagnostic ultrasound 2013 gave the following dimensions for the uterus of a pluriparous woman: length 8 cm; width 4 cm; thickness 5 cm; and volume 60–80 mL.[1714]

1661 Lam relied on the findings of a bulky uterus in the July 2017 and February 2018 ultrasounds and Dalton's reported findings in June 2018 of eccentric myometrial thickening, myometrial changes consistent with adenomyosis, and a bulky uterus.

1662 Lam agreed that if a woman was experiencing symptoms that were later confirmed by histopathology to be caused by adenomyosis, he would expect there to be features of adenomyosis picked up on transvaginal ultrasound at the time she was symptomatic.[1715] It was put to him that on this basis, the 2016 ultrasound should have shown features consistent with adenomyosis if that diagnosis was correct. Lam responded that in an early case of adenomyosis, the microscopic progression of the disease may be scattered and small and therefore not discernible on ultrasound examination. He said that the absence of features on ultrasound does not exclude the possibility of an early stage of adenomyosis.[1716] Lam agreed that if Turner experienced disabling symptoms of pelvic pain, dysmenorrhea and menorrhagia since at least 2015, the absence of features on the April 2016 ultrasound meant it was unlikely she had adenomyosis at that time.[1717]

1663 Lam agreed that the radiologist who examined the February 2017 ultrasound noted a bulky uterus and uniform endometrial thickness, but did not raise the possibility of

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1713 T1743 (TRA.500.018.0001_2 at 0009_18).
1714 Lam at 19-20 (EXP.001.002.0006).
1715 T1815 (TRA.500.018.0001_2 at 0081_11).
1716 T1816 (TRA.500.018.0001_2 at 0082_27).
1717 T1819 (TRA.500.018.0001_2 at 0085_1).

adenomyosis. He agreed that the only condition raised by the radiologist as a possible explanation for Turner's symptoms was PCOS.

1664 Lam agreed that measurements of a uterus on a transvaginal ultrasound were somewhat subjective, but said it should be reproducible given a standard approach radiologists should follow.[1718] Lam also agreed that measurements of the anterior and posterior walls of the uterus can differ depending on the axis or rotation of the image, and that a radiologist observing the ultrasound is in a better position to take accurate measurements.[1719] He agreed that one possible explanation of the different measurements in the April 2016, February 2017 and February 2018 ultrasounds was that they were carried out by different practitioners. Another possible explanation is differences in the axis or angle of observation. These factors may explain the reported progressive uterine enlargement.[1720]

1665 Lam agreed that his position was effectively that Turner had adenomyosis, and that this was missed by the radiologists who reported on the 2017 and February 2018 ultrasounds.

1666 White said that transvaginal ultrasound is not completely reliable in diagnosing adenomyosis. In a percentage of women where ultrasound appearance is suggestive or consistent with adenomyosis, upon histological examination the diagnosis cannot be made.[1721] She said that there were a number of reasons for this. Interpretation of ultrasound is quite subjective and involves a degree of judgement. Whether or not adenomyosis is identified may depend on the skill of the practitioner performing the ultrasound.[1722] Further, findings such as heterogeneity of the myometrium and enlargement of the uterus are fairly non-specific. White noted that ultrasound technology has become a useful tool, along with a patient's history and clinical findings, to explain to a woman what her likely pathology is. She said, however, that

1718 T1822 (TRA.500.018.0001_2 at 0088).
1719 T1821 (TRA.500.018.0001_2 at 0087_24).
1720 T1823 (TRA.500.018.0001_2 at 0089).
1721 T1744 (TRA.500.018.0001_2 at 0010); T1743 (TRA.500.018.0001_2 at 0009_4).
1722 T1749 (TRA.500.018.0001_2 at 0015_23-5).

ultimately adenomyosis can only be accurately diagnosed by histological examination and the most that can be achieved without it is a strong provisional diagnosis.[1723]

1667 White said that the observed increase in Turner's uterus size was consistent with, but not diagnostic of, adenomyosis.

Under-diagnosis following histological examination

1668 The experts agreed that because the haphazard distribution of adenomyosis in the myometrium, the frequency of positive findings on histological examination of tissue increases if more sections are taken from a uterus after hysterectomy.[1724] This means that histological diagnosis of adenomyosis is necessarily dependent on the number and extent of tissue samples reviewed. Lam referred to a study conducted in 1969 involving histological analysis of 200 uteri following hysterectomy ('Bird 1972').[1725] When three blocks of uterine wall were taken for examination, adenomyosis was identified in 62 specimens (31%).[1726] When six extra blocks of uterine wall were taken from predetermined sites and examined, an additional 61 uteri were found to contain adenomyosis.[1727] Three of these blocks were taken from the anterior wall of the uterus, and three from the posterior wall. White and Lam agreed that there had been no improvement in histological science or examinations since this study was performed.

1669 White agreed with the general proposition that the harder a pathologist looks for adenomyosis, the more likely it is they will find it.[1728] She added that in clinical practice, most gynaecologists would have a degree of confidence in their pathologist and would accept a finding that adenomyosis was not identified on histological examination. White said that if there was no other pathological process to explain a woman's symptoms, two possibilities remained: that adenomyosis was present but

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1723 T1751 (TRA.500.018.0001_2 at 0017_7).
1724 T1751 (TRA.500.018.0001_2 at 0017_26).
1725 Charles C Bird, Thomas W McElin and Pacita Manalo-Estrella, 'The elusive adenomyosis of the uterus* - revisited' (1972) 112(5) *American Journal of Obstetrics and Gynecology* 583 (PUB.500.001.0423) *('Bird 1972')*.
1726 Ibid at 3.
1727 Ibid.
1728 T1752 (TRA.500.018.0001_2 at 0018_28).

not identified on histological examination, or that the woman had the symptoms without a specific pathological explanation.[1729]

1670 White said that she assumed a competent pathological examination was performed on Turner's uterus. The pathologist did not identify adenomyosis. She accepted that it is possible that adenomyosis was present in parts of the uterus that were not sampled and tested.[1730]

1671 Lam said that a routine pathological examination involved taking one axial block through the anterior wall of the uterus, another through the posterior wall, a transverse block through the fundus, and blocks of each fallopian tube. He said that adenomyosis is 'haphazard' and not well defined, unlike a fibroid.[1731] These matters explain the findings in Bird 1972 and are consistent with his clinical experience.[1732]

1672 Lam acknowledged that the studies he relied on in his report to establish the accuracy of ultrasound imaging in detecting adenomyosis tested ultrasound accuracy against histopathological examination. He agreed that histopathology remains the gold standard when confirming the diagnosis of adenomyosis.[1733]

1673 The pathologist report of histological examination in Turner's case indicates that six blocks of uterine wall were taken for examination, with three taken from the anterior and three from the posterior. That is three more blocks than the routine pathological examination contemplated in Bird 1972, and three less blocks than the more comprehensive examination referred to in that study.

1729 T1756 (TRA.500.018.0001_2 at 0022).
1730 T1794 (TRA.500.018.0001_2 at 0060_9).
1731 T1764 (TRA.500.018.0001_2 at 0030_2).
1732 T1764 (TRA.500.018.0001_2 at 0030_9).
1733 T1773 (TRA.500.018.0001_2 at 0039_14).

Lam's examination of ultrasound images

1674 Lam said that on his review of four still images from the February 2017 ultrasound, he identified the following signs that were suggestive to him of adenomyosis. First was uterine enlargement, which the reporting radiologist also recorded.

1675 Second was asymmetrical thickening between the anterior and posterior walls of the uterus. Lam said that he gained an impression of the relative thickness of the anterior and posterior walls of the uterus by measuring the distance from the serosal layer of the anterior wall to the endometrium and the corresponding distance between the endometrium and the posterior wall serosal layer on the computer. Lam agreed in oral evidence that the quality of the image he reviewed for this purpose was 'not crash hot'.[1734] Lam agreed that there was no obvious asymmetry in one of the images he reviewed.[1735]

1676 Third was the heterogeneity in the myometrium, with the presence of cystic spaces. Lam said that the image he relied on to make this finding was of the fundal part of the uterus, and was probably oblique but possibly longitudinal. He said that there were obvious cystic changes in the myometrium that covered a large part of the image and extended from the front wall of the fundus to the posterior wall of the uterus. He said that the changes on the image were widespread.[1736]

1677 Lam said that the myometrial cystic changes and heterogeneity were of greater significance to a diagnosis of adenomyosis than the asymmetrical thickening of the uterine wall. He said that the changes were more marked than in images included in scientific publications on which he relied, which were said to be indicative or suggestive of underlying adenomyosis.

1678 In his report, Lam referred to guidelines for describing ultrasound images of normal and pathological myometrium called the Morphological Uterus Sonographic Assessment ('MUSA guidelines'). The MUSA guidelines contain a diagram of 'direct'

1734 T1831 (TRA.500.018.0001_2 at 0097_26-7).
1735 T1821 (TRA.500.018.0001_2 at 0087_31).
1736 T1831 (TRA.500.018.0001_2 at 0097).

and 'indirect' signs and features associated with adenomyosis.[1737] Lam agreed that he did not know how to interpret the diagram, or why certain features were categorised as 'direct' and others 'indirect'. He was not aware of any study comparing or validating certain features of adenomyosis over others.[1738]

1679 Lam agreed that the MUSA guidelines are directed to technicians performing ultrasounds and radiologists reporting on them.[1739] He accepted that this is because those technicians and radiologists are best placed to undertake the thorough analysis required.

1680 Lam agreed that a transvaginal ultrasound is a dynamic process, and that the technician conducting the examination and the radiologist observing are at an advantage compared to someone who examines the still image later.[1740]

1681 Lam said that some gynaecologists are certified in obstetric and gynaecological ultrasound. He agreed that interpretation of ultrasounds involves specialised medical skills and requires further training beyond standard medical training. Lam said he did not have the relevant ultrasound certification.[1741]

1682 Lam agreed that he could not identify any features consistent with adenomyosis in the report or images from the April 2016 ultrasound. He agreed that his report contained no mention of having reviewed those images. He said that he referred only to ultrasound images he thought were relevant to the Court in his report, those being images of the February 2017 ultrasound.[1742]

1683 White said that she viewed some of the still images from Turner's ultrasounds but did not attempt to interpret them. She said that ultrasound is a dynamic process and that the examiner forms their assessment based on their observations throughout the

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1737 Lam at 28 (EXP.001.002.0006).
1738 T1770 (TRA.500.018.0001_2 at 0036).
1739 T1825 (TRA.500.018.0001_2 at 0091_19).
1740 T1811 (TRA.500.018.0001_2 at 0077_22).
1741 T1770 (TRA.500.018.0001_2 at 0036).
1742 T1812 (TRA.500.018.0001_2 at 0078).

procedure. She said that she would not attempt to interpret a single static image because of her lack of skill in this area, and because it would not be particularly helpful.[1743]

Lam's examination of surgical images

1684 Lam said:

> Photos taken at the time of hysterectomy showed a *bulky* uterus and *serosal adhesions* with *myometrial asymmetrical thickening* in the posterior wall. These features indicate to me that there was some kind of inflammatory process such as associated with adenomyosis, myoma, or chronic inflammation[.][1744]

1685 White did not agree with Lam's observations of the surgical photograph. She said that it was not possible to tell from a single image that the uterus was bulky; that she did not see anything that clearly looked like a serosal adhesion; and that it was not possible to say there was myometrial or asymmetrical thickening because this implies the cavity of the uterus was not midline, which you could not determine from the external appearance of the uterus.[1745] She added that serosal adhesions have not been suggested at any point as a feature of adenomyosis and hence were irrelevant.

1686 White said that the presence of serosal adhesions would suggest inflammation that has led to lesion formation. She said a bulky uterus and myometrial asymmetrical thickening were not suggestive of an inflammatory process.[1746]

Weight of uterus

1687 Lam said that fibroids and adenomyosis are amongst the most common pathologies accounting for the development of an enlarged, heavy uterus. In Turner's case, pathologic examination found only a small uterine fibroid that measured 8 mm. Lam reasoned on that basis 'that adenomyosis was the most likely dominant pathology to account for Ms Turner's pain symptoms'.[1747]

1743 T1786 (TRA.500.018.0001_2 at 0052_8).
1744 Lam at 54 [7.9.5] (EXP.001.002.0006).
1745 T1791 (TRA.500.018.0001_2 at 0057_1).
1746 T1791 (TRA.500.018.0001_2 at 0057_23).
1747 Lam at 34 [2.6.5](c) (EXP.001.002.0006).

1688 Lam was asked:

> So what you've done is you've said her uterine weight was 158 grams, which is heavy and consistent with adenomyosis, yes?---Yes.
>
> And then the comparator you've used to bolster your argument about the heavy uterine weight under 2.6.1 and 2.6.2 is that of a nulliparous woman?---Yes.
>
> Given that Ms Turner was para 3, and given that you agree that with parity uterine weight increases, it is, to compare her uterine weight there of 158 grams to that of a nulliparous woman, is an invalid comparison?---The statement which I put in 2.6 is there with context, that is that not only does it appear to be final uterine weight being heavy, but that's consistent with the ultrasound findings that we referred to and we have mentioned, and consistent with the laparoscopic findings, and therefore in that context that's what, the kind of patients that I would get the report back expecting to see adenomyosis.
>
> …
>
> There's no mention there of her uterine weight being within the mean, being within two standard deviations of the mean of para 3?---No, but I think the evidence that where weight, where no other weight or prior weight was present for us to rely upon, then we rely on other evidence that was included in the materials that we have examined, and that is the ultrasound change from 2016 to subsequent ultrasound onwards, from 2017 onwards, that clearly provided us with another estimate of the overall potentially significant change in the volume and hence indirectly potential change in the weight of the uterus.[1748]

Lam's report included a table showing that the mean uterine weight for para 3 women was 121 g, plus or minus 35 g.[1749] Lam acknowledged that Turner's uterine weight was effectively one standard deviation from the mean.

1689 White said that when Turner's uterus was weighed after hysterectomy 'it was largeish, but not strikingly abnormal'.[1750] She agreed that Turner had 'a slightly bulky uterus', but said this was a fairly non-specific finding which was not particularly significant and did not strongly suggest pathology. White said that uterus size does vary in women as they get older.[1751]

1748 T1807-8 (TRA.500.018.0001_2 at 0073_4-0074_17).
1749 Lam at 20 (EXP.001.002.0006).
1750 T1780 (TRA.500.018.0001_2 at 0046_22).
1751 T1788 (TRA.500.018.0001_2 at 0054).

1690 Lam said, when asked to comment on White's opinion, that uterine weight and size were only one element to take into account when considering diagnosis. He said the other matters he considered were the symptoms recorded in the clinical history, the progression of those symptoms, when they began, the examination findings and the results of imaging. He said that he took account of all of those things in considering the diagnosis of adenomyosis in Turner's case.[1752]

PCOS

1691 White explained that PCOS is a complex metabolic disorder that manifests in a wide variety of ways. The identifying characteristics of the disorder fall into three categories: characteristic polycystic appearance of ovaries on transvaginal ultrasound; evidence of hyperandrogenism with male hormones having an unusual influence, which can present with symptoms such as acne or hirsutism; and irregular ovulation and associated irregular or infrequent periods. The experts agreed that a woman must present with at least two of the three characteristics for a diagnosis of PCOS to be made.[1753] Women with PCOS may also present as infertile. As PCOS is a metabolic disorder, there may be other presenting features such as obesity, diabetes, or gestational diabetes.[1754]

1692 Lam said:

> … on the basis of Ms Turner's history of menstrual irregularities /oligomenorrhoea, prolonged and heavy menstrual bleeding, and ultrasound findings of polycystic ovaries, and bulky ovaries, she would meet 2 of the 3 criteria (ovulatory dysfunction and PCOM) of the Rotterdam definition of PCOS. Therefore, I believe that Ms Turner's menorrhagia may be due to combination of PCOS and adenomyosis.[1755]

1693 Lam was challenged on whether Turner satisfied the characteristic of ultrasound findings of polycystic ovaries. He agreed that polycystic ovarian morphology is defined using strict criteria including a minimum follicle number per ovary. He

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1752 T1810 (TRA.500.018.0001_2 at 0076_15–29).
1753 Lam at 47 [6.5](g) (EXP.001.002.0006).
1754 T1847 (TRA.500.019.0001_2 at 0002).
1755 Lam at 48 [6.5](j) (EXP.001.002.0006).

agreed that this is because polycystic ovaries are not solely indicative of PCOS,[1756] and that a patient with polycystic ovaries may be asymptomatic or have irregular periods. White said that the criteria for identifying the disorder were established to differentiate between the finding of a polycystic ovary on ultrasound, which may have no clinical correlation at all, and an accurate diagnosis which requires two of the three criteria. An isolated appearance of polycystic ovaries can be seen in a perfectly healthy woman and means very little unless other criteria for the syndrome are observed.[1757] Lam agreed that polycystic ovaries are frequently present in women who are otherwise healthy and do not have PCOS.[1758]

1694 It was put to Lam that the radiologist reporting on the February 2017 ultrasound concluded that Turner did not meet the strict follicular number criterion for a PCOS diagnosis. Lam said in his report:

> Recent evidence-based international guidelines have suggested an FNPO [follicle number per ovary] threshold of 20 to 25 follicles per ovary. Alternatively, ovarian volume (OV) ≥10 ml may be used when follicle resolution is suboptimal.[1759]

He said he could not clearly recall how many ultrasound images he had reviewed, but he recalled 'that there were in the order of about 20 plus [follicles] there'.[1760] Lam did not record that observation in his primary report. I note that the February 2017 ultrasound report recorded ovarian volume of 13 mL on the right and 7 mL on the left.[1761]

1695 Lam said that an irregular menstrual cycle relevant to PCOS is defined as a range of varying lengths of bleeding-free intervals exceeding 20 days within one 90-day reference period. He said that when a woman complains of an irregular menstrual cycle, it is usually indicative of an ovulatory disorder. PCOS is among the many

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1756 T1849 (TRA.500.019.0001_2 at 0004_21).
1757 T1851 (TRA.500.019.0001_2 at 0006).
1758 Ibid.
1759 Lam at 48 [6.5](i) (EXP.001.002.0006).
1760 T1860 (TRA.500.019.0001_2 at 0015_10–31).
1761 TUR.001.001.0359_R at 3–4.

causes of such disorders. Turner's history of up to six weeks without a period is consistent with ovulatory dysfunction and meets the first criteria for PCOS.

1696 Lam agreed that the range and degree of symptoms described on history or found on examination was important to whether the first criteria for PCOS was made out.[1762] He agreed that menstrual irregularity was the only clinical feature consistent with PCOS was Turner's history. Lam said Turner's pattern of regular, heavy and prolonged bleeding was not uncommon in women with PCOS.

1697 White emphasised that menstrual disturbance due to PCOS is usually indicated by absent or infrequent ovulation. These infrequent periods may be very light or prolonged and heavy, depending on the patient's underlying hormonal status.[1763]

1698 White explained that because PCOS is a metabolic disorder, it will affect women for most of their reproductive life. While symptoms may fluctuate, they normally present relatively early. Prior to 2014 or 2015, Turner did not present with symptoms relevant to PCOS other than menstrual irregularity, which in itself does not necessarily mean she had an ovulatory disorder.[1764]

1699 White said that only one of Turner's ultrasounds suggested the possibility of polycystic ovaries. Turner did not have any symptoms of hyperandrogenism or a metabolic disorder. She did not have any particular difficulty conceiving. While Turner did experience menstrual disturbance, it presented as frequent heavy periods that occurred monthly and would last for up to three weeks. This history of menstrual disturbance would not normally be associated with PCOS. White concluded that on that basis, the diagnosis of PCOS could not be made out.[1765]

1700 White was asked about Lam's evidence that a history of heavy bleeding is consistent with PCOS. She responded:

1762 T1863 (TRA.500.019.0001_2 at 0018).
1763 T1853 (TRA.500.019.0001_2 at 0008).
1764 T1864 (TRA.500.019.0001_2 at 0019).
1765 T1854 (TRA.500.019.0001_2 at 0009).

> Look, I have to say we've all acknowledged that the reason a woman with PCOS may have heavy periods is because she is not ovulating regularly. And I agree with Dr Lam, that usually will mean that her periods are further apart and when they come they may be very heavy. I agree with that. But in my own clinical experience it is very unusual for a woman who's getting a period roughly every month, lasting for three weeks and heavy, to be anovulatory. That's just not usually the pattern that you see. And if a woman has PCOS, the problem is anovulation. So I think that pattern of a period regularly, heavy and prolonged, is not consistent with ovulatory disorder. It might be, but it's certainly in my own clinical experience that would be very unusual.[1766]

Expert evidence on causation of Turner's symptoms

1701 White said that until 2013, Turner did not have any gynaecological problems that troubled her. She did not complain of period pain or heavy bleeding. She managed to conceive naturally and had fairly straightforward pregnancies and births. In the five-year period after Essure was implanted, Turner developed gynaecological symptoms, particularly painful periods, persistent pain and sharp pain on one side of the pelvis. Turner had a number of ultrasounds that did not demonstrate a clear cause of her symptoms. She proceeded to a hysterectomy which resolved her symptoms. Pathology examination did not detect adenomyosis. White said that when a woman presents as Turner did with menorrhagia, dysmenorrhea, pelvic pain and dyspareunia, it is appropriate for a treating gynaecologist to think, as Turner's gynaecologist did, that she was probably suffering adenomyosis and endometriosis. However, in Turner's case, no cause was found for her symptoms. White said that in those circumstances, one plausible explanation is that Essure was a cause of her troublesome symptoms and that those symptoms resolved completely once the devices were removed.[1767]

1702 White said that she could not explain the mechanism by which Essure caused Turner's symptoms, and accepted that her conclusion was based on excluding other pathological causes that were considered.[1768] White accepted that in a significant number of women who have a hysterectomy because of heavy and painful periods, histological examination does not reveal specific pathology. She said it is assumed

1766 T1869 (TRA.500.019.0001_2 at 0024_2–16).
1767 T1882 (TRA.500.019.0001_2 at 0037).
1768 T1886 (TRA.500.019.0001_2 at 0041_9).

that the mechanism of heavy bleeding for those women is related to some dysfunction in the endometrium. White agreed that if Turner had not had Essure implanted, she would fall into this category.[1769] White did not accept that if Turner's symptoms only began in early 2016, it was less likely they were related to Essure. She said that in the absence of a mechanism that explains causation, it is not possible to predict when symptoms might develop.[1770]

1703 White acknowledged the possibility that the pathologist missed features of adenomyosis. She said that it was not inappropriate to look for evidence of adenomyosis and accepted that this was the diagnosis Dalton adopted. However, she added:

> But to go back retrospectively and say that's what it was, the evidence just isn't there. It required reinterpretation of ultrasound scans to say, 'I think I can see adenomyosis', and it requires an assumption the pathologist was incomplete and missed a diagnosis. So, yes, I mean I can't rule out the possibility that Ms Turner did have adenomyosis not seen on most of her ultrasound scans and not picked up the pathologist, that is possible. But that's really as far as you can take it.[1771]

White said that she was confident in excluding PCOS as a diagnosis because Turner did not meet the diagnostic criteria.[1772]

1704 Lam said that the rapid resolution of Turner's symptoms following hysterectomy raised the question of whether the Essure devices contributed to her symptoms. However, he said that while possible, it was not likely that Essure was a cause of Turner's symptoms.[1773]

1705 It was put to Lam:

> Your conclusion that the device was not a probable cause is predicated upon your opinion that there were other underlying causes, namely adenomyosis and PCOS?---Yes.

1769 T1889 (TRA.500.019.0001_2 at 0044_25).
1770 T1890 (TRA.500.019.0001_2 at 0045).
1771 T1891 (TRA.500.019.0001_2 at 0046_16–24).
1772 T1892 (TRA.500.019.0001_2 at 0047_1).
1773 T1898 (TRA.500.019.0001_2 at 0053_26).

> Let's assume there is in fact no other convincing explanation for her pain. If she did not have adenomyosis and PCOS, then you would agree the Essure Device remains, as you've already said, a possible cause?---Yes.
>
> …
>
> Assuming, Dr Lam, that adenomyosis was not a cause and PCOS was not a cause, then the Essure Device remains, as you've said, a possibility, yes?---It is always a possibility, yes.
>
> And what I'm suggesting, in the absence of any other persuasive cause, if there is no other persuasive cause, the Essure Device looms large?---No, it doesn't.[1774]

Submissions

Turner

1706 Turner was not aware that she might suffer CPP or AUB as a result of having Essure devices implanted, or that removal of the devices might involve hysterectomy. The only warning Turner recalls receiving was that there was a chance she would require tubal ligation if the devices could not be inserted correctly while she was under general anaesthetic. Turner was not ready to lose her uterus when she required hysterectomy surgery at only 32 years old. Had she been warned of the risks associated with Essure, she would not have had the devices inserted and would instead have 'gone down the path of tubal ligation or something that didn't involve major surgery'.[1775]

1707 Turner had not experienced painful periods before having Essure inserted. She began to experience pelvic pain, dysmenorrhea and menorrhagia in 2014. The pain and AUB became progressively worse over the years.[1776]

1708 The defendants' contention that Turner's pelvic pain and heavy bleeding did not commence until 2016 is inconsistent with the cogent evidence given by Shields. Turner accepted that she did not attend medical practitioners regularly for her gynaecological symptoms until she was living in Ballarat in 2017 and 2018. The lack

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1774 T1907-8 (TRA.500.019.0001_2 at 0062-3).
1775 T1003-4 (TRA.500.011.0001_2 at 0040–1); SBM.001.001.0004 at 331.
1776 SBM.001.001.0004 at 332 [1126].

of attendance and absence of a reported complaint is explained by Turner's acutely stressful domestic situation at the time.[1777]

1709 Lam's justification for why the April 2016 ultrasound images did not reveal the signs of adenomyosis that he said he identified on the February 2017 scans, namely that the disease was not sufficiently progressed in 2016, is purely speculative.[1778] Further, Lam conceded that if it was accepted that Turner was symptomatic since 2015, then given the 2016 ultrasound images it is likely she did not have adenomyosis at the time. In light of that concession, Lam's ultimate thesis that adenomyosis was the cause of Turner's symptoms must be rejected.[1779]

1710 Lam's opinion about what can be seen in images from the 2017 ultrasound should also be rejected. This is particularly so in light of Lam's concessions that scanning of the uterus is a dynamic process, and that the person performing the ultrasound was better placed to analyse the images than he was on a limited review of the still images. It is relevant that a number of features Lam said he identified from the images were not reported by the ultrasound radiologists.[1780]

1711 Lam's evidence that widespread cystic changes were shown in a February 2017 ultrasound image is inconsistent with his thesis that the pathologist missed the adenomyosis diagnosis by reason of inadequate tissue sampling. Further, Lam's opinion about inadequate tissue samples was not predicated on any analysis of the histopathological report relevant to Turner, but instead relied on the 50-year-old Bird 1972 study. There is no evidence that examination by the pathologist of Turner's tissue samples was in any way inadequate.[1781]

1712 Lam's evidence as to PCOS was unpersuasive. While Turner did have polycystic ovaries, as demonstrated on pelvic ultrasound, she did not meet the strict follicular

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1777 T1020 (TRA.500.011.0001_2 at 0057); Ibid at 334.
1778 SBM.001.001.0004 at 342-3 [1152].
1779 Ibid at 343 [1153].
1780 Ibid at 344 [1154].
1781 Ibid at 344 [1156].

number criteria required for a PCOS diagnosis. Turner had no other features demonstrative of PCOS, hence White's confident exclusion of that diagnosis.

1713 An observation made at hysterectomy was that Turner's fallopian tubes were swollen. Lam said that the left fallopian tube appeared distorted on an image taken at the time of hysterectomy. Lam agreed that a swollen fallopian tube may indicate some kind of inflammatory process within the tube. He agreed that an inflammatory process in a left fallopian tube could produce left-sided pain.[1782]

1714 Badylak said that swelling was a criterion of active inflammation. The pre-hysterectomy study showed that inflammation tended to be localised immediately around the Essure device. Robertson explained how a localised chronic inflammatory reaction to Essure could be responsible for AUB and CPP:

> To be clear, the absence of immune cell changes in tissue at a site some centimeters from the site of an Essure Device, doesn't mean that the physiology and function of that tissue is not affected by the Device. … [A] chronic inflammation response within a fallopian tube due to presence of an Essure Device is highly likely to exert effects in the reproductive tract and pelvic cavity and systemically (elsewhere in the body), including but not limited to abnormal uterine bleeding, chronic pelvic pain, and systemic changes to the immune response. These changes can occur without immune cell changes that are detectable by histological analysis of those tissue sites. This is because … chronic inflammation gives rise to soluble pro-inflammatory mediators, including cytokines, prostaglandins, microRNAs and other mediators that emanate from the site and travel to other sites via the lymphatic drainage, the peripheral blood system, and neural networks. In the case of the Essure device, soluble pro-inflammatory factors travelling to the uterus, draining lymph nodes, peritoneal cavity, and elsewhere in the body can affect the function of those tissues, despite their large distance from the site of the Device.[1783]

As-Sanie agreed, as a matter of scientific principle, that it is biologically plausible that persistent inflammation will cause pain.[1784] This evidence is consistent with a localised chronic inflammatory reaction being present in Turner's fallopian tubes.

1715 Korda said it can be assumed that if 'someone is totally pain free and has no history of pain before[,] and then has a device inserted which causes [a] chronic inflammatory

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1782 T1878 (TRA.500.019.0001_2 at 0033).
1783 Robertson at 152 [427] (EXP.001.002.0015_2).
1784 T2572 (TRA.500.028.0001_2 at 0035).

response, then the pain is due to [the insertion of the device]'.[1785] Further, Korda said that if such a patient has chronic pain which they did not experience before the device was inserted, and the pain ceases when the device is removed, it can be assumed that the pain was likely due to the presence of the device.[1786]

1716 The fact that no chronic salpingitis was observed in Turner's fallopian tubes following hysterectomy does not negate the contention that Essure was a cause of her CPP. Murdock noted that it was not clear where the tissue sections were obtained in relation to the location of the Essure device.[1787] Robertson said that unless a tissue sample was taken in the immediate vicinity of the device, it would not be informative on whether chronic inflammation existed associated with the device.[1788] Sokol agreed that the utility of histological analysis of excised fallopian tube tissue in the context of identifying the presence of inflammation 'can be limited by [the] requirement for tissue that is immediately adjacent to the device'.[1789]

1717 Lam accepted as possible that there was a causal connection between Essure and the chronic pain and AUB experienced by Turner. The opinions of White and Korda establish the causal connection to a reasonable satisfaction. As in *Metro North Hospital Service v Pierce,*[1790] the real difference between the experts on the issue of causation turns on matters of high-level scientific proof. The causal mechanism espoused by Korda is supported by the opinions of As-Sanie, Badylak, Chrzanowski and Robertson as referred to above. For the reasons set out above, the opinion of White should be preferred to that of Lam.[1791]

Defendants

1718 Even if it was found Turner had established that Essure:

1785 Ibid.
1786 T2573 (TRA.500.027.0001_2 at 0036).
1787 Murdock at 26 [63] (EXP.001.002.0008).
1788 Robertson at 151 (EXP.001.002.0015_2).
1789 Immunology JER at 23 (EXP.500.001.0004).
1790 [2018] NSWCA 11 at [152].
1791 SBM.001.001.0004 at 349 [1166].

(a) caused the pleaded specified symptoms or adverse events in some women; and

(b) was a possible cause of the gynaecological symptoms in her case,

such evidence is incapable of rising higher than Essure being but one of at least three possible causes of her gynaecological symptoms.[1792]

1719 Lam's evidence establishes that Turner's symptoms were most likely caused by adenomyosis. The Court should find, on the balance of probabilities, that this was the case. Indeed, this was the contemporaneous diagnosis made by Turner's treating gynaecologist Dalton. Tellingly, Turner did not call Dalton to give evidence in this trial or provide any reason for not doing so.

1720 For the following reasons, the Court should reject any submission that because adenomyotic changes were not found in the post-hysterectomy histopathology, a diagnosis of adenomyosis is excluded. First, it was Lam's evidence that it is not uncommon for pathologists not to identify adenomyosis even though it exists. He said that in his experience, adenomyotic tissue is often found when a review examination is requested.[1793]

1721 Second, the positive ultrasound findings made by Dalton and Lam cannot be treated as if they do not exist just because they are not referred to in the pathology report.[1794]

1722 Third, the absence of evidence of any pathology or clinical findings suggestive of another cause of Turner's gynaecological symptoms makes adenomyosis the most likely cause. For example, there is no evidence that Turner had inflammation in the endometrium or fallopian tubes. In light of these points, adenomyosis is the most likely cause of Turner's gynaecological symptoms.

1723 The Court is under no obligation to find a probable cause of Turner's gynaecological symptoms. If adenomyosis is excluded, the evidence does not enable any such finding

1792 SBM.500.001.0003_2 at 108 [2.4].
1793 SBM.500.001.0003_2 at 111 [2.17]-[2.18].
1794 Ibid at 111 [2.19].

to be made.[1795]

1724 There is no statistical evidence which provides any basis to find that Essure was the cause of Turner's gynaecological symptoms. The available data tends against that conclusion. There are three answers to any contention by Turner that she can 'plug the epidemiological void' in her case by reference to hypotheses of biological causal mechanisms proffered by expert witnesses.[1796]

1725 First, the hypotheses do not rise as high as *proving* that Essure caused the pleaded harm in some women.

1726 Second, even if Turner did overcome this hurdle, she has failed to prove that those biological mechanisms operated in her case, or that she had biological indicia of those mechanisms. Relevantly, White accepted that if Essure was a cause of Turner's symptoms, it was by some mechanism of injury that she could not identify.[1797]

1727 Third, there is compelling evidence that among the population of women of reproductive age who suffer from CPP and AUB, it is not uncommon that the cause of such symptoms cannot be identified. This conclusion is consistent with the evidence of White, Korda and As-Sanie. White said that in a significant number of women who have had hysterectomies to treat CPP and AUB, there is no pathology that identifies the cause of the symptoms. Even if it *is* found that Essure does increase the risk of CPP and AUB, Turner has not established that such an increase in risk makes it a more probable cause than alternatives like adenomyosis or other unidentified causes.[1798]

1728 Assuming that Turner has discharged her onus of proving that Essure was a cause of her symptoms, it is then necessary to determine whether she has proved that the absence of any requisite information or warning provided in connection with Essure

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1795 Ibid at 112 [2.21]-[2.23].
1796 Ibid at 112 [22.7]-[22.8].
1797 Ibid at 114 [2.32]; T1890 (TRA.500.019.0001_2 at 0045_1).
1798 SBM.500.001.0003_2 at 114-5 [2.35]-[2.39]

caused her to proceed with its implantation. This requires determination of:

(a) what would constitute the minimum information or warning required in the circumstances;

(b) whether such warning or information was provided; and,

(c) if such warning or information was not provided, whether such provision would have dissuaded Turner from proceeding to have the Essure device implanted.[1799]

At no stage did Turner plead, particularise, lead evidence of, or make a submission about the content of an allegedly required warning or information. This places the Court in a very difficult position when it comes to determining whether a warning would have made a difference in Turner's own case.[1800]

1729 Even if Turner otherwise discharged her onus of proof, any requisite information or warning needed to do no more than identify that there was a very small additional risk of suffering CPP and AUB (compared to the background rate in women of reproductive age) caused by Essure, which would only rarely require a hysterectomy. In that hypothetical scenario, it would then have been appropriate for Turner's treating doctor to counsel her that the rates of CPP, AUB and hysterectomy were similar between Essure and laparoscopic sterilisation.[1801]

1730 Turner's evidence that had she been told of the risks, she would have decided to have tubal ligation instead of Essure implantation, must be given virtually no weight. Turner did not articulate what she would have done had she been told of a low risk of CPP and AUB arising from Essure implantation. The evidence is that she had a strong preference for the Essure procedure. It should not be accepted that a warning of a small increase in the risk of future AUB or CPP, which might require a

1799 Ibid at 116 [2.42].
1800 Ibid at 115 [2.41]-[2.44].
1801 Ibid at 116 [2.45].

hysterectomy, would have altered Turner's decision.[1802]

Analysis

When did Turner's gynaecological symptoms develop?

1731 Turner's menstrual cycle was irregular before she underwent the Essure procedure in September 2013. Lam suggested it was possible that symptoms of AUB were regulated and/or reduced by pregnancy and Turner's use of the OCP.[1803] I conclude that this is unlikely. Turner's use of the OCP was sporadic and infrequent. I accept White's evidence that the 'niggly' pain Turner experienced at the beginning of her period was not abnormal, and that the history does not suggest a pathological cause for Turner's irregular menstrual cycle.

1732 The parties are at odds about when Turner's gynaecological symptoms commenced. Turner's recollection, supported by the evidence of Shields and Smith, is that she started to experience symptoms of bleeding and pain in 2014 or 2015. Turner described these symptoms as being quite significant from this time, such that her 'bleeding became much heavier', and pelvic and abdominal pain was 'regular sharp, severe', 'extremely strong', and at a 'particularly severe and excruciating level perhaps once every couple of weeks'.[1804] Shields described observing Turner having days where she was quite debilitated by abdominal and back pain from about mid-2015.

1733 The first clinical entry that Turner relates to her symptoms is of a GP attendance on 2 February 2015. In her witness statement, Turner said:

> The first time that I recall attending a GP about my pelvic and abdominal pain and tiredness was on 2 February 2015. Dr Mohammad Al Naima referred me to have blood tests and a pelvic x-ray. I recall having the x-ray a few days after my appointment. I cannot recall the outcome of that x-ray.[1805]

1734 The note of that attendance records the following history and treatment plan:

> feeling tired

1802 Ibid at 117 [2.47]-[2.49].
1803 T1895 (TRA.500.019.0001_2 at 0050_4-12).
1804 Turner at 6 [47]-[48] (LAY.001.001.0001_R).
1805 Ibid at 7 [53].

no sleep apnea
mood is up and down
no energy [sic]
4 cigarette per day
3 nights per week couple of drinks
upper GIT pain
B wieghT [sic] 65.5
no alarming signs
modd [sic] flactuate [sic]
Plan
Bloods and Urine
may discuss on sleep pattern change[.][1806]

The note is detailed and makes no reference to pelvic or abdominal pain. It is not clear from the note or Turner's evidence why a pelvic x-ray was ordered. In her oral evidence, Turner could not recall what symptoms she complained of at that consultation with her GP, but said that she did 'recall requesting blood tests to find out why I was feeling the way I was'.[1807] I am not satisfied that Turner made a complaint or reported a history of pelvic or abdominal pain at the 2 February 2015 attendance.

1735 The clinical entry for an attendance on 16 February 2016 for a pap smear includes a reference to Turner's irregular menstrual cycle.[1808]

1736 The clinical entries of 12 April 2016 and 28 July 2016 are relevant to symptom commencement and development. They are consistent with symptoms of pelvic pain and AUB commencing in around early 2016, and being unrelated to Turner ceasing use of the OCP. On the other hand, the clinical entry of 2 February 2017 is consistent with Turner having suffered menorrhagia and possibly pelvic pain for some years prior to that attendance.[1809]

1737 Turner did not challenge the accuracy of the GP clinical notes, other than perhaps the reference to upper gastrointestinal pain in the entry of 2 February 2015.

1806 TUR.001.001.0262_R at 8.
1807 T928 (TRA.500.010.0001_2 at 0068_31).
1808 TUR.001.001.0262.
1809 TUR.001.001.0359_R at 3.

1738 It is difficult to reconcile the witness evidence about when Turner's gynaecological symptoms commenced and the severity of those symptoms with the clinical notes for the following reasons. First, there was no complaint of pelvic pain or AUB symptoms to any medical practitioner until April 2016. Turner explained the lack of complaint by saying she was going through a turbulent time in her life, with the breakdown of her marriage and the need to safely extricate herself and her young children from the marital home. Turner said in effect that at the time, her personal health was not a priority. I accept that 2015 was a very difficult and unsettled period for Turner.

1739 However, I note that Turner did attend with her GP on four occasions during 2015 and on two further occasions in early 2016 in relation to issues including recurrent eczema and anxiety, and with a nurse for a periodic pap smear. I accept that there would have been occasions during 2015 when Turner was distracted from focusing on her personal health issues. However, this does not adequately explain why, if Turner was experiencing serious, recurrent and worsening pelvic and abdominal pain and AUB from 2015, she made no mention of those matters to any treater. Turner accepted in cross-examination that if she was experiencing recurring or serious pain, she would have told her doctor.

1740 Second, the 2016 clinical notes do not bear out the severity of symptoms that Turner says she was experiencing by that time. The note of 13 April 2016 suggests the experience of acute rather than chronic or recurrent pain. The note of attendance on 28 July 2016 records the reason for contact as dysmenorrhea and records a history of dyspareunia, but does not record complaints about the frequency or severity of symptoms.[1810] There was no complaint of pelvic pain or AUB at the time of two GP attendances later that year.

1741 Third, the quite detailed GP note of attendance on 28 July 2016 records the onset of AUB in January 2016. This appears to be a careful note of attendance. Commencement of symptoms is recorded in two different ways: 'onset six months ago'; and

[1810] TUR.500.001.0262 at 5.

'menstruation being fine and regular until January this year'.[1811] This entry is more precise than the clinical note of 2 February 2017, which records a history of 'menorrhagia since years'. Read as a whole, the clinical notes support the conclusion that Turner's AUB symptoms commenced at around the start of 2016. The notes are not as clear in relation to pelvic pain. However, there is nothing expressly stated in the notes to the effect that pelvic pain commenced before 2016.

1742 The clinical notes of GP attendances on 2 May and 12 June 2018 record a history that Turner's symptoms were longstanding and had commenced after the Essure procedure.[1812] Turner said that by that time, she suspected Essure was responsible for her symptoms. I conclude that the clinical notes reflect the causal association Turner had made in her own mind, and are not a reliable record of the development of her symptoms.

1743 The defendants submitted that the episode of severe pain recorded in the GP notes of attendances on 12 and 13 April 2016 was an isolated incident that was not related to the development of Turner's gynaecological symptoms.[1813] The letter from the treating GP of 13 April 2016 referring Turner to the local hospital emergency department relevantly reads:

> Thank you for seeing Patrice for ?Appendicitis
> She has a h/o intermittent RIF pain for 2-3 days, now becoming constant & moving towards ubmilical [sic], it is associated with anorexia & nausea but no vomiting. Nil significant urinary/bowel symptoms.
>
> On Examination she is afebrile, HR:101/m, BP:104/64mmHg, She has marked tenderness in RIF.[1814]

I note that while the GP raises the possibility of appendicitis in that referral letter, the clinical note recorded on the pelvic ultrasound report the day before includes 'ovarian/tubal pathology'.[1815] The GP did not arrive at a diagnosis for Turner's

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1811 Ibid.
1812 TUR.001.001.0138_R at 2.
1813 SBM.500.001.0003_2 at 135 [3.75].
1814 TUR.001.001.0381_R.
1815 TUR.001.001.0262_4 at 37.

symptoms. The location of pain in the right iliac fossa is consistent with later reports of pelvic pain. This episode is consistent with Turner's description of sharp, severe pains in the area of her pelvis and abdomen. I reject the defendants' submission that this episode of pain was not related to the gynaecological symptoms that culminated in Turner requiring hysterectomy surgery.

1744 The defendants draw attention to the fact that Turner remained quite physically active until at least mid-2016. Turner was living in Mount Gambier at the time. In November 2015 she began her relationship with Smith, who lived in Ballarat. Turner said that Smith would visit her in Mount Gambier every second weekend, and that while she tried to remain as active as possible there were times when she could not do much at all because of the pain she experienced.[1816] In cross-examination, Turner accepted that her diary entries showed that in the period from January to July 2016, she drove from Mount Gambier to Ballarat on multiple occasions. The travel time for that journey is three and a half hours. There are no diary entries in 2016 that suggest that Turner's activities were restricted by pain or other symptoms.

1745 There are reasons to doubt the reliability of Shields' recall of events. In her witness statement, Shields said that Turner lived with her from November 2015 to March 2016. In cross-examination, she agreed that Turner may have moved out of her home in January 2016. Shields said that she could not recall when Turner started her relationship with Smith. Shields said that when she noticed Turner was experiencing symptoms, she recommended that her daughter see the doctor to 'have the pain investigated because it was debilitating'.[1817] Shields said she could not remember exactly when this was, but agreed that Turner did go to the doctor on her recommendation during the period they lived together. There is no medical attendance that corresponds with Shields' memory of events. Shields was asked whether it might have been July 2016 when she recommended Turner go to the doctor.

1816 T883 (TRA.500.010.0001_2 at 0023).
1817 T1009 (TRA.500.011.0001_2 at 0046).

She said that she 'honestly [didn't] recall dates of doctors' appointments'.[1818] Turner lived with Shields again for a few months from late 2016. Shields said she recalled that on both occasions when Turner was living with her, there were times when Turner spent much of the day in bed complaining of back, abdominal and pelvic pain. However, it seems more likely these complaints were made on the second occasion Turner was living with Shields, and not the first.

1746 Smith's evidence does not take the matter any further.

1747 I accept that Turner and Shields were doing their best to give an accurate account of the commencement and development of Turner's gynaecological symptoms. However, I conclude their memory of events is imperfect.

1748 Taking into account all of the evidence, I conclude that it is likely Turner began to suffer significant symptoms of AUB and pelvic pain from around January 2016. I conclude that the symptoms were progressive and became particularly severe and debilitating in 2018.

Cause of Turner's symptoms

Adenomyosis

1749 Turner consulted with Dalton on 18 June 2018. Dalton diagnosed adenomyosis on the basis of the history of Turner's gynaecological symptoms, a physical examination and the results of a transvaginal ultrasound. The matters noted by Dalton that appeared to be consistent with or supportive of that diagnosis are the history of increasing dysmenorrhea, menorrhagia and left-sided pelvic pain, and findings of a bulky uterus, eccentric myometrial thickening of the uterus, and myometrial changes consistent with adenomyosis. Dalton confirmed the diagnosis of adenomyosis immediately post-hysterectomy surgery on 25 June 2018.[1819]

1750 The histopathology report relating to Turner's uterus and fallopian tubes is dated 27

1818 T1014 (TRA.500.011.0001_2 at 0051).
1819 TUR.001.001.0181_R at 16.

June 2018.[1820] The examining pathologist did not report evidence of adenomyosis.

1751 Dalton was in a position to give relevant evidence in relation to the cause of Turner's gynaecological symptoms. Given that causation was a central issue in her case, Turner would be expected to call her treating surgeon to give evidence. There was no explanation for her not doing so.

1752 The principle in *Jones v Dunkel* has been summarised as follows:

> The content of the rule in *Jones v Dunkel* is uncontroversial. Two consequences *may* flow from the unexplained failure of a party to call a witness who that party may be expected to call. First, the court may infer that the evidence of the absent witness would not assist the case of the party. Second, the court may draw an inference unfavourable to the party with greater confidence. In the latter case the inference must already be available on the evidence. Also, the uncalled witness must be one who appears to be in a position to cast light on the facts relied on as the ground for the inference. However, the rule in *Jones v Dunkel* does not permit an adverse inference that the uncalled evidence would have been positively damaging to the party. The absence of the witness cannot be used to make up any deficiency of evidence.[1821]

1753 On one view, it is unnecessary for the defendants to rely on *Jones v Dunkel* in relation to Dalton's evidence. Dalton's clinical notes record that his diagnosis was adenomyosis. The notes record in summary form matters that are likely to have been relevant to Dalton's diagnosis. I note that Dalton made this diagnosis in the context of receiving a history that implicated Essure, at least temporally, as a possible cause of Turner's symptoms. In a letter dated 16 June 2018 to the referring GP, Dalton noted a history of 'increasing dysmenorrhea and menorrhagia over the last five years', and that '[Turner] also had an Essure tubal sterilisation performed after her last delivery. She feels that her left-sided pain commenced shortly after this'.[1822] However, Turner submitted that Dalton's adenomyosis diagnosis was provisional and that it is clear that after receiving the histopathology report he changed his diagnosis to 'normal findings'.[1823] Turner submitted that she had tendered and relied on Dalton's evidence. She submitted there was no need for her to call Dalton as a witness at trial in

1820 Ibid at 23.
1821 *Knell v QAV Pty Ltd* [2020] WASCA 23 at [96] (Quinlan CJ) (citations omitted).
1822 TUR.001.001.0181_R at 19.
1823 T5044 (TRA.500.053.0001_2 at 0088).

circumstances where she was not putting a case contrary to the evidence in Dalton's clinical records.

1754 Turner attended a consultation at Dalton's clinic with a Vicki Pumphrey on 6 August 2018 for a post-hysterectomy check-up. The note of that attendance includes:

> GENERAL WELL BEING:
> Menopausal Symptoms: Hot flushes
> Bladder function: normal
> Bowel function: constipation
> Bleeding: slight
> Sexual Activity: no
> :
> Wounds Healed: Yes
> Complications: nil
> Treatment plan:
> Medications: nil[.][1824]

1755 Dalton wrote a final letter to the referring GP the following day that included:

> Presenting Problem: Post-operative check-laparoscopic hysterectomy
>
> At todays visit Patrice has recovered well.
>
> Examination findings: Her wounds had healed nicely. Gentle vaginal examination confirmed a normally healed vaginal [vault].
>
> Diagnosis: Post-operative check-normal findings.
> Recommended treatment: Return to normal activities.[1825]

1756 I reject Turner's submission that I should infer that Dalton altered his diagnosis of the cause of Turner's presenting gynaecological symptoms to 'normal findings'. The more likely inference is that 'normal findings' refers to Turner having an uncomplicated recovery from hysterectomy surgery with no abnormal findings on examination at the post-operative check. I am more confident in drawing that inference because of the failure to call Dalton.

1757 There are competing inferences as to the cause of Turner's gynaecological symptoms. The failure to call Dalton also means that I can more confidently draw an inference

1824 TUR.001.001.0181_R at 1.
1825 Ibid at 13.

that adenomyosis was the cause of Turner's symptoms.

1758 I accept White's evidence that a definitive diagnosis of adenomyosis depends on a positive histological finding. However, my task is not to make a definitive diagnosis. Rather, it is to determine whether it is likely that Essure was a cause of the gynaecological symptoms suffered by Turner. It is relevant to the determination of this issue to consider whether the features to which I have referred mean that adenomyosis is the likely cause of Turner's symptoms.

1759 I accept White's evidence that the pre-hysterectomy signs consistent with or indicative of adenomyosis are not definitive of the disorder. In Turner's case, those indicative signs were the nature of symptoms she complained of; that those symptoms progressively worsened over time; the bulky, enlarged uterus; and myometrial changes of the uterus. It is relevant that signs of adenomyosis were not reported by the pathologist who undertook histological examination of the uterine sections following hysterectomy. However, I note the experts agreed that histological examination frequently fails to detect adenomyotic tissue.

1760 The gynaecological symptoms experienced by Turner have a range of potential causes. The experts agreed the differential diagnoses included endometriosis, PCOS and adenomyosis. Further, as White said, it is not infrequently the case that evidence of a pathological cause of pelvic pain and AUB is not found following hysterectomy. The experts agreed that endometriosis should be dismissed as a possibility. I accept White's reasons for dismissing PCOS.

1761 The progressive worsening of Turner's symptoms from around early 2016 to hysterectomy surgery in mid-2018 is consistent with the diagnosis of adenomyosis.

1762 The table relied on by Lam as a means of assessing uterine weight is reproduced as follows:[1826]

1826 Joel Platt et al, 'Ultrasound of the Norman Nongravid Uterus: Correlation with Gross and Histopathology' (1990) 18(1) *Journal of Clinical Ultrasound* 15, 17 (PUB.500.001.0424 at 3).

Mean Values and Suggested Upper Limits of Normal for Premenopausal Uterine Weight as a Function of Parity

Parity	N	Uterine Weight*	Two Standard Deviations above Mean Uterine Weight
		g	g
0	9	60 ± 20	100
1	9	109 ± 26	161
2	18	108 ± 28	164
3	12	121 ± 35	191
>4	13	130 ± 35	200
Total	61	109 ± 37	

*Mean ± SD.

The table suggests that two standard deviations above mean uterine weight represents the upper limit of normal. Turner's uterus weighed 158g, which is only marginally more than one standard deviation above the mean for para 3 women and is well within the normal weight range.

1763 In Bird 1972, the mean uterine weight of 50 para 2 and 3 women found to have adenomyosis was 132g.[1827] Lam referred to another study which found that '[t]here was no relationship between symptoms such as menorrhagia, dysmenorrhea and abdominal pain and uterine weight' when adenomyosis is the sole pathology.[1828]

1764 This evidence suggests that while uterine enlargement may be relevant, it is not a strong indicator of adenomyosis. I accept White's evidence that considered alone, enlargement of the uterus is not a particularly specific sign of adenomyosis.

1765 The progressive changes to Turner's uterus are of greater relevance. I accept, consistent with Lam's evidence, that the normal finding on the April 2016 ultrasound is consistent with the disease being in the early stage, evidenced by Turner beginning to suffer symptoms from around the start of 2016 that were initially milder and intermittent. Turner's symptoms had progressed by the time of the February 2017 ultrasound, which showed a very bulky uterus. The finding of a bulky uterus was

1827 Bird 1972 at 5 (PUB.500.001.0423).

1828 Lam at 21 [2.4.1](k) (EXP.001.002.0006); M Levgur, 'The enlarged uterus. Relation of uterine size and histopathologic findings' (1996) 41(3) *Journal of Reproductive Medicine* 166.

repeated in the February 2018 ultrasound, the examination by Dalton in June 2018, and in the histopathology report.

1766 The ultrasound findings made by Dalton were of '55mm eccentric myometrial thickening' and 'myometrial changes consistent with adenomyosis'. It is not clear whether the second comment is a reference to the first finding, or is a separate observation of tissue changes observed within the myometrium. It is again relevant that Turner has chosen not to call Dalton to clarify his ultrasound findings.

1767 The finding of asymmetrical myometrial thickening is supported by Lam's review of the February 2017 ultrasound images. However, there is no mention of that feature in the pathologist report of histological examination post-hysterectomy, or the radiologist reports of the February 2017 and February 2018 ultrasounds.

1768 There are limits to the weight that should be attributed to Lam's evidence about features consistent with adenomyosis that he observed on still images of the February 2017 ultrasound that were not reported by the radiologist. I accept that the ultrasound scanning process is dynamic, and that as a consequence the ultrasonographer and attending radiologist were in the best position to observe relevant features and take measurements. The relative advantage enjoyed by the ultrasonographer and radiologist is reinforced in relation to the question of asymmetrical thickening because, as Lam agreed, measurements at the anterior and posterior walls of the uterus can differ depending on the axis or rotation of the still image being assessed. Further, Lam is not certified in obstetric and gynaecological ultrasound.

1769 On the other hand, Lam emphasised the importance of both ultrasound experience and relevant clinical and surgical experience to the assessment of ultrasound images. Lam has practiced as a gynaecologist for over 30 years predominantly consulting with women who present with menstrual disorders, which typically include adenomyosis, endometriosis and chronic pelvic infection and fertility issues. Lam has extensively taught in and demonstrated surgery in this field.

1770 Taking all these matters into account, I conclude that some weight should be attributed to Lam's evidence that he observed asymmetrical thickening of the uterus, myometrial cystic changes and heterogeneity on still images of the February 2017 ultrasound. Lam's evidence lends some support to Dalton's June 2018 ultrasound findings.

1771 I asked Lam whether his evidence that two images from the February 2017 ultrasound showed relatively widespread changes was inconsistent with the presence of adenomyotic tissue that he missed on histopathological examination of Turner's uterus. Lam said that he could only comment on the February 2017 ultrasound images that he examined. He said that in his practice, he would 'take the effort of specifying the clinical history in the pathology request form and then further specifically [ask] the pathologist to look for adenomyosis' to expect a 'more reliable test result'.[1829] Lam said it was also his practice, in similar circumstances where the clinical history and ultrasound findings supported a diagnosis of adenomyosis, to request a review if the pathologist did not initially find adenomyosis on histopathological examination.

1772 I place little weight on Lam's observations based on a photograph taken at the time of hysterectomy. I accept White's evidence that it would be difficult to determine from such an image that the uterus was bulky because it cannot be seen in context, or that there was asymmetrical thickening because only the external appearance of the uterus is seen. I accept that the finding of the serosal adhesion, if it was present, is not particularly significant to the diagnosis of adenomyosis.

1773 In summary, I conclude that a diagnosis of adenomyosis is supported by:

(a) the history of Turner's symptoms;

(b) the progressive worsening of those symptoms over time;

[1829] T1835 (TRA.500.018.0001_2 at 0101_3).

(c) the finding of a bulky and heavy uterus, particularly in the context of the development of symptoms;

(d) Dalton's findings of eccentric myometrial thickening and myometrial changes consistent with adenomyosis, which is supported by Lam's evidence about what is seen in the February 2017 ultrasound images; and

(e) Dalton's diagnosis of adenomyosis.

Essure

1774 In Turner's case, there is no examination finding, radiology or test result, operation finding or observation on histopathological examination that supports a causal connection between the implanted Essure devices and the gynaecological symptoms she experienced.

1775 I reject Turner's submission that the swollen and distorted appearance of her fallopian tubes at hysterectomy is evidence of an inflammatory process within the tubes that was causally relevant to her experience of pelvic pain and AUB. A handwritten post-operative information form that appears to have been completed by Dalton includes a diagram depicting swelling to the distal parts of both tubes together with the note: 'swollen tubes (Essures located. Normally placed)'.[1830] There is no suggestion in Dalton's clinical records or the pathologist report that there was an active inflammatory or pathological process present within the fallopian tubes. The note and diagram made by Dalton are consistent with the swelling having been caused by a normal fibrotic response to the Essure devices. Turner did not call Dalton to explain his post-surgery note.

1776 Turner sought to rely on Lam's evidence that the bulky uterus, serosal adhesions and myometrial asymmetrical thickening seen on the operative photo, were features indicating that there was some kind of inflammatory process occurring. Lam identified the inflammatory process in the wall of the uterus, not in the fallopian tubes.

1830 TUR.001.001.0181_R at 7.

He said that the distortion seen at the cornua was consistent with the presence of an Essure device.[1831] Lam said that if he saw these signs on laparoscopy and did not know the patient had Essure, he would be concerned about whether there was a chronic inflammatory process 'that might have caused a blockage in that area'.[1832]

1777 Read in context, I understand Lam's evidence to be that the swelling and distortion to the fallopian tube and cornua seen on the surgical image was an expected response to the presence of the Essure device. Lam did not suggest that there was in fact a pathologic chronic inflammatory process present in the fallopian tube.

1778 White said, in response to a question about factors that would indicate active inflammation in the fallopian tubes or endometrium:

> But in the end if a woman had active inflammation of the fallopian tubes you would expect there to be an abnormality seen on the histological examination, which was not seen. And as Dr Lam said, Ms Turner did have swabs taken looking for the possibility of an infectious cause and I don't think anything was ever found. So there's really no clinical basis to substantiate - she did not really meet any of the criteria for active inflammation of either the endometrium or the fallopian tubes. [1833]

Lam agreed, and added:

> I'd just like to add one further and that is the opportunity that the pathologist had in the final examination of the removed uterus and the pathologist report which we have on p9 of my report, 1.35. In the microscopy section the pathologist was quite clear 'no endometritis is seen', and as far as the fallopian tubes assessment, 'no specific diagnostic abnormality'. So that, to me, means no evidence of endometritis or salpingitis.[1834]

1779 The evidence does not support Turner's submission that the swelling and distortion of the fallopian tubes seen at operation is evidence of the presence of an active chronic inflammatory process within each fallopian tube.

1780 White reasoned it was likely that Essure caused Turner's pelvic pain, dysmenorrhea and dyspareunia on the basis that she was a fit, healthy, fertile woman before having

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1831 T1878 (TRA.500.019.0001_2 at 0033_2).
1832 T1878 (TRA.500.019.0001_2 at 0033_8).
1833 T1875 (TRA.500.019.0001_2 at 0030_18–27).
1834 T1876 (TRA.500.019.0001_2 at 0031_2–10).

the devices inserted; there was no confirmed gynaecological condition that explained her symptoms; and that her symptoms resolved immediately after surgical removal of the devices.[1835] White explained her reasoning in the following way:

> Up until 2013 I don't believe Ms Turner had any gynaecological problem that troubled her. She didn't ever complain of troublesome period pain, heavy bleeding that was a problem for her, she managed to conceive naturally and had fairly straightforward pregnancies and births. In 2013, as we know, she had the Essure Device inserted. In the subsequent years, I guess then over a period of five years, she developed gynaecological symptoms, particularly pain, various sorts of different pain, painful periods, persistent pain, sharp pain on one side of her pelvis, and she developed periods that became very troublesome to her, to the point where those symptoms really had a significant impact on her quality of life. So she saw a number of general practitioners, had a number of tests done, she had some ultrasound scans done and really I think up until that point no one really had any clear - I guess in a sense no one really quite knew what was going on. Anyway, she was eventually referred to a specialist gynaecologist, Dr Dalton, who took a history, examined her, did his ultrasound scan and not unreasonably made a provisional diagnosis of … adenomyosis.
>
> …
>
> So she had the hysterectomy done. Dr Dalton [noticed] at the time that, yes, she did have a bulky uterus, which would be consistent with adenomyosis. … When the pathology examination was conducted on her uterus, no evidence of adenomyosis was found. Following her hysterectomy - obviously her menstrual problems were solved, that was going to happen whatever the underlying cause was, but she also said, and this is what she said to me, what she says in her own report, quite strikingly her pain disappeared and has never come back to be a problem for her. … And not unreasonably people thought, well, was there a diagnosis that was missed? Although she had lots of scans and a pathology examination, could something have been missed? And on that basis this question of adenomyosis came up again and retrospectively scans have been reviewed and perhaps Professor Lam thought he could see things that weren't reported at the time and he suggested that the pathology missed a diagnosis of adenomyosis. But it seems to me it is a plausible explanation of that sequence of events and the findings that occurred along the way, the ultrasound scans and the pathology examination of the uterus, one plausible explanation is that it was in fact the Essure coils that caused all these troublesome symptoms and why they, particularly her pain, resolved completely once the Essure coils were removed. So that's my understanding of the situation and why, as I said in my report, I think it is a plausible explanation that the Essure coils were the cause of her symptoms. I don't know that it's possible to say that they caused one or other. I think it's plausible they caused both her bleeding problems and her pain.[1836]

1835 Plaintiff JER at 8 (EXP.500.001.0005).

1836 T1880-2 (TRA.500.019.0001_2 at 0035_14-0036_4, 0036_13-0037_14).

1781 White referred to a study that identified underlying pathological conditions in cases of women who had Essure devices implanted and developed troublesome gynaecological symptoms.[1837] She said:

> Yes, in most of those women some cause will be found, but there will be a small number of women in whom no cause is found to account for their symptoms and that, it seems, is the case with Ms Turner, that no other pathological explanation was found for the symptoms and raising the possibility that the Essure was the cause of those symptoms.[1838]

1782 There was an inconsistency between White's rejection of adenomyosis as a cause of Turner's symptoms on the basis that the condition was not definitively diagnosed on histopathological analysis, and her conclusion that Essure was the likely cause of symptoms. White said that adenomyosis was a common disorder. She said that the features of Turner's case which were consistent with adenomyosis included the nature of symptoms experienced by Turner, the progressive increase in those symptoms over time, the bulky uterus and the myometrial changes reported by Dalton. She accepted that adenomyosis was not eliminated as a cause of Turner's symptoms by the absence of any finding of histopathological examination. White said that adenomyosis could only be diagnosed based on positive histological findings, which were absent in Turner's case. She reasoned that '[d]espite her clinical and ultrasound findings, Ms Turner was not found to have adenomyosis'.[1839] In contrast, White's conclusion about the causal relevance of Essure was based only on the temporal connection described above and was not otherwise supported by the symptom history, clinical examination, radiology, operation findings or histology.

1783 Further, White's opinion about the causal relevance of Essure does not sit comfortably with her conclusion that in some cases of women presenting with a history of pelvic pain and AUB, no pathological cause is found. I asked White:

> So you've got a history of symptoms that are suggestive of adenomyosis, you

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1837 Huse Kamencic et al, 'Does Essure Cause Significant De Novo Pain? A Retrospective Review of Indications for Second Surgeries After Essure Placement' (2016) 23(7) *Journal of Minimally Invasive Gynecology* 1158 (PUB.001.001.03842).

1838 T1884 (TRA.500.019.0001_2 at 0039_9-14).

1839 White at 3 (EXP.001.002.0010).

> perhaps have something on ultrasound such as enlargement of the uterus or perhaps even something else that's suggestive of adenomyosis, you undertake a hopefully definitive procedure of hysterectomy, and then there's histology which doesn't find adenomyosis. Where does that leave you? Are there differential diagnoses which then come into play?---Exactly, yes. There is other pathological processes that will particularly fit with the symptoms and the findings other than adenomyosis. If you've gone through that process and the pathologist hasn't identified it, you've got two options. You say either the pathologist missed it or in fact it was some other pathological process that caused this woman's symptoms and clinical findings.
>
> And what might be a culprit?---I think it's important to say a lot of women, well, a significant number of women who have a hysterectomy because of heavy and painful periods don't have any specific pathological finding identified when they have a hysterectomy.
>
> Yes?---So you can't - yeah, so just, you know, some woman you examine the uterus and you don't really identify anything and so you're left with two possibilities. Maybe there was adenomyosis and it wasn't identified, or this woman just happened to have heavy painful periods and perhaps a bulky tender uterus, but did not have adenomyosis.[1840]

White said that where no pathological cause is found, AUB may result from an unidentified abnormality within the endometrium that controls menstrual bleeding. In relation to pain, White said:

> In some women who have chronic pelvic pain there will be a diagnosis for why they've got that pain, such as endometriosis, adenomyosis, chronic pelvic inflammatory disease. In some of those women there will not be any pathologically detectable pathology as to explain why they've got that pain.[1841]

1784 In her final comment on the matter, White said:

> Look, this is obviously a very difficult intellectual exercise to go through. And there's really only three possibilities ultimately for Ms Turner. Either it was the Essure, she had some other pathology that was not identified, or she just would have developed all these problems anyway, whether she had the Essure or not.
> …
>
> The reason I did come down in the end to saying I think it is plausible, the question of likely or probable is very difficult for me to come to terms with. Is it plausible the Essure caused the problems? I think it is just on the basis of good - reported good health, problems that developed following the Essure and then almost total resolution of her pain once the Essure was removed.[1842]

1840 T1756 (TRA.500.018.0001_2 at 0022_4–29).
1841 T1889 (TRA.500.019.0001_2 at 0044_1–6).
1842 T1910-1 (TRA.500.019.0001_2 at 0065_3–14, 31; 0066_1–8).

White stopped short of saying that it was probable or likely that the Essure devices were the cause of Turner's symptoms.

1785 There is no evidence in Turner's case that any of the causal mechanisms hypothesised by Robertson, Chrzanowski or Korda by which Essure could cause ongoing chronic inflammation leading to AUB and CPP were operating. Turner submitted that the likely explanation for the absence of evidence of chronic inflammation on histological examination was that sections were not taken from tissue proximate to the device where chronic inflammation would be localised. There is nothing in Turner's medical records to indicate that Dalton or any other treater had a clinical suspicion that Turner's symptoms were caused by pathological chronic inflammation in the fallopian tubes. It is for Turner to prove her case. The task of establishing that Turner's symptoms were caused by a chronic inflammatory response present in her fallopian tubes that was not detected on histological examination and, where there were no clinical signs or suspicion of its presence, is made even more difficult where there are other plausible explanations for Turner's symptoms.

1786 Turner relied on the temporal connection between the gynaecological symptoms she experienced and the implantation and explantation of her Essure devices. White's evidence on this issue is set out above. Turner also relied on Korda's opinion (also set out above) that if a person has no chronic pain before a medical device is inserted and that chronic pain ceases after removal, the pain was likely due to the presence of the device.

1787 The temporal connection between the devices being inserted and symptoms commencing is not strong. White's evidence that the delay in symptoms commencing did not make Essure a less likely causal candidate can be discounted because she did not propose a mechanism to explain how Essure caused Turner's symptoms. Robertson reasoned in relation to Hoogendam 2020 that neuropathic pain resulting from chronic inflammation often takes a period of time to build up. There are two reasons why that evidence does not assist Turner. First, As-Sanie explained,

nociceptive pain arises from actual tissue damage such as inflammation.[1843] Robertson's evidence does not adequately explain why there would be a two-year delay in pain commencing if the cause of that pain was pathologic chronic inflammation resulting from Essure. Second, the evidence Turner relies on does not explain why there was a two-year delay before symptoms of AUB commenced. The delay in commencement of Turner's gynaecological symptoms makes it less likely that Essure was the cause.

1788 The logical fallacy of post hoc ergo propter hoc reasoning was considered by McDougall J in *Nguyen v Cosmopolitan Homes*[1844] ('*Nguyen*'). The plaintiffs in *Nyugen* called evidence from two experts in relation to the cause of a fire that damaged their property. Each expert proposed a different causal mechanism and said the mechanism proposed by him was the only one that could withstand challenge. The causation theories proposed by the experts were inconsistent. The plaintiffs submitted on appeal that it was unnecessary to resolve the difference of opinion between the experts, and that it did not matter which failure mechanism was chosen because breach was established and the cause of action was made good on either.[1845] McDougall J rejected that submission and said:

> Having regard to Mr Alexis' submission set out at [39] above, I should add that proof, on the balance of probabilities, that event A caused result B is not achieved merely by showing that B followed A: the "post hoc propter hoc" fallacy. Proof that the fire occurred after the electrical cables were laid on brick ties (assuming, for the moment, that this is what happened) does not prove the existence of a causal relationship between the two events. This is not a case where mere evidence of temporal sequentiality, without more, is capable of proving causation.
>
> Where B (not having occurred before) closely follows A, and where there is expert evidence to suggest that an event of the nature of A may cause a result of the nature of B, then the inference of causation may be drawn if, on the evidence, there is no acceptable alternative cause available… I would add that the same inference may be available if ordinary human experience, rather than expert evidence, suggests that "A" events have been [known] to cause "B" results, and if there is no evidence of any other acceptable cause.

1843 As-Sanie at 38 [122] (EXP.001.002.0005).
1844 [2008] NSWCA 246.
1845 Ibid at [39] (McDougall J).

> Finally, in this context, it is necessary to distinguish between inference and speculation. As Spigelman CJ pointed out in *Seltsam* at 275 [84], those two concepts occur "on a continuum in which there is no bright line division". An inference may be drawn from other facts where, as a matter of reason, those other facts make it more probable than not that the thing to be inferred exists. If they do no more than show a possibility that the thing in question exists, then its existence is a matter of conjecture, not inference.[1846]

1789 The causation argument in Turner's case amounts to barely more than post hoc propter hoc reasoning. There is no cogent evidence that ongoing chronic inflammation was present in Turner's fallopian tubes, or that any of the hypothesised causal mechanisms were operating in her case. Further, two plausible alternative causes for Turner's symptoms remained available.

1790 I am satisfied, for the reasons stated above, that adenomyosis is the most likely cause of Turner's gynaecological symptoms. If I am wrong in that conclusion, there would be three *possible* causes of Turner's symptoms. The first is adenomyosis, which White agreed remained a plausible diagnosis. The second is that Turner is among the group of women of reproductive age who suffer symptoms of CPP and AUB, where there is no pathology found following hysterectomy and the cause of the symptoms cannot be determined. The third is Essure. There is no evidence on which I could be satisfied that Essure is the most likely of those three possibilities. In those circumstances I would conclude that, having regard to those competing possibilities, the evidence does not support an inference that Essure was a cause of Turner's gynaecological symptoms.

Warnings in Turner's case

1791 It is appropriate, though not strictly necessary, that I consider the evidence and submissions relevant to the warnings aspect of Turner's case.

1792 To establish causation in relation to the statutory causes of action and negligence to the extent it is based on alleged failure to give a warning, Turner must prove that had

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1846 Ibid at [62]–[64].

an adequate warning been given she would have decided not to have the Essure procedure.[1847]

1793 The defendants accept that patients considering the Essure procedure were not told that there was a risk of developing a pathologic chronic inflammatory response which caused CPP and AUB.

1794 It was necessary for Turner to establish her general causation case before any statutory obligation or common law duty to give a warning arose. The content and nature of the warning or information that was required necessarily depended on the degree and magnitude of the risk that was established.

1795 This presented a fundamental difficulty for Turner's case. Had Turner's general causation case succeeded, there was very little evidence on which a determination could be made about the degree and magnitude of the risk of Essure causing chronic inflammation resulting in CPP and/or AUB. It may be, as the defendants submitted, that if Turner had discharged her burden of proving general causation, all that would have been established was that Essure was associated with a very small additional risk of causing gynaecological symptoms above the background rate in women of reproductive age. The defendants submitted that in those circumstances, all that would be required was a warning that there was a very small increase in the risk that Turner would suffer the gynaecological symptoms and may require a salpingectomy or hysterectomy.

1796 Accepting for a moment that Essure can cause active chronic inflammation in the fallopian tubes in some women, there is no evidence to establish the proportion of women in whom the ongoing inflammatory response is, on Robinson's evidence, low level or not productive of symptoms, and the proportion of women who develop serious symptoms of CPP and AUB that may require surgery. On Turner's case, Hoogendam 2020 came within the latter group. Had I accepted that this was the case,

1847 *Ethicon Sarl v Gill* (2021) 288 FCR 338 at [888] (Jagot, Murphy and Lee JJ) ('*Gill Appeal*').

then it was open to conclude that Hoogendam 2020 was a rare example of Essure causing the gynaecological symptoms.

1797 In the context of these difficulties, Turner did not identify with any precision the warning or information that the defendants were required to provide to her and other prospective Essure recipients in order to meet their statutory and common law obligations.

1798 It is relevant to consider what warnings and information Turner *was* given about Essure and the other contraceptive options available to her, her response to those warnings, and the reasons she decided to have the Essure procedure.

1799 Turner's first specialist consultation in relation to permanent sterilisation was with gynaecologist registrar Thalluri on 8 August 2013. The note of that attendance reads:

> 3 children, all NVD, all to the same partner
> no sig PMH
> no allergies
> had NVD 6 weeks ago, not breastfeeding
> presenting for discussion of ESSURE.
> pap smear due, has appointment with GP next week. Tolerates smears ok.
> detailed alternative options for patient, but patient sure she wants a permanent sterilisation procedure.
> pt will commence OCP.
> d/w dr weatherill.
> pt booked for ESSURE, to be done under GA, and proceed with lap sterilisation with filshie clips if need be.
> **Treatment/Plan:** Booked for ESSURE.[1848]

The risks set out in the consent form Turner signed during this consultation included bleeding, infection and damage to local structures.[1849] Turner's evidence about that consultation is set out at [1616] above.

1800 On the day of that consultation, Thalluri wrote to Turner's GP as follows:

> I saw Patrice today for discussion regarding permanent sterilization.

[1848] TUR.001.001.0087_R at 2.
[1849] Ibid at 22.

> As you know Patrice has had three children now all to the same partner and is keen for permanent contraception.
>
> I have detailed extensively the alternative options available for Patrice and explained the permanent nature of a procedure such as Essure. Patrice understands this and is still very keen to proceed.
>
> As such I have booked Patrice for an Essure sterilization procedure which will occur in the near future. We will keep you informed of her progress.[1850]

1801 On 25 September 2013, Turner consulted with anaesthetist Dr Thea Thyagarajan who undertook a pre-operative anaesthetic assessment and completed with Turner a consent to anaesthetic procedure.[1851] The risks associated with anaesthetics as set out in the consent form included brain damage, pneumonia, kidney or lung failure, death (extremely rare) and permanent disability.[1852] The consent form stated that most risks occur only rarely.

1802 In cross-examination, Turner said that she was not aware prior to the Essure procedure that there were any long-term risks associated with having the device implanted.[1853] She was asked:

> Did you ask any questions about risk?---Yes.
>
> What questions did you ask?---I don't recall the exact questions, I just recall that there might have been some bleeding and pain for the first day after having coils put in and that it wouldn't last long.
>
> You recall that was a warning you were given?---That one, yes. But just said you didn't recall any warnings?---Sorry, I misunderstood.
>
> Did you recall any other warnings? What else were you told? Were you told anything else?---That was what I recall.
>
> Did you ask any questions?---Not that I recall.
>
> Can you remember before you had the procedure that you received warnings about the risk of anaesthetic?---Yes.
>
> And can you recall what those warnings were?---No.
>
> Were you troubled by any of them?---Not that I can recall.

1850 Ibid at 3.
1851 TUR.001.001.0001_R at 24-30.
1852 Ibid at 25.
1853 T910 (TRA.500.010.0001_2 at 0050).

> Did you ask any questions about any of them?---I don't recall asking questions.[1854]

1803 I accept the evidence in the clinical records of Thalluri and Thyagarajan. I accept that during the consultation with Turner on 8 August 2013, Thalluri 'detailed extensively the alternate [contraceptive] options available' to her; explained that the Essure devices were permanent; discussed relevant risks; and obtained agreement that microscopic sterilisation with Filshie clips would be performed in the event that the Essure procedure was unsuccessful.

1804 Turner said that she could 'not recall being told that there were risks that having the device inserted may result in pelvic pain or heavy menstrual bleeding'.[1855] There is nothing in the clinical records to indicate that Turner was told that there was a risk that Essure could cause active chronic inflammation in her fallopian tubes resulting in CCP and/or AUB. There is no reason why such a warning would have been given to Turner in the circumstances where the defendants do not accept that there was such a risk.

1805 The evidence demonstrates that Turner was keen on proceeding with the Essure procedure before she consulted with Thalluri, and that the most significant factors bearing on her decision was the desire for permanent sterilisation, and that Essure was a day procedure which was less intrusive and had a much faster recovery time than tubal ligation.[1856]

1806 In her witness statement Turner said:

> If I had been told that I may suffer the pelvic and back pain, heavy bleeding, tiredness, hair loss and headaches that I experienced, and that I may need a hysterectomy, I would not have had Essure inserted. I would have chosen to have tubal ligation instead.[1857]

Turner was asked in re-examination about the issue of long-term risk:

1854 T910 (TRA.500.010.0001_2 at 0050_4-20).
1855 Ibid at 5 [35].
1856 Turner at 4 [32] (LAY.001.001.0001_R).
1857 Turner at 13 [107] (LAY.001.001.0001_R).

> Prior to having the device put in, if you had been told by Dr Thalluri or any other doctor that there were risks including a risk of chronic pain, bleeding and then, if you needed the device removed, a likelihood of losing your fallopian tubes or your uterus, what would you have done?---I wouldn't have had that done. I would have gone down the path of tubal ligation or something that didn't involve major surgery.
>
> And why do you say you wouldn't have gone down the Essure path?---I was not ready to lose my uterus. That wasn't something I ever thought was going to be a part of what went on.[1858]

1807 While Turner's evidence about what she would have done had further warnings been given to her is admissible as relevant to causation,[1859] it has been observed that in most cases evidence of this kind will be 'so hypothetical, self-serving and speculative as to deserve little (if any) weight, at least in most circumstances'.[1860]

1808 A difficulty with assessing and weighing this evidence results from the fact that by the time it was given, Turner had concluded that the risk about which she should have been warned had in fact eventuated. Turner had experienced serious and debilitating symptoms of CPP and AUB that had resulted in the need for hysterectomy surgery and loss of her uterus. By early 2018, Turner attributed those consequences to Essure. Turner's evidence about what she would have done in response to an adequate warning was inevitably influenced by her certainty that the risk had eventuated.

1809 The following further matters are relevant. First, Turner wished to have a permanent sterilisation procedure.

1810 Second, before she attended with Thalluri, Turner already had a preference for the Essure procedure.

1811 Third, the alternative contraceptive options were canvassed extensively with Turner by Thalluri, and she received advice about relevant risks including those associated with general anaesthesia.

1858 T1003-4 (TRA.500.011.0001_2 at 0040_27-0041_7).

1859 *Wrongs Act* s 51(3).

1860 *Hoyts v Burns* (2003) 201 ALR 470 at [50] (Kirby J); quoted in *Odisho v Bonazzi* [2014] VSCA 11 at [41] (Beach JA, McMillan AJA).

1812 Fourth, Turner agreed that if the Essure procedure was unsuccessful she would undergo laparoscopic sterilisation. She understood that this was a more invasive procedure with a recovery time of 6 weeks. I conclude that Turner was advised about the risks associated with that procedure.

1813 Fifth, Turner has not called Thalluri or any of her other treating practitioners to say what specific information and warnings were communicated to her about risks associated with Essure. This is particularly relevant because the PTMs and IFUs warned that hysterectomy may be required if it became necessary to remove the Essure devices. Turner gave as a reason why she would not have undergone the Essure procedure that she was 'not ready to lose [her] uterus'. However, it is clear the defendants did warn about that risk, although not as a result of the chronic inflammation, CPP or AUB for which Turner contends.

1814 What Turner would have done in response to a warning about the risk of active chronic inflammation, CPP and AUB might depend on the content of a warning that was required. Turner was told that there were grave risks associated with general anaesthesia. She was prepared to accept those risks and proceed because she had previously undergone general anaesthesia without incident, and the risks were rare. Further, Turner was prepared to expose herself to the risks associated with tubal ligation. Turner may have been told by Thalluri, consistent with the contents of the PTMs and IFUs, about the risk that salpingectomy or hysterectomy surgery may be required if for some reason the Essure devices needed to be removed. In those circumstances it is distinctly possible that, had Turner been warned that there was a small risk that Essure could cause CPP and AUB that might require treatment by salpingectomy or hysterectomy, she would have chosen to proceed. There is considerable doubt about whether the retrospective evidence given by Turner reliably reflects the choice she would have made in September 2013 had she received a further warning about the risk of chronic inflammation, CPP and/or AUB, and the possible need for hysterectomy.

1815 There are two reasons why the warnings counterfactual has not been established in Turner's case. First, accepting for this purpose that there is a risk that Essure can cause CPP and AUB that might require surgical treatment by salpingectomy or hysterectomy, the degree of the risk, and consequently the warning that was required, has not been proved.

1816 Second, Turner has not shown that she would have acted differently and not undergone the Essure procedure had she been told there was any risk of CPP, AUB and hysterectomy.

Assessment of damages

1817 I have concluded that Turner's statutory and negligence causes of action have failed. However, the parties led evidence and made submissions at trial about the damages that Turner would be entitled to if her case was to succeeded. In those circumstances, it is appropriate that I consider the assessment of damages.

1818 The statutory cause of action damages are governed by Part VI of the *Competition and Consumer Act 2010* (Cth) ('*CCA*').

1819 The maximum for non-economic loss damages may only be awarded in the most extreme case.[1861] Where the severity of injury is at least 33% but less than 100% of the most extreme case, the equivalent percentage of the maximum amount applies.[1862] For a severity of 15% to 32% of the most extreme case, the award is calculated on a sliding scale set out in s 87R of the *CCA*. Where severity is assessed at less than 15% of the most extreme case, non-economic loss damages must not be awarded.[1863]

1820 Turner's entitlement to damages on the negligence cause of action was to be assessed pursuant to Parts VB and VBA of the *Wrongs Act*.

1821 Turner has satisfied the significant injury threshold in Part VBA of the *Wrongs Act* and

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1861 *CCA* s 87P(1). A 'most extreme case' is a case in which the plaintiff suffers non-economic loss of the gravest conceivable kind: *CCA* s 87P(2).

1862 *CCA* s 87Q.

1863 *CCA* s 87S.

is therefore entitled to recover damages for non-economic loss. Damages for non-economic loss are, subject to the maximum fixed by s 28G of the Act, to be assessed pursuant to common law.

1822 If Turner had succeeded in both her negligence action and her claim pursuant to the ACL, she would be required to elect which remedy to take.[1864] Had it been necessary I would have reserved leave to Turner to make that election.

1823 Turner submitted that her non-economic loss damages should be assessed at $280,000.[1865] The defendants submitted that an appropriate award of non-economic loss damages under the *Wrongs Act* was $150,000, and that pursuant to s 87R of the *CCA* Turner's injuries should be assessed at 25% of the most extreme case.[1866]

1824 Turner suffered increasingly severe and debilitating chronic abdominal and pelvic pain and AUB for about two and a half years before she was required to undergo hysterectomy surgery at the age of 32. Turner's physical symptoms resolved with hysterectomy surgery.

1825 Before she underwent a hysterectomy, Turner's mood state deteriorated and became unstable, she was less energetic, and there was an adverse impact on her parenting and other aspects of her life. Her sleep was disturbed due to pain and discomfort. She felt low, flat, sad, down, anxious, frustrated and irritable.

1826 I accept Weissman's opinion that Turner 'suffered from significant — probably moderate — mixed reactive depressive and anxiety symptoms, themes and features' in the context of the physical symptoms of CPP and AUB.[1867] I accept Weissman's opinion that:

> There was a significant change in her personality, temperament, character, mood state, behaviour and activity, which affected her parenting as well as her work enjoyment, performance and at times, work capacity (due to both

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1864 *Alameddine v Glenworth Valley Horse Riding Pty Ltd* [2015] NSWCA 219 at [72] (McFarlan JA); *Gill v Ethicon Sarl (No 5)* [2019] FCA 1905 at [4866] (Katzmann J) ('*Gill*').

1865 SBM.001.001.0004 at 350 [1174].

1866 SBM.500.001.0003_2 at 116 [8.12]-[8.13].

1867 Weissman at 14 (EXP.001.001.0009_R).

physical and mental factors).[1868]

It took some months following hysterectomy for Turner's psychological and emotional state to improve. Her chronic adjustment disorder with depressed and anxious mood has fully remitted/resolved.[1869] Turner's psychiatric prognosis is relatively good and favourable.[1870]

1827 Turner had hysterectomy surgery at 32 years of age. There is a progressive inverse relationship between age at the time of hysterectomy and the risk of adverse long-term health impacts. Possible adverse impacts include increased risks of developing osteoporosis, cardiovascular disease and loss of sexual function associated with a possibility of premature or early menopause.[1871] These risks cannot be fully corrected with hormone replacement therapy. In the gynaecology JER, Korda and As-Sanie agreed:

> The experts agree that in addition to the known risk of postoperative surgical complications associated with hysterectomy, published evidence indicates that there are numerous potential long-term risks of hysterectomy that extend beyond surgical complications. Most of these risks are highest in women who undergo hysterectomy with concomitant removal of the ovaries, but recently publishes [sic] data also indicate that these risks are also present in women who undergo hysterectomy and preserve the ovaries. These include an increased risk of de novo cardiovascular disease, stroke, diabetes, obesity, certain cancers (thyroid cancer, bladder cancer, renal cancer), depression, and anxiety.[1872]

In Turner's case, hysterectomy surgery did not involve removal of the ovaries.

1828 I conclude that the sum of $200,000 represents a fair and reasonable assessment of the pain, suffering and loss of enjoyment of life Turner has suffered, together with the future risks she faces. I assess the award to Turner pursuant to s 87R of the *CCA* at 25% of the most extreme case.

1829 The parties agreed special damages assessed as follows:

1868 Ibid.
1869 Ibid at 15.
1870 Ibid at 16.
1871 Robertson at 196 [815]-[817] (EXP.001.001.0127_2).
1872 Gynaecology JER at 18 [65] (EXP.500.001.0001).

(a) Past medical expenses $11,157.71;

(b) Past loss of earnings $724.95;

(c) Gratuitous care $10,008.40;

(d) Total $21,891.06.[1873]

XX. WARNINGS

Essure product information

1830 The potential sources of information available to patients about Essure included:

(a) information provided in consultation by the treating gynaecologist before performing the Essure procedure. The defendants submitted it is relevant that treating gynaecologists were required to undergo Essure device training and that PTMs and IFUs were available to them;

(b) PIBs accessed by patients; and

(c) Webpages relating to the Essure device.

1831 Turner relied on the PIBs and websites as marketing material published by the defendants. She argued that the marketing material promoted Essure as a safe and gentle alternative form of contraception which was free of significant adverse health risks. Turner argued that the marketing material did not disclose the existence of the inherent defects, failure defects, risk of adverse events and/or removal limitation, or did not do so adequately ('the marketing conduct'). Turner alleged that by reason of the marketing conduct, along with the inherent defects, failure defects, risk of adverse events and removal limitation, Essure had a defect/safety defect and was not of merchantable/acceptable quality under the *TPA* and ACL. Further, Turner alleged that Bayer had breached its duty of care to her and group members by failing to warn

1873 PAR.001.001.0042 at 6.

them of the defects, adverse events and removal limitation.

1832 The defendants alleged that the information available to doctors who performed the Essure procedure (including PTMs, IFUs and Essure training), and the specialist training, skill and experience of those doctors, was relevant to the information, advice and warnings about any risks associated with Essure that were provided to patients.

1833 Different iterations of the PIBs, IFUs and PTMs were published by the defendants over time. Some versions of those documents were made available in other countries but were not distributed in Australia. Turner submitted that the defendants had not established that the IFUs and PTMs were made available to gynaecologists performing the Essure procedure at different times during the period Essure was supplied in Australia, or when the different iterations were in use. Turner submitted that in those circumstances, the defendants were not able to rely on the contents of any particular version of the IFUs and PTMs having been communicated to gynaecologists who performed the Essure procedure, and to group members via those doctors.

1834 The defendants submitted that Turner's position misunderstood the law by impermissibly seeking to impose on them the onus of proving that an adequate warning was given in relation to any established defect or adverse event. The defendants submitted that Turner's evidentiary onus necessarily extended to identifying the information and warnings available and the study, training and expertise of gynaecologists who performed Essure procedures.

Instructions for use

1835 Exhibit D2 is a cardboard box marked 'Essure permanent birth control'. As tendered, it contained an IFU, a patient identification card, two Essure delivery catheter devices and an Essure device. Exhibit D2 was a version of the box in which Essure was supplied in the US, not Australia.

1836 Rosen identified Exhibit D2 as being broadly consistent with the box in which the Essure device was packaged when he used it during the period from early 2000 to

2017 in Australia. He said that the boxes in which Essure was supplied to him for use during that period always contained:

(a) two Essure Inserts, which were wound up and contained within two disposable introducers (each in separate sterile packaging);

(b) a copy of the Instructions for Use (**IFU**) for the Essure Device; [and]

(c) a patient identification card… .[1874]

Rosen said that he also received copies of the IFUs in the training manuals which were provided to him initially by Conceptus, and later by the Australian distributors.

1837 Gytech was the exclusive distributor of Essure in Australia from about 19 August 2010 until 31 December 2014.[1875] Padgham said that throughout the Gytech distribution period, Conceptus provided it with materials related to Essure in both hard and soft copy.[1876] Conceptus provided Gytech with sealed boxes of Essure devices for resale. Padgham said that she would open a sealed box from time to time and find that it contained the components of the Essure device and an IFU.

1838 Rosen performed over 150 Essure insertion procedures in the period from 2000 to 2017. I accept his uncontradicted evidence that there was an IFU in every Essure box provided to him. Padgham and Saad gave consistent evidence. Turner accepted that it was open to infer that there was an IFU in the boxes in which Essure devices were supplied to gynaecologists in Australia.[1877] I draw that inference.

1839 In an aide memoire to their final submissions, the defendants identified 11 IFUs covering the period March 2001 to October 2017. In an annexure to their final written submissions, the defendants set out the evidence dealing with the provenance of each IFU. The defendants submitted that the evidence established that the 11 IFUs were provided to physicians for the periods specified in the aide memoire, and that if there was a time gap in the evidence I should infer that the content of the IFUs relevant to

1874 MSC.500.001.0006, p 1, [3].
1875 Padgham at 2 [4] (LAY.500.001.0027_2).
1876 Ibid at 6 [16].
1877 T4974 (TRA.500.053.0001_2 at 0018_3).

the pleaded defects and adverse events did not vary materially.[1878] The aide memoire is reproduced at Schedule 3.

Australian IFU distribution

IFU 1

1840 The first Australian IFU for the STOP device is identified as document 'LS-01354'. A two-page Conceptus document records the dates of three revisions to this document, with the third revision (revision 'C') having an effective date of 5 March 2001.

1841 Revision C of LS-01354 (IFU 1) is a Conceptus document headed 'Instructions for use – Australia'.[1879]

IFU 2

1842 On 12 March 2002, the Conceptus regulatory affairs manager wrote to a doctor assisting Conceptus with regulatory matters in Australia enclosing materials to support changing the name of the device from STOP to Essure.[1880] Enclosed with the letter was IFU 2, which uses the Essure name and is identified as document 'LS-01354-01 Rev.Q'.

IFU 3

1843 IFU 3 is identified as document 'L2610'.[1881] In June 2006, Conceptus provided Stenning & Co (the Australian distributor at the time) documents and information for submission to the TGA in relation to a regulatory change, including of 'the standards and guidelines that were used in the design and manufacture of the current Essure device'.[1882] The documents referenced L2610,[1883] and relevantly included the statement that 'instructions for use must be included in the packaging for every device'.[1884] The documents also set out the requirements for the Essure carton,

1878 T4801 (TRA.500.051.0001_3 at 0090).
1879 BES.001.001.0029.
1880 BES.001.001.0031.
1881 BAY-EDPA-3576314 at 63.
1882 BAY-EDPA-2423580 at 8.
1883 Ibid at 3.
1884 Ibid at 17.

including that it contain instructions for use.[1885] The enclosed documents included a copy of IFU 3 and recorded the revision date for the Australian version as '9/15/04'.[1886] The IFU applicable to Australia included in the documents is identical to IFU 3.[1887]

IFU 4

1844 The revision date of IFU 4 is recorded as 'L2766 Rev. 03/08/06'.[1888]

1845 A duplicate of IFU 4 was also contained in the bundle of documents that Conceptus provided to Stenning & Co in June 2006.[1889]

IFU 5

1846 When the proceeding commenced, Padgham reviewed documents held by Gytech relating to Essure. She said that those documents included IFU 5 (identified as 'L3002 Rev 09/09/09'),[1890] and a second IFU which she agreed was not distributed in Australia.[1891] Padgham accepted that this second IFU was for the US only, and was provided 'to the TGA regarding some data reporting'.[1892] Padgham was asked:

> This isn't a copy of an IFU in relation to the product that was used in Australia, is it, this is the US version?---That's correct, but in the IFU that was supplied to Australian customers was the long version, the whole 54 pages. Page 27 to 30 was the appropriate part of that IFU for the Australian market.[1893]

1847 A number of the IFUs are composite documents, with sections in different languages which are applicable to different jurisdictions. The section applicable to Australia in IFU 5 appears on pages 27 to 30 of the document and is indexed as follows:

English GB/CA/AU/NZ only [1894]

1885 Ibid at 47–51.
1886 Ibid at 121.
1887 Ibid at 160.
1888 BAY-EDPA-2425528 at 67.
1889 BAY-EDPA-2423580 at 55, 97.
1890 GYT.001.001.3669.
1891 T1657-8 (TRA.500.017.0001_2 at 0042-3).
1892 T1567 (TRA.500.017.0001_2 at 0042_24).
1893 T1568 (TRA.500.017.0001_2 at 0043_5).
1894 GYT.001.001.3669 at 1.

IFU 6

1848 Padgham identified a third IFU in her evidence, which is IFU 6.[1895] However, Padgham gave no evidence about the provenance of that document.

1849 The revision date on IFU 6 is 'ART-3002 Rev. A (09/20/2011)'.

1850 In IFU 6, the section applicable to Australia again appears on pages 27 to 30 and is indexed:

> English Outside the USA only [1896]

1851 The second IFU identified by Padgham indexes each version of the instructions for use from pages 1 to 55, including the version applicable to Australia at pages 27 to 30, but contains only the pages marked 'USA only'. This section is identical to the US instructions for use in IFU 6, and the revision date is the same as appears on IFU 6. I infer that the second IFU identified by Padgham is an extract from IFU 6.

IFU 7

1852 The revision date is recorded on IFU 7 as follows: 'L3002 (ART-3002 Rev. D. 03/19/2012).[1897]

IFU 8

1853 The revision date recorded on IFU 8 is '3002 02/27/2013'. IFU 8 is revision E of document '3002' (being IFU 7).

IFU 9

1854 The revision date on IFU 9 is recorded as '82269495 11/07/2013'.

1855 On 26 August 2014, as part of an email chain between representatives of Bayer AG and Bayer Australia relating to an adverse event report,[1898] IFU 9 was described by Bayer AG as the 'most recent version of the IFU'.[1899]

1895 GYT.001.001.4299.
1896 Ibid at 1.
1897 BAU.001.001.4133 at 55.
1898 BAG.001.001.2361.
1899 Ibid at 1.

IFU 10

1856 There is no revision date recorded on IFU 10. The reference to revision on the document reads 'PN-84248797 ART Rev. A'.[1900]

1857 In an email to the TGA sent 11 December 2014, Jennifer Steinmetz, a Bayer Australia employee, attached what she called 'a copy of the latest IFU that is used in Australian Essure packs'.[1901] The document attached to the email is a duplicate of IFU 10.

IFU 11

1858 Saad identified two IFUs that he said were, to the best of his recollection, distributed during the period of AMSL's distributorship of Essure in Australia. The first is IFU 11[1902] and the second[1903] was not included in the IFU aide memoire. Saad agreed that this second IFU was not distributed prior to the recall of Essure in October 2017.[1904]

1859 IFU 11 is, in fact, a PTM which contains an IFU marked 'English outside USA only'.[1905] Saad said it was only the IFU, not the entire PTM, that was included in the Essure device boxes.[1906]

1860 There is no revision date on IFU 11 or on the broader PTM. The defendants submitted that it should be inferred that IFU 11 was used and distributed in Australia for about the whole of the AMSL distribution period.

IFU content

1861 The content of IFU 9 is an example of the information that was generally set out in the IFUs. IFU 9 is five pages in length. Information is presented under various headings. Relevantly, under a heading 'Warnings', IFU 9 includes:

> • The Essure procedure should only be performed by skilled hysteroscopists who have completed the Bayer Healthcare LLC training programme for this

1900 BAU.001.001.5676 at 55.
1901 BAU.001.002.1103 at 1.
1902 AMS.001.001.0010.
1903 AMS.001.001.0137.
1904 T1408 (TRA.500.015.0001_2 at 0027_15).
1905 AMS.001.001.0010 at 84.
1906 T1409, 1427 (TRA.500.015.0001_2 at 0028_3, 0046_8).

procedure.

• Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.

• When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.

• Do not continue to advance the Essure system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.

• If a tubal perforation occurs or is suspected, do not continue with the Essure micro-insert placement attempt. A very small percentage of women in the Essure clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[1907]

1862 The mechanism of action is described as follows:

> Under hysteroscopic visualisation, the Essure system delivers an Essure micro-insert to the proximal section of the fallopian tube lumen. When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[1908]

1863 Information under the heading, 'Risks associated with the micro-insert placement procedure' includes:

> • Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.
>
> • There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.
>
> • There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.
>
> • There is a risk that the Essure micro-insert may be inadvertently placed into

1907 AID.500.001.0014 at 2.
1908 Ibid.

the myometrium of the uterus and not into the fallopian tube lumen. … If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.

• There is a risk that the Essure micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.

• There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, Essure micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal-is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.

• There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[1909]

1864 The following information is included beneath the heading 'Risks associated with Essure micro-insert wearing':

• There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.

• As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the Essure micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.

• Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.

• Intermenstrual bleeding or heavier than normal menstrual bleeding may be

1909 Ibid.

experienced.[1910]

1865 IFU 9 contains a warning that Essure insert removal should not be attempted hysteroscopically once placed unless 18 or more coils are trailing into the uterine cavity. The IFU continues:

> Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.
>
> Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.
>
> A cornual resection of the proximal fallopian tube will be required if the micro-insert is properly located across the utero-tubal junction (UTJ).
>
> An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[1911]

1866 Information under the heading 'Essure micro-insert placement procedure' includes:

> 4. Insert a sterile hysteroscope, with attached camera and operating channel (≥ 5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.
>
> …
>
> 9. Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[1912]

1867 The following information is included under the heading 'Precautions':

1910 Ibid.
1911 Ibid at 5.
1912 Ibid at 3.

- In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.

- Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort.[1913]

1868 The 11 IFUs contain similar information relevant to the pleaded defects, with some minor variation in wording. The IFU aide memoire provided by the defendants records that generally, though not uniformly, the following information is conveyed:

(a) Migration and expulsion:

> There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro- insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events. [1914]

(b) Breakage and fragmentation:

> There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 20 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro- insert may break, leaving a fragment of the micro- insert in vivo. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro- insert placement procedure.[1915]

(c) Perforation:

> A very small percentage of women in the Essure clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.
>
> …

1913 Ibid at 2.
1914 AID.500.001.0002 at 3.
1915 Ibid at 5.

There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required. There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.

…

There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua which could result in the micro-insert being released into the peritoneal cavity. Post- operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[1916]

(d) Allergic reaction to nickel-titanium:

Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[1917]

(e) Pain:

Pain, cramping and vaginal bleeding may occur during and following the micro- insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.

…

Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[1918]

(f) Bleeding:

Pain, cramping and vaginal bleeding may occur during and following the micro- insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.

…

1916 Ibid at 6-7.
1917 Ibid at 9.
1918 Ibid at 10, 15.

> Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.[1919]

(g) Removal limitation:

> The Essure micro-inserts are permanent implants.
>
> …
>
> As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the Essure micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[1920]

Turner did not contest the accuracy of the tables in the IFU aide memoire that set out the content of the 11 IFUs that is relevant to the pleaded defects.

Alleged deficiencies in Australian IFUs

1869 Turner submitted that the deficiencies in the 11 IFUs identified by the defendants were evident when compared with IFUs used in the US[1921] and with an IFU proposed for use in Australia dated May 2017 ('proposed 2017 IFU').[1922]

US IFU

1870 Turner submitted that an IFU distributed in the US with a revision date of November 2002 ('US IFU') included more comprehensive disclosures than the Australian IFUs.[1923] She submitted that the US IFU:

(a) identified a chronic inflammatory response;[1924]

(b) gave specific incidence and more detail as to adverse events and risks such as expulsion, pain and bleeding in the first year of reliance;[1925]

1919 Ibid at 13.
1920 Ibid at 17.
1921 BAY-JCCP-0000110.
1922 AMS.001.001.0137.
1923 SBM.001.001.0004 at 140 [431](a)–(d).
1924 BAY-JCCP-0000110 at 4.
1925 Ibid at 11.

(c) used language around pain and bleeding that included references to 'severe' pain and bleeding and to dysmenorrhea and dyspareunia;[1926] and

(d) had at least one reference to persistent pain and potential removal due to pain.

1871 The reference to chronic inflammation in the US IFU is in the context of tissue in-growth:

> The tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibers. It is believed that the tissue in-growth into the device caused by the PET fibers results in both device retention and pregnancy prevention.[1927]

1872 The US IFU included the following under a 'Warnings' heading:

> A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested device removal due to pain; however, if device removal is required for any reason, it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.[1928]

1873 The US IFU contained more information and data from Essure clinical trials. This included a table of adverse events rated by the Pivotal trial investigators 'to be at least "possibly" related to the Essure micro-insert or micro-insert placement procedure'.[1929]

Proposed 2017 IFU

1874 The proposed 2017 IFU was developed following the 2015 OGDAP meeting, where Bayer was required to include further warnings and information in the US IFU. It contained a boxed warning on the first page that included:

> There have been reports of perforation of the uterus and/or fallopian tubes, inserts located in the intra-abdominal or pelvic cavity, persistent pain, and allergy or hypersensitivity reactions in some patients. Some of these reported events resulted in insert removal that required abdominal surgery. Device removal may lead to improvement or resolution of symptoms when: the onset is shortly after placement, imaging indicates an unsatisfactory insert location, and other etiologies for these symptoms have been considered. This information should be shared with patients considering sterilization with

1926 Ibid.
1927 Ibid at 4.
1928 Ibid at 7.
1929 Ibid at 10.

> Essure during discussion of the benefits and risks of the device.[1930]

A further warning about the risk of acute or persistent pain in the body of the IFU included that:

> Individuals with a history of pain are more likely to experience both acute and chronic pelvic pain following Essure placement … Not all pain will be related to the Essure insert.[1931]

The IFU stated that '[s]urgery including device removal, hysterectomy or other procedures may be required to treat the pain'.[1932]

1875 The hypersensitivity warning in the proposed 2017 IFU relevantly extends to nickel, titanium, stainless steel and PET fibre, and 'includes both patients with or without a history of metal allergies'.[1933]

1876 The proposed 2017 IFU is 53 pages long and includes far more detail than the IFUs used in Australia.

Analysis

1877 The defendants submitted that the IFUs identified in the aide memoire appear, either on their face or by reference to other documents or evidence, to be the IFUs distributed in Australia.[1934]

1878 Turner submitted that the defendants did not lead adequate evidence to establish which versions of the IFUs were distributed in Australia and at which points in time.[1935] Turner submitted that a date appearing on an IFU is likely to be the date the document was revised by the defendants, but is not self-evidently the date on which the document was put into circulation in Australia. Turner submitted that there was no evidence from the defendants about practices that existed in Australia for the updating of IFUs and other instructional or training material.

1930 AMS.001.001.0137 at 1.
1931 Ibid at 5.
1932 Ibid at 6.
1933 Ibid.
1934 SBM.500.001.0003_2 at 850 [1.13].
1935 SBM.001.001.0004 at 128 [390].

1879 Turner submitted that both Padgham and Saad were mistaken about IFUs they identified as being distributed in Australia, and that it was clear they had little if any knowledge about what versions of the IFUs were distributed.

1880 For the following reasons, I conclude that the IFU aide memoire accurately sets out the 11 IFUs that were distributed in Australia in the period March 2001 to October 2017.

1881 First, the evidence suggests a systematic approach to production and distribution of the IFUs. In most cases, the IFUs were compilation documents with different sections applicable to the different jurisdictions in which Essure was distributed. I have concluded that there was an IFU in each of the Essure boxes distributed in Australia. Most of the IFUs had revision dates and version numbers that assist in placing them in sequence. It is likely that where an IFU has a revision date, it began to be used from around that time.

1882 Second, each of the IFUs set out in the IFU aide memoire appear on their face, or by reference in other documents, to be prepared for distribution in Australia.

1883 Third, where other evidence is available, it confirms that IFUs were used and distributed consistent with the revision dates. There is no evidence to suggest that any other IFU was used and distributed in Australia during the commercial supply period, or that any of the 11 IFUs were distributed otherwise than in accordance with the sequence described.

1884 The evidence does not allow for a precise conclusion about the dates on which distribution changed from one IFU to the next. However, I accept that the 11 IFUs were distributed in Australia for the approximate periods:

- IFU 1 - March 2001 to March 2002;
- IFU 2 - March 2002 to September 2004;
- IFU 3 - September 2004 to March 2006;

- IFU 4 - March 2006 to September 2009;
- IFU 5 - September 2009 to October 2010;
- IFU 6 - September 2011 to September 2012;
- IFU 7 - September 2012 to February 2013;
- IFU 8 - February 2013 to November 2013;
- IFU 9 - November 2013 to December 2014;
- IFU 10 - December 2014 to 2015; and
- IFU 11 - 2015 to October 2017.[1936]

Physician Training Manuals

1885 The defendants submitted that four PTMs were circulated in Australia from 2000 to 28 August 2017:

(a) 'PTM 1' in 2000/2001;

(b) 'PTM 2' from 1 May 2003;

(c) 'PTM 3' from 7 January 2008 to January 2014; and

(d) 'PTM 5' from 2015 to 28 August 2017.

PTM distribution

PTMs 1 and 2

1886 Rosen identified PTM 1 as the manual used for a two-day training forum he attended in 1999–2000. Rosen said he was involved as a trainer of other gynaecologists in the period 2001 to 2005, and that the course was based on PTM 1 and later PTM 2.[1937] He said that the only change in materials during the time he was involved as an Essure device trainer involved the development of PTM 2.[1938] Rosen acknowledged that his CV indicates he was an investigator and training supervisor for the Essure device between 2000 and 2002. He said that he believed that he trained fellow doctors up to

1936 AID.500.001.0002 at 2.
1937 Rosen at 5 [1.2.62] (EXP.001.002.0002_2).
1938 Ibid at 4–5.

2005, but was uncertain of the exact dates.[1939]

1887 There is no revision date on PTM 1. However, the title of the document is 'STOP Training Manual', indicating that it was in use before the name of the device changed to Essure.

1888 The PTM 2 revision is recorded as 'TR2468-11 01/05/03'. The defendants submitted that this date should be understood as 1 May 2003.

PTM 3

1889 Padgham said that she believed PTM 3 was provided to Gytech by Conceptus at the commencement of the Gytech supply period.[1940] In cross-examination, Padgham agreed that she had found PTM 3 among the Essure documents in Gytech files, but did not know precisely how Gytech obtained each of the documents.

1890 The revision date on PTM 3 is recorded as 'CC-1687 07Jan08F'.[1941]

1891 PTM 3 displays 'U.S. Physician Training Manual' at the foot of each page. There are also some terms specific to the US in the document.

PTM 5

1892 The defendants referred to two versions of PTM 5, both of which have the revision reference 'PN-84248797, ART Rev. A'. The only difference between the documents is that one has an additional page bearing the AMSL logo and contact details.

1893 Merrell said that both versions of PTM 5 were 'used during the period of AMSL's distributorship' in Australia.[1942] Turner did not challenge Merrell on this evidence, but did challenge Merrell's evidence about the way in which the PTMs were used.

PTM content

1894 The PTMs are described as a 'comprehensive resource that [provide] clinical

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1939 T2049 (TRA.500.021.0001_2 at 0027_13).
1940 Padgham at 4 [11] (LAY.500.001.0027_2).
1941 GYT.002.001.0131 at 1.
1942 Merrell at 17 [56](c) (LAY.500.001.0011).

instruction and information' on a number of matters including the history of Essure; selecting appropriate patients; counselling patients; performing the Essure procedure; and conducting and evaluating results of the Essure Confirmation Test.[1943]

1895 There is significantly more variation in the content of the PTMs than the IFUs. Nonetheless, there are similarities in the information and warnings provided. The defendants prepared an aide memoire setting out the content of the PTMs, which is at Schedule 4 to these reasons.

1896 In brief summary, PTM 1:

(a) lists migration and expulsion as risks associated with the placement procedure and device wearing, which could result in pain, menstrual disturbance or other adverse event and may require surgery for device removal;

(b) identifies a risk of breakage of the device or perforation of the fallopian tube or uterine cornea in the event that the device is incorrectly placed;

(c) lists pelvic pain and cramping as possible risks associated with the placement procedure and device wearing, which it said could be more likely during menstruation, after sexual intercourse or with another physical activity;

(d) lists vaginal bleeding as a risk associated with the placement procedure, intermenstrual bleeding or heavy bleeding as a risk associated with device wearing, and says:

> Pain, cramping and vaginal bleeding may occur during and following the device placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication;[1944]

(e) sets out advice for physicians in relation to counselling patients on the permanence of the device, and warns that device removal due to adverse events

1943 GYT.003.001.0001 at 2.
1944 AID.500.001.0004 at 33.

or patient demand will require surgery and may require salpingostomy, salpingectomy or hysterectomy; and

(f) summarises clinical data of adverse events from various studies including the peri-hysterectomy study, pre-hysterectomy study and Phase II study.[1945]

1897 PTMs 2 and 3:

(a) summarise clinical data in relation to migration, expulsion, and perforation;

(b) identify hyper-sensitivity to nickel as a contraindication;

(c) summarise clinical data from the Phase II study and Pivotal trial in relation to pain, including abdominal, back, and pelvic pain; dyspareunia; and uncharacterised pain/discomfort, and include data from a patient with recurrent persistent pelvic pain which led to surgical removal of the insert;

(d) identify a risk of pain including persistent uterine cramping and bleeding post-procedure;

(e) summarise clinical data from the Phase II study and Pivotal trial in relation to persistent increase in menstrual flow, abnormal bleeding, menorrhagia/prolonged menses and changes in menstrual function; and

(f) identify the permanence of the device and warn that device removal will necessitate surgery and possible hysterectomy.[1946]

1898 PTM 5:

(a) summarises clinical data and warns that there is a risk of expulsion, migration or perforation;

1945 Ibid.
1946 Ibid.

(b) states that persons allergic to nickel titanium may suffer an allergic reaction to Essure, lists the nickel titanium alloy makeup of the device as an 'additional consideration' for patient selection and counselling, and lists 'typical allergy symptoms reported' as including rash, pruritus, and hives;

(c) summarises clinical data from the Phase II study and Pivotal trial in relation to pain including abdominal, back, and pelvic pain; dyspareunia; and uncharacterised pain/discomfort. In relation to chronic pain, it states that:

> There are rare reports of chronic pelvic pain in women with Essure.
>
> - Chronic pelvic pain may be related to malposition of device, cornual perforation or complications with concomitant ablation.
> - Patients with preexisting chronic pain diagnoses may be at increased risk of developing pelvic pain.
> - Other causes might explain chronic pelvic pain with Essure but remain unknown[.]
> - Micro-insert removal via laparoscopy is recommended in such cases[;][1947]

(d) summarises clinical data from the Phase II study and Pivotal trial in relation to persistent increase in menstrual flow, abnormal bleeding, menorrhagia/prolonged menses and changes in menstrual function;

(e) states that intermenstrual bleeding or heavier than normal bleeding may be experienced during Essure wearing;

(f) states that a patient will likely require surgery and possibly hysterectomy to manage perforation or persistent pelvic pain; and

(g) identifies the permanence of the device and warns that device removal will require surgery and possible hysterectomy.

1899 The PTMs describe the mechanism of action of the device as a benign, occlusive tissue response that results in tissue in-growth which permanently anchors the micro-insert

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1947 Ibid at 30.

in the fallopian tubes. PTM 1 states that the histology evidence demonstrates that the tissue reaction is predictable and localised to the device. PTM 5 states that the tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibres.[1948]

Analysis

1900 I accept Rosen's evidence identifying PTMs 1 and 2 as the training manuals used from 1999 until the end of his involvement as an Essure device trainer. I conclude that PTM 2 was in use from at least around May 2003.

1901 I accept Merrell's uncontradicted evidence that PTM 5 was used during the AMSL distribution period. What PTM/s were in use between 2005 and the end of 2014 is less clear. The revision references on PTMs 2, 3 and 5 do not link those documents. There is no revision date on PTM 5 to assist in determining when this document was first used.

1902 Padgham was not involved in Essure device training. Her evidence amounts to no more than that she found PTM 3 while searching Gytech files after this proceeding commenced. There is no evidence about how or why PTM 3 came to be in the Gytech files. An IFU originally identified by Padgham as being distributed in Australia during the Gytech period was in fact a US-only document provided to Gytech for a purpose other than distribution.

1903 The evidence does not allow me to conclude:

(a) when PTM 2 ceased to be used;

(b) if PTM 3 was used in Australia, and for what period; or

(c) when the use of PTM 5 commenced.

1904 There is no evidence that a training manual other than PTMs 1, 2 and 5 was used in

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1948 Ibid at 5.

Australia.

Essure device training programs

1905 Rosen said that in the period from 1999 to 2000, he undertook specialist training on the Essure device which included:

(a) attending a two-day training forum on the STOP 2000 manual (PTM 1);

(b) receiving personal instruction on the Essure procedure from Professor John Kerin, who Rosen described as the inventor of the device. Kerin was an investigator for one of the early clinical trials of the Essure device conducted at the Queen Elizabeth Hospital in Adelaide;[1949]

(c) receiving ongoing support by the Conceptus team (in Australia and the US) during the Pivotal trials and trials of the coil catheter system; and

(d) receiving resources to help in the preparation of lectures and the Essure training course to gynaecologists in Australia.

1906 Rosen was engaged as a contractor by Conceptus from 2000 to approximately 2005 to train fellow gynaecologists in the Essure procedure. He facilitated training programs and travelled to multiple sites around Australia where preceptor colleagues who had successfully completed the Essure training program were performing their initial cases.[1950] Rosen conducted training, lectured and published in Australia and internationally on the Essure procedure. He was involved in the Essure clinical trials in Australia and went on to perform over 150 Essure implantation procedures.

1907 Rosen said that Essure training for gynaecologists involved:

(a) attending a full-day course in which Rosen and his colleague Dr Geoff Reid provided didactic training in the Essure procedure, based on a pre-prepared three to four hour lecture programme provided by Conceptus in the US and

1949 BAY-EDPA-4197110 at 4.
1950 Rosen at 4 (EXP.001.002.0002_2).

modified by Rosen and Reid for local audiences. The course was based on the information contained in PTM 1 and PTM 2. Rosen said that the course provided gynaecologists with extensive information about the procedure, patient selection and counselling, operative and post-operative care and confirmation of tubal occlusion;

(b) watching two demonstration procedures performed under local anaesthesia after the lectures;

(c) performing a minimum of two procedures in their own facility with an Essure trainer and Conceptus representative in attendance; and

(d) being 'signed off' to perform procedures without supervision once they had demonstrated competence in the technique and an understanding of the product.[1951]

I accept that Rosen's evidence accurately describes the Essure training program for gynaecologists in the period that he was involved as a specialist trainer.

1908 In Australia, the Essure procedure was performed under anaesthesia by a gynaecologist in an operating theatre setting.[1952] Rosen said that 'when a patient [sought] referral to a specialist gynaecologist for discussion regarding contraceptive options, they would usually seek advice from their general practitioner and obtain appropriate referral'.[1953] He said that all available contraceptive options and the relevant risks and benefits of each were discussed by the gynaecologist with the patient.[1954]

1909 Rosen said that when women attended a consultation regarding contraception, all available options were discussed, along with the most relevant risks and benefits. He said the consultation would take into account factors such as patient age and desire

1951 Ibid at 5 [1.2.6].
1952 Ibid at 9 [2.3].
1953 Ibid at 9 [3.0].
1954 Ibid at 9 [3.1].

for future fertility, previous obstetric history, previous surgical history and other relevant health considerations. He said:

> Patients [were] provided with relevant documentation which may take the form of RANZCOG pamphlets on contraception and sterilization, referral to a practitioner's website with information about certain procedures and other relevant websites. After considering all the permutations noted above and depending on the desires of the individual patient, a decision [was] made on a form of contraception or a further consultation scheduled after the patient has had further time to digest the information and make an informed decision.
>
> In my practice, because of my history with the procedure and association with teaching the process, many patients arrived to see me with a referral for the Essure procedure and had made their own research into the procedure, and having done their own research, they requested a referral from their General Practitioner or their regular Gynaecologist who did not perform the Essure procedure, to see me for the Essure procedure, a decision having been made ahead of the consultation and reiterated during our consultation.[1955]

1910 I understand that Rosen's evidence about patient discussions reflects his practice as a specialist gynaecologist. The defendants submitted that in circumstances where Turner made a forensic decision not to call any doctor who was trained in and used the Essure device, I should infer that Rosen's experience of the patient consultation process is unlikely to be unique to him.[1956]

1911 Padgham said that Gytech sales employees delivered Essure device training to physicians who wished to offer it as a permanent birth control option to their patients.[1957] She said the distribution agreement required that this training be based solely on the materials provided to Gytech by Conceptus. She said that training was carried out in person, and that Gytech employees would then attend implantation procedures with physicians until they were competent to perform the Essure procedure without support. She said that to the best of her knowledge, 'no Essure devices were ever supplied by Gytech to Gytech customers or potential customers [who] had not completed training'.[1958]

1955 Ibid at 13 [3.1.8]–[3.1.9].
1956 SBM.500.001.0003_2 at 360 [4.3].
1957 Padgham at 8 [23] (LAY.500.001.0027_2).
1958 Ibid at 8 [25].

1912 In cross-examination, Padgham agreed that she did not have any direct involvement with the Essure device sales and training and that Daniel Tidey, a former Gytech employee, was responsible for those matters.[1959] She explained that her knowledge of those matters was because Gytech had processes in place and Tidey reported to her frequently.[1960] She said that Gytech's processes for selling products to customers involved using PIBs and PTMs, and that there was nothing to indicate that this process was not followed.[1961] Padgham said that Tidey reported on training that had taken place in monthly meetings and that this was recorded in minutes.[1962]

1913 Turner submitted that Tidey should have been called to give evidence about Essure training and the provision of IFUs and other material during the Gytech period.[1963] Tidey left Gytech's employment on what Padgham described as 'unfavourable grounds' in 2016. Padgham said she did not know Tidey's current whereabouts. I accept the defendants' submissions that the failure to call Tidey has been adequately explained.[1964] Further, in these circumstances the defendants were not reasonably expected to call Tidey as a witness.

1914 Saad said that the AMSL sales team received 'refresher' training on the marketing and distribution of Essure in meetings held two or three times a year. He said that during these meetings, sales team staff would typically be advised that sales and marketing activities had to be consistent with the training and written materials received from the manufacturers about their products, and comply with local regulations.[1965]

1915 Saad and Merrell both said that when AMSL took over the distributorship of Essure, a number of short introductory appointments with gynaecologists identified as actual or potential Essure device users were arranged.[1966] Both said that they had a role in

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1959 T1618 (TRA.500.017.0001_2 at 0003_22).
1960 T1654 (TRA.500.017.0001_2 at 0039_28).
1961 T1673 (TRA.500.017.0001_2 at 0058_11).
1962 T1733-4 (TRA.500.017.0001_2 at 0118-9).
1963 SBM.001.001.0004 at 264.
1964 T4796-7 (TRA.500.051.0001_3 at 0085-6).
1965 Saad at 12 [57] (LAY.500.001.0025).
1966 Merrell at 11 [45] (LAY.500.001.0011).

training sales members in how to conduct these appointments. Saad said that part of these meetings included providing a doctor with written materials about the product if they had not used Essure before.[1967] Merrell said that she attended a number of these appointments in NSW and the ACT herself,[1968] and in the first few months of AMSL's distributorship attended appointments with other members of the sales team.[1969] She said that during both AMSL's initial appointments and the AMSL training of users, PTMs were provided to gynaecologists and other healthcare professionals.[1970] Merrell referred to PTM 5 as one of the PTMs distributed to users by AMSL as part of the above sessions.[1971]

1916 The distribution agreement between AMSL and Bayer includes:

> 2.6 Training. The Essure procedure should only be performed by skilled hysteroscopists who have completed the Bayer-Approved Training Program for this procedure or physicians where the Distributor has verified that they have previously received appropriate training and are competent to place the Product.
>
> …
>
> Distributor shall ensure that physicians are properly trained on any Product enhancements that may influence the placement procedure of the Product. Bayer shall provide a training guide on any Product enhancements to support physician training. This shall supplement the Bayer physician training manual.[1972]

The distribution agreement defines the 'Bayer-Approved Training Programme' as a 'physician training programme for the Product using the Bayer Physician Training Manual and given by a Product Trainer'.[1973]

1917 Both Saad and Merrell agreed that Merrell and another AMSL staff member Garima Walia delivered training to gynaecologists. Saad said that he did not ordinarily attend these training sessions, but did discuss the contents of the training with Merrell and

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1967 Saad at 14 [65] (LAY.500.001.0025); Merrell at 11 [45] (LAY.500.001.0011).
1968 Merrell at 16 [53] (LAY.500.001.0011).
1969 Ibid at 16 [55].
1970 Ibid at 11 [45](b), 16-17 [56(c)], 21 [74](c).
1971 Ibid at 21.
1972 AMS.001.002.0098 at 8.
1973 Ibid at 3.

Walia. The content involved use of slides prepared and provided by Bayer.[1974]

1918 Merrell said that she and Walia attended Essure training in Europe over a period of four or five days in early 2015.[1975] Part of the training schedule refers to 'IFU' training.[1976] The slides annexed to Merrell's statement, which she said were used to introduce part of the European training, include a reference to a 'Global Training Manual' which is a '[c]linical resource manual to be used for training and as [a] reference book in daily clinical practice'.[1977]

1919 Merrell said that she and Walia delivered three days of internal training to the AMSL sales team about Essure in February 2015.[1978] The agenda for this training includes subject headings 'Essure Instructions for Use' and 'Training Manual'.[1979] She said that during this training, she told the AMSL sales team that they must strictly follow the contents of the training material and the other written material provided to AMSL by Bayer. She said that she expected her team would follow this direction when communicating with gynaecologists. She said that she accompanied members of the sales team to several of their initial appointments with gynaecologists and witnessed them doing so.[1980]

1920 Merrell said that Essure training was a pre-requisite for using the product.[1981] She said that refresher training, while offered as an option to existing users, was not mandatory.[1982]

1921 Merrell said that training sessions usually ran for between three and five hours.[1983] The topics covered were set out in PowerPoint slides prepared by Bayer and included details of the device and mechanism of action; the Essure procedure and

1974 Saad at 23 [99] (LAY.500.001.0025).
1975 Merrell at 4 [20] (LAY.500.001.0011).
1976 BAG.001.001.0384 at 1.
1977 BAG.001.001.9187 at 24.
1978 Merrell at 7 [31] (LAY.500.001.0011).
1979 AMS.001.0015423 at 2.
1980 Merrell at 7 [33] (LAY.500.001.0011).
1981 Ibid at 11 [45](a)(ii).
1982 Ibid at 20 [69]; T1529 (TRA.500.016.0001_2 at 0030_30-1).
1983 Merrell at 21 [73] (LAY.500.001.0011).

insertion/removal techniques; benefits and risks; the three-month confirmation test; troubleshooting of technical issues; and a summary of adverse events reported in clinical studies.[1984] Merrell said that she demonstrated the Essure procedure using a simulator during the sessions and that gynaecologists were given time to practise the procedure using the simulator at the end of the presentation. She said that copies of PTM 5 were typically provided to gynaecologists during the training sessions.[1985] She said this was done because the document provided the doctors with a step-by-step guide, and avoided them needing to call AMSL.[1986]

1922 Merrell said:

> After 'new' users of the Essure Device had received this training, it was a requirement of Bayer that the first six procedures carried out by each new user be supervised by AMSL. Typically, this supervision was done by a member of the AMSL sales team who was responsible for the State or Territory in question, plus either [Walia] or me.[1987]

1923 Merrell said it was her usual practice, and a practice she encouraged with the sales team, to offer further supervision of procedures and training assistance to gynaecologists who had completed their training with AMSL and to those trained under previous distributors.[1988] Merrell said that it was the usual practice at AMSL to record gynaecologist appointments, training sessions and the supervision of procedures.[1989]

1924 Merrell's direct involvement in Essure device training was limited to the initial few months after AMSL was appointed as Australian distributor.[1990] She said that while she could not recall how long she attended training sessions or gynaecologist supervision with the sales team, she worked 'very closely' with each member.[1991]

1984 AMS.001.001.6993; AMS.001.001.6557; AMS.001.001.6995; AMS.001.001.6996; AMS.001.001.8826; AMS.001.001.4048; AMS.001.002.3250.
1985 Merrell at 21 [74](c) (LAY.500.001.0011).
1986 T1531 (TRA.500.016.0001_2 at 0032_14).
1987 Merrell at 21 [75] (LAY.500.001.0011).
1988 Ibid at 23 [84]; T1527 (TRA.500.016.0001_2 at 0028).
1989 Merrell at 23 [85] (LAY.500.001.0011).
1990 T1521 (TRA.500.016.0001_2 at 0022_25).
1991 T1523 (TRA.500.016.0001_2 at 0024_12).

1925 Turner criticised Merrell's evidence about training and provision of PTM 5 as being vague and imprecise, and on the basis that her direct involvement with training did not extend beyond the first few months of AMSL's distributorship and did not involve direct interaction with each relevant member of the sales team. Turner submitted that Merrell was an unimpressive and unreliable witness. This submission was based on three matters. The first was the cross-examination of Merrell on an email chain relevant to an FDA issue and negative media reporting about Essure, and what the members of the sales team should tell doctors about the issue. In one email in the chain, Merrell said she would pass information provided by Saad to the sales team as she thought 'they [were] all panicking'.[1992] Merrell said, when asked why the sales team were panicking:

> ---We had a team at that stage of panickers, so they were an interesting bunch, but it was just, that's the way that they were - they were an interesting bunch of panicking sales team.
>
> Right. Were they inexperienced and that's why they were panicking?---No, they were just very passionate people.[1993]

I reject Turner's submission that Merrell's observations about the sales team somehow reflects poorly on her as a witness.

1926 The second criticism involved cross-examination of Merrell about the prospect of a woman experiencing persistent pain resulting from the Essure device. Turner criticised Merrell's description of that pain as a non-life threatening 'mild ongoing complication' which was 'not like dying of cancer', and her refusal to adopt the description of that complication as 'serious'.[1994] Merrell said that while no one would want to experience such a complication, whether it can be described as 'serious' depends on how the word is defined. Merrell's evidence about the gravity of ongoing pain resulting from Essure reflects her use of the descriptor 'serious' and was not an attempt by her to downplay the experience.

1992 AMS.001.001.2617 at 2.
1993 T1477 (TRA.500.015.0001_2 at 0096_27).
1994 T1513-4 (TRA.500.016.0001_2 at 0014–5).

1927 The third issue arose on the second morning of Merrell's evidence, when she volunteered a clarification of evidence she had given the previous day. Merrell was asked:

> Can I just clarify, have you spoken with anyone about your evidence overnight?---No. It was in my dream.[1995]

It is not unusual for a witness under cross-examination to think overnight about evidence they have given, and whether any clarification is required. The clarifying evidence Merrell gave was not criticised by Turner. Merrell's response suggests that she woke in the night with a thought about the need to clarify something she had said. I reject Turner's criticism of this aspect of Merrell's evidence.

1928 Merrell's evidence was not vague or imprecise. While there were limits to Merrell's involvement in Essure device training, she described these limits in her evidence without apparent hesitation. Contrary to Turner's submission, I found Merrell to be a clear and reliable witness.

1929 Turner also criticised the defendants' failure to lead evidence about training from Khan, or to call other witnesses who could give evidence about staff training at AMSL and interaction with doctors in relation to the Essure device, in particular Walia. Turner submitted that Walia could have given evidence about the content of that training, what transpired at initial doctor appointments, and what written materials were given to doctors. Turner submitted this evidence would have been relevant in circumstances where Merrell was only directly involved in training in the early part of 2015. Turner submitted other AMSL sales staff could have said what Essure written materials were distributed to gynaecologists.[1996] Turner submitted that deficiencies in Merrell's evidence, and the failure to lead evidence from other witnesses, meant there was no direct evidence on which the defendants could rely to prove the general distribution of PTM 5 to doctors in Australia during the AMSL distribution period, and that the evidence was not sufficient to draw any inferences about distribution. I

1995 T1506 (TRA.500.016.0001_2 at 0007_5).
1996 SBM.001.001.0004 at 265.

reject Turner's submission. Merrell gave quite detailed evidence about her Essure training, and the systems and procedures at AMSL. There is no reason to doubt Merrell's evidence as to the general procedures and systems adopted by AMSL in relation to Essure device training. Turner did not lead any evidence to contradict what Merrell said. In the circumstances, no reasonable expectation arises that the defendants should have called Walia to give evidence.

1930 Gytech and AMSL sales representatives attended conferences during the distribution periods of those companies to promote the Essure device,[1997] and marketed Essure to existing and new customers.[1998] The Essure device simulator was used and demonstrated at a number of these conferences. I accept that this evidence is consistent with representatives of Gytech and AMSL providing an opportunity for medical professionals to learn about Essure and to engage in relevant training.

1931 The requirement that gynaecologists undergo Essure device training before being approved to perform the Essure procedure and the comprehensive nature of the training is confirmed by the contents of the PTMs. This is demonstrated in PTM 1 by the training overview diagram, reproduced at Schedule 5 to these reasons.[1999]

1932 The following training requirements set out in the PTM are relevant:

(a) physicians are required to meet a minimum hysteroscopy experience;

(b) training participants must meet the objectives of the one-day training session in order to be 'signed off';

(c) the self-review of program material indicates copies of the training manual are provided to participants;

(d) training includes patient counselling and evaluation; and

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1997 Merrell at 8-9 [61]-[66] (LAY.500.001.0011); GYT.001.001.4553; GYT.001.001.3365; GYT.001.001.2977; GYT.001.001.2790.

1998 Padgham at 7 [18] (LAY.500.001.0027_2); AMS.001.001.8648.

1999 MIS.500.001.0005.

(e) successful completion requires a physician to demonstrate competence in two to three procedures.

1933 The following training requirements were set out in PTM 2:

> 1. Knowledgeable hysteroscopist (prior to Essure training).
>
> 2. Successful completion of a Physician's Didactic Training Course.
>
> 3. Successful completion of Essure Simulator Training.
>
> 4. Completion of the initial procedures under the observation of a Conceptus designated preceptor until competency in performing Essure is established (typically expected to be achieved in 5 cases).
>
> Upon successful completion of the initial training program, the Physician Training Record will be completed by a Conceptus representative. The training record will be filed at Conceptus and the physician's name will be added to the list of those trained to perform the procedure.[2000]

1934 PTM 5 contains the following introductory summary instruction:

> The Essure procedure should only be performed by skilled hysteroscopists; have read and understood the instructions for Use and this Physician Training Manual; and have successfully completed the Essure training program.[2001]

1935 I accept the evidence of Rosen, Padgham, Saad and Merrell to the effect that Essure training programs were conducted in Australia for gynaecologists during the period Rosen delivered the training until 2005, and the Gytech and AMSL distribution periods. I infer, consistent with the evidence of those witnesses and the documents to which I have referred, that training programs were also conducted in Australia from 2005 until the start of the Gytech distribution period.

1936 The Essure device training programs:

(a) required successful completion of the program, which included demonstration of at least two Essure procedures, as a precondition to ongoing performance of the Essure procedure;

2000 MIS.500.001.0017 at 2.
2001 AMS.001.001.5208 at 1.

(b) involved participants reading and understanding the PTM; and

(c) involved consideration of the benefits and risks associated with Essure and patient consultations.

Patient information brochures

1937 Turner identified and relied on 15 PIBs which she said the defendants published or caused to be published during the period that Essure was commercially supplied in Australia, as a way to promote the device to patients.[2002]

PIB distribution

1938 Padgham and Merrell identified PIBs used in the Gytech and AMSL distribution periods. Both said that the PIBs were provided to gynaecologists and Gytech customers, to be made available to patients.[2003] Under cross-examination, Padgham said that 'brochures were being provided to display in clinics, as well as to provide direct to patients'.[2004] Merrell said that at least during the first few months of AMSL's distributorship, she and other sales team members 'would take and hand out' PIBs to gynaecologists during initial appointments with them.[2005]

1939 I accept Turner's submission that the PIBs are public facing documents with form and language that show that they are intended to be read by patients rather than doctors. Further, I accept that the PIBs are framed as marketing material with the target audience being women seeking or contemplating an effective contraceptive solution, and that they are intended as direct communications with these women.

1940 The defendants submitted that Turner had not led evidence to establish which of the PIBs (if any) were distributed and for what periods.

1941 The defendants made positive allegations in their pleaded defence relying on 10 of the 15 PIBs identified by Turner. For example, in response to allegations by Turner about

2002 SBM.001.001.0004 at 121 [361].
2003 Padgham at 8 [21] (LAY.500.001.0027_2); Merrell at 16 [56](a) (LAY.500.001.0011).
2004 T1650 (TRA.500.017.0001_2 at 0035).
2005 Merrell at 16 (LAY.500.001.0011).

failure defects associated with Essure, the defendants alleged that during the commercial supply period, the publications available to doctors and patients in Australia regarding Essure contained information and risk warnings about matters such as migration, expulsion, breakage or fragmentation and perforation. The documents particularised by the defendants include the 10 PIBs.

1942 The following PIBs were not specifically relied on by the defendants:

(a) PIB 1 bears the date 1999 and the STOP and Conceptus logos. There is nothing on the face of the document that identifies it as having been used in Australia.[2006]

(b) PIB 2 has the Conceptus logo and the Conceptus (Australia) Pty Ltd address and contact details. It has a copyright dated 2001 and an identifying reference that I interpret as including a date of August 2001.[2007]

(c) PIB 4 has the address and contact details of Conceptus (Australia) Pty Ltd, a copyright dated 2001, and an identifying reference that I interpret to include a date of May 2001.[2008]

(d) PIB 11 contains reference to Conceptus, has a copyright date of 2012 and an identifying reference that I interpret to include the date of October 2012. There is nothing on the face of PIB 11 that links it to Australia.[2009]

(e) PIB 14 contains the details of Bayer Australia and AMSL.[2010] Merrell and Saad both said that PIB 14 was among the PIBs used during the AMSL distribution period.[2011]

1943 I conclude that the 10 PIBs identified and relied on by the defendants in their defence

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2006 BAU.001.002.1946.
2007 BAU.001.002.2200.
2008 BAU.001.002.2209.
2009 TUR.002.001.0002.
2010 AMS.001.001.3824.
2011 Saad at 19 [88](a) (LAY.500.001.0025); Merrell at 17 [56] (LAY.500.001.0011).

were used in Australia during the commercial supply period. I conclude that PIBs 2, 4, and 14 were also used in Australia on the basis that they have the names and addresses of relevant Australian companies on their face. In relation to PIB 14, this conclusion is reinforced by the evidence of Merrell and Saad.

1944 There is no evidence, of which I am aware, of PIB 1 and PIB 11 having been used in Australia. Both those documents have on their face the details of Conceptus Inc, and contain no reference to Australia.

PIB content

1945 Turner referred to two PIBs as examples of the information conveyed to patients.

PIB 3

1946 The introductory comments in PIB 3, under a heading 'Your choice about permanent birth control', include:

> Because it is intended to permanently prevent pregnancy, it is similar to other permanent birth control procedures such as tubal ligation ('having your tubes tied') or vasectomy. Essure pbc [permanent birth control] is a lower impact approach that is gentler on your body because it is performed without general anaesthesia, does not involve cutting through the skin and recovery is quick.
>
> This brochure will provide you with information about Essure pbc as well as the benefits and risks, however, this information is not intended to be comprehensive as all women have individual needs and concerns. Your doctor will advise you whether the procedure is appropriate for you with regards to your circumstances and medical history.[2012]

Essure is described in the PIB as 'a small, flexible device … made from materials that have been well studied and used successfully in heart and other surgeries for many years'.[2013] After some further description of the procedure, the brochure states that '[y]our GP or specialist will be able to explain the procedure to you in more detail'.

1947 The PIB addresses associated risks as follows (original emphasis):

> **As with all procedures, there are risks associated with Essure pbc**
>
> You should be aware of these risks and discuss them in detail with your doctor

2012 BAU.001.002.3721 at 2.
2013 BAU.001.002.3721 at 2.

> before you make your decision. There is a list of risks detailed in this brochure. Many of them are rare. You should talk to your doctor about the likelihood of these risks, particularly in relation to your own situation.[2014]

This information is repeated later in the brochure:

> As with all procedures, there are risks associated with the Essure pbc procedure and micro-insert. Below is a brief summary of the known or possible risks. There may be more risks that have not yet been identified. If you decide to have the procedure, your doctor will provide more detailed information about these risks and their likelihood for your particular circumstances. Many of these risks are rare.[2015]

The particular risks identified in the PIB relevantly include:

(a) improper placement of the Essure device, including the risk of '[p]erforation (eg a small hole in the wall of the fallopian tubes or uterus)', expulsion and breakage of the device;[2016] and

(b) pain, cramping and vaginal bleeding.

The PIB also described risks which had not been experienced by women in the clinical studies but were still possible, including perforation of an internal bodily structure other than the uterus or fallopian tube.

PIB 15

1948 PIB 15 was used during the AMSL distribution period.[2017] The front page of the PIB is headed 'When your family is complete ask your doctor about Essure® permanent birth control'. The brochure describes Essure as being 'designed to bend and conform to the shape of your fallopian tubes while remaining securely in place', and to be made of the same material used in heart stents and other medical devices.[2018] The PIB states:

> The Essure® insert is made of materials that include a nickel-titanium alloy. Patients who are allergic to nickel may have an allergic reaction to the inserts. Symptoms include rash and itching. Please tell your doctor if you may be

2014 Ibid at 4.
2015 Ibid at 6.
2016 Ibid.
2017 AMS.001.001.0001.
2018 Ibid at p 2.

allergic to nickel.[2019]

1949 Risks are relevantly described in the PIB as follows (original emphasis):

> **During the procedure, potential risks may include:**
>
> - Pain, cramping and vaginal bleeding during and following the micro-insert placement. This is typically tolerable and transient.
>
> …
>
> - In rare cases, part of an Essure® insert may break off or puncture the fallopian tube requiring surgery to repair the puncture. Uterine perforation by the hysteroscope, Essure® system or other instruments used during the procedure may also occur
>
> **What are the potential long-term risks?**
>
> - There are rare reports of chronic pelvic pain in women who have had Essure®
> - In rare instances, an Essure® insert may migrate through the fallopian tubes into the lower abdomen and pelvis. It may be necessary to surgically remove the migrated device if you experience this side effect
> - The Essure® insert is made of materials that include a nickel-titanium alloy. Patients who are allergic to nickel may have an allergic reaction to the inserts. Symptoms include rash and itching [2020]

After setting out circumstances relevant to whether the Essure device is a suitable contraceptive option, the brochure states: '[t]alk to your doctor about the Essure procedure and whether it is right for you'.[2021]

1950 The PIB states that the Essure procedure is not reversible, but does not state that salpingectomy or hysterectomy surgery would be required to remove the devices.[2022]

1951 Turner sought to highlight what she alleged were inadequacies of the PIBs by comparing them to a PIB that was produced in 2017 but was never in use ('2017 PIB') and PIBs used in other jurisdictions.

2019 Ibid.
2020 AMS.001.001.0001 at 3, 6.
2021 Ibid at 4.
2022 Ibid at 5.

2017 PIB

1952 The 2017 PIB was attached to a recall notice circulated by AMSL in October 2017.[2023]

This PIB contains the following warning:

> - There have been reports of perforation of the uterus and/or fallopian tubes, inserts located in the intra-abdominal or pelvic cavity, persistent pain, and allergy or hypersensitivity reactions in some patients. Some of these reported events resulted in insert removal that required abdominal surgery. Device removal may lead to improvement or resolution of symptoms when: the onset is shortly after placement, imaging indicates an unsatisfactory insert location, and other etiologies for these symptoms have been considered. This information should be shared with patients considering sterilization with Essure during discussion of the benefits and risks of the device.[2024]

1953 The 2017 PIB states that you should tell your doctor if:

> - Pain (e.g. acute or persistent) of varying intensity and length of time may occur and continue following Essure placement. Women with a history of pain prior to placement of Essure are more likely to experience both acute and persistent pelvic pain following Essure placement. Not all pain will be related to the Essure insert. Other gynecological conditions (such as endometriosis) or non-gynecological conditions (such as irritable bowel syndrome) can cause pain. Contact your doctor if you are experiencing significant pain or if the pain persists.
>
>   Surgery may be required to remove the insert. This may range from looking in the uterus (hysteroscopy), removal of the insert alone, or removal of the insert with the fallopian tube and/or uterus (hysterectomy). Device removal may lead to improvement or resolution of symptoms when: the onset is shortly after placement, imaging indicates an unsatisfactory insert location, and other etiologies for these symptoms have been considered.
>
> - You have, or think that you have an allergy to nickel, titanium, [stainless] steel, polyester fiber (PET), platinum or silver-tin or you have had metal allergies. You may experience an allergic reaction to the insert. In addition, some patients may develop an allergy to nickel or other components of the insert following placement. Typical allergic symptoms such as hives, rash, swelling, and itching have been reported in patients who have had Essure placed. Talk to your doctor if you think you may have a nickel allergy and he or she will help to determine if Essure is right for you.[2025]

1954 The 2017 PIB includes, under the heading 'Important factors you need to be aware

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2023 AMS.001.001.0139.
2024 Ibid at 2.
2025 Ibid at 4.

when considering Essure':

> Part of an Essure insert may perforate the wall of the uterus or fallopian tube during the procedure. This occurred in 1 out of 50 women in the original premarket study for Essure. A perforation may lead to bleeding or injury to bowel or bladder, which may require surgery. If removal of the insert is necessary, surgery will be needed. In that case, your doctor may tell you that you must use another form of birth control to prevent pregnancy. This surgery may range from looking in the uterus (hysteroscopy), removal of the insert alone, or removal of the insert with the fallopian tube and/or uterus (hysterectomy).[2026]

1955 The 2017 PIB describes the possible long-term consequences of having Essure implanted as including persistent pain and:

- Bleeding between periods or heavier than usual bleeding during menstruation (this may be due to discontinuation of hormonal contraception).

- Patients with a known hypersensitivity (allergy) to polyester fiber, nickel, titanium, stainless steel, platinum, silver-tin or any of the components of the Essure system may experience an allergic reaction to the insert. This includes patients who have had metal allergies. Some patients may develop an allergy to nickel or other components of the insert following placement. Typical allergic symptoms such as hives, rash, swelling and itching have been reported for this device. There is no reliable test to predict who may develop a reaction to the inserts.[2027]

1956 The 2017 PIB sets out a 'Patient-Doctor Discussion Checklist' which includes (original emphasis):

> <u>To the patient considering the "Essure® System for Permanent Birth Control" ("Essure"):</u>
> The review and completion of this form is a critical step in helping you decide whether or not to have Essure implanted. You should carefully consider the benefits and risks associated with the device before you make that decision. After reviewing the Essure Patient Information Booklet, please read and discuss the items in this checklist with your doctor. You should not initial or sign the document, and should not undergo the procedure, if you do not understand each of the elements listed below.[2028]

The long-term risks previously discussed in the PIB are again set out in the checklist for discussion with the patient's doctor.[2029] The following appears after the

2026 Ibid at 5.
2027 Ibid at 12.
2028 Ibid at 16.
2029 Ibid at 18.

consultation checklist:

> CONFIRMATION OF DISCUSSION OF RISKS
>
> Patient: I acknowledge that I have received and read the Essure Patient Information Brochure, and that I have had time to discuss the items in it and on this form with my doctor. I have had the opportunity to ask questions and understand the benefits and risks of the device and procedure, and understand that alternative methods of birth control are available.
>
> _____
> Patient Signature and Date [2030]

1957 The 2017 PIB also contains a glossary of medical terms.

US PIBs

1958 Turner submitted that a comparison of the Australian PIBs with some of the US PIBs published at around the same time further highlighted the comparative inadequacy of the Australian brochures in terms of the warnings given. An example is a PIB bearing the date 14 June 2001, titled 'Information About Your STOP™ Procedure'.[2031] This US PIB certainly contains more clinical information than the Australian PIBs. It states that '[t]here is a comprehensive list of both risks and benefits in this brochure.'[2032] The identified risks include, under the heading 'What Problems did the Women Have?':

> 1.3% Product Breakage
> 1.3% Perforation of uterus or tube
>
> All of the following adverse events occurred in less than 1% of procedures
>
> …
>
> - Expulsion of the STOP product …[2033]

The risk of perforation is further explained in the document (original emphasis):

> *Perforation:* The catheter used could poke a hole in (perforate) the wall of either the fallopian tubes or the uterus. This could cause bleeding and/or scarring. Typically, treatment is not required, but if the inserter damages an organ,

2030 Ibid at 19.
2031 BAY-EDPA-4610013.
2032 Ibid at 1.
2033 Ibid at 7.

surgery may be required.

> In rare instances, the hysteroscope (small telescope) or other instruments used inside of your uterus could poke a hole in your uterus and possibly damage your bowel, bladder or major blood vessels. Surgery may be needed but is unlikely. Should surgery be required, it would be considered major surgery.[2034]

1959 The PIB refers to the risk of pain, bleeding and discomfort following device placement procedure and says that:

> Usually this is short term and not severe. If it becomes a serious problem, you should talk to the doctor about removal.
>
> Removal of the STOP product WILL require surgery and it may be necessary to take out your fallopian tubes and, perhaps, your uterus (a hysterectomy) to get the product out safely. However, removal would only be considered in the case of severe pain.[2035]

1960 The PIB refers to the risk of abnormal bleeding as follows:

> Bleeding between your normal menses may occur. Bleeding during your menses may be heavier than normal.[2036]

1961 The PIB sets out a table of pregnancy rates for different birth control methods. The patient was directed to sign the end of the document as an acknowledgement of having read and understood the contents.

1962 The PIB contains detailed information about the Essure mechanism of action and procedure. It states, in relation to the procedure:

> The STOP procedure could take place in a day surgery, in a clinic or in a hospital. The doctor or nurse will discuss the location with you.
>
> On the day of the procedure, the doctor or nurse is available if you have any questions about the risks and benefits of the STOP procedure.[2037]

1963 Another US document relied on by Turner is dated November 2016 and headed 'Patient Information Booklet'. This is a detailed 22-page document that includes an index and glossary of terms. Like the US PIB discussed above, it contains substantial clinical information and details the risks relevant to Essure. In relation to pain, it

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2034 Ibid at 8.
2035 Ibid at 9.
2036 Ibid at 9.
2037 Ibid at 3.

includes that '[t]here are reports of chronic pelvic pain in women possibly related to Essure'.[2038] The document contains a more detailed comparison of Essure with other contraceptive methods. The document also provides for the patient to sign an acknowledgement of having received and read it.

Webpages

1964 Turner submitted that from at least 2003, Bayer Essure, Bayer HealthCare and Bayer AG published or caused to be published webpages relating to Essure which were accessible to patients in Australia at the following addresses:

(a) http://www.essure.com.au ('Australian webpage); and

(b) http://www.essure.com.

1965 Turner tendered a number of 'screengrabs' from those webpages. Turner submitted that the webpages marketed Essure as a safe and gentle sterilisation alternative, and contained inadequate warnings of the risks associated with it.

1966 Turner referred to two sets of screengrabs of the Australian webpage as examples of the information conveyed on webpages published by the defendants.

1967 First was a set of screengrabs dated February 2003.[2039] One page of the screengrab describes Essure as 'a gentler approach to permanent birth control', and continues:

> Finally, women and their partners have a gentler option in permanent birth control. Unlike tubal ligation and vasectomy, there are no punctures, and no cutting, clipping or cauterizing of tubes. Also, it's typically performed without general anesthesia. You'll be on your way in about 45 minutes! It's a gentler approach. It's Essure.[2040]

Another page describes Essure as 'a soft, flexible micro-insert designed and made by Conceptus, with the same materials used for years in heart valve replacements and blood vessel grafts'.[2041] On another page, under the heading 'Is it safe?,' the following

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2038 TUR.001.001.3565.
2039 TUR.002.001.0003.
2040 Ibid at 1.
2041 Ibid at 2.

appears:

> As with all medical procedures and birth control options, there are risks. However, in two clinical studies involving more than 700 women, there was a low rate of complications, none of which were life-threatening.[2042]

1968 The second screengrab is dated April 2013. Essure is described as 'a permanent contraception procedure that works with your body to create a natural barrier against pregnancy'.[2043] Another page contains the following:

> Trusted by women and doctors for over 10 years, Essure works with your body to create a natural, permanent barrier against pregnancy. …
>
> Essure blocks the sperm and egg from meeting, so unlike some coils, conception cannot occur. Additionally, unlike oral contraceptives, rings and the leading coil, Essure does not contain hormones to interfere with your natural menstrual cycle. Your periods should be mostly unaffected by the Essure procedure. …
>
> The Essure procedure does not require any incisions. Instead, a gynecologist inserts soft, flexible inserts through the body's natural pathways (vagina, cervix, and uterus) and into your fallopian tubes.[2044]

Turner drew attention to description of implantation as a 'gentle procedure'.[2045] She submitted that the results of clinical trials were described in positive terms without reference to any risks,[2046] that there was no reference to the risk of ongoing chronic inflammation, CPP or AUB. While the screengrab did refer to surgery being required in the event of removal, the consequence of enduring organ loss was not mentioned.[2047] However, a page of the screengrab dealing with benefits and considerations did state (original emphasis):

> **Risks of the Essure procedure**
>
> As with all medical procedures, Essure may not be suitable for all women and there are risks associated with Essure. The following are the key risks associated with Essure:

2042 Ibid at 7.
2043 TUR.002.001.0013 at 1.
2044 Ibid at 2.
2045 Ibid.
2046 Ibid at 6.
2047 Ibid at 7; SBM.001.001.0004 at 127 [383].

- The procedure should be considered irreversible
- Like all methods of birth control, the Essure procedure should not be considered 100% effective
- Not all women who undergo the Essure procedure will achieve successful placement of both inserts
- You must use another method of birth control for at least three months after the procedure
- Removal of the Essure inserts would require surgery

> The Essure system is only available through a qualified physician. Conceptus does not give medical advice, diagnoses, treatment or other medical services. It is important that patients considering the Essure procedure rely on the advice of a physician who, by exercising good clinical judgment and taking into consideration the medical history and circumstances of the patient, is best able to advise whether the Essure procedure is appropriate for an individual patient.[2048]

1969 I conclude for the following reasons that the webpage material adds little, if anything, to Turner's case. First, it is not possible to determine from the material tendered what information was available to be accessed by group members on either webpage address at any particular time. The tendered documents represent snapshots of some of the information that was available. However, that information can only be understood in context if there is evidence of the total information that was available at that time, and how the webpage could be navigated to access that information.

1970 Second, the webpage information must be considered in the context of the nature of the medical procedure under consideration, the process leading to that procedure being performed, and the other information that was likely to be made available to a patient as a result. The Essure procedure was performed by gynaecologists in medical facilities. A woman who had access to information on a webpage would have consulted with the gynaecologist before the procedure was performed. That consultation was an opportunity for the woman to receive information, advice and counselling from the gynaecologist about the relative benefits and risks of contraceptive options, including Essure. This consultation process was informed by

[2048] TUR.002.001.0013 at 7.

the gynaecologist's skill and expertise, the Essure device training based on the PTMs, and the IFUs. It is likely that the woman would also have had access to a PIB. This process is confirmed by the final extract from the 2013 screengrab set out above.

'Informed Consent Protocols' during the clinical trial period

1971 Prior to 2001, the STOP device was available to some women who participated in clinical trials conducted in Australia. Information and warnings were given to clinical trial participants in accordance with informed consent protocols.

1972 The pre-hysterectomy study was not conducted in Australia.[2049]

Peri-hysterectomy study

1973 The clinical protocol for the peri-hysterectomy study first used in June 1998, revised in May 1999 and again in December 1999, included that the investigator (or their designee) inform the participant of the potential risks and benefits of participation in the study. According to the document this was done in accordance with the informed consent protocol approved by the overseeing institutional review ethics board. Informed consent was part of the inclusion criteria for the study.

1974 The June 1998 consent form explains:

> This consent form describes the research study and your role as a participant. Please read this form carefully. Do not hesitate to ask anything about the information provided; it should stimulate your questions. Your doctor or nurse will describe the study and answer your questions. Additionally, should you choose to participate in this study, you will be given a copy of this form to keep.[2050]

1975 The form then explains the STOP device, describes the purpose of the study as determining 'if the device can be placed in the correct position in the fallopian tube', and that the device is being tested in patients already scheduled for hysterectomy.

1976 The form describes a number of 'possible risks' including:

2049 SBM.500.001.0003_2 at 402 [9.10].
2050 BAY-ESSURE-0004422 at 159.

(a) the possibility that the device or delivery system could perforate or damage the uterus, fallopian tubes, or other organs;

(b) a 'theoretical' risk that the device could migrate outside the uterus or fallopian tubes; and

(c) pain, cramping and bleeding following hysteroscopy if the procedure is performed without general anaesthesia.

1977 The form includes the following warning:

> With any experimental device there are unknown risks which may occur. If a complication does occur, you will be asked to remain in the study for observation until your complication has resolved, and you can seek treatment for the complication from the study investigator, or any other physician you wish.[2051]

1978 The form also provides space for the study investigator's name and phone number for participants to contact for questions about 'the study, its procedures, risks or benefits or your alternatives or your rights'.

Phase II study

1979 The Phase II study followed a similar informed consent process to the peri-hysterectomy study.

1980 The Phase II study informed consent form provides under the heading 'Making Your Decision':

> The device placement procedure and the STOP device are experimental. Currently, the effectiveness of the device in preventing pregnancy is unknown, as are all of the risks associated with the device placement procedure and "wearing" the device as a permanent implant. There are several temporary and permanent contraception alternatives available to you which have a known safety and effectiveness profile. You can discuss the merits of each of these with your physician.[2052]

1981 The form lists a number of possible device placement and 'wearing' risks. Those risks include pain and cramping, and perforation of the reproductive tract and surrounding

2051 Ibid at 162.
2052 BAY-ESSURE-0008291 at 122.

organs.[2053] The 'wearing' risks include device movement, pain or other discomfort, and the need for device removal.

1982 The following warning is provided in relation to pain and discomfort:

> You may also experience some pain or cramping during the time that you wear the devices. The pain or cramping may be more likely to occur during your menstrual period or during or after sex. This pain is expected to be minor and similar to that experienced with a normal menstrual period.[2054]

1983 In relation to the removal limitation, the form states:

> Due to pain or other reasons, the devices may need to be removed from you[r] body. This will first be attempted by trying to "unscrew" the devices during a hysteroscopic procedure similar to the one performed to place the devices originally. If this is unsuccessful, however, surgery may be required. It may be necessary to remove your fallopian tubes and possibly your uterus in order to safely remove the devices.[2055]

1984 The form also includes the following general warning as to risks of participation in the study:

> As with any experimental device, it is possible that unknown risks exist.
>
> You should contact your doctor if you experience any of these possible risks, or if you notice anything unusual in your health or well being. If you have a complication, your doctor will follow your progress until the complication has resolved or is not expected to change.[2056]

1985 Like the peri-hysterectomy form, the contact details of the relevant investigator are included for questions about the study or the participant's rights.

1986 The FDA PMA application for the study noted some deviations from the informed consent protocol, including inaccurate recording of contact details for the ethics committee on 15 patients' consent forms. This was remedied by a follow-up letter from Conceptus.

2053 Ibid at 123.
2054 Ibid at 124.
2055 Ibid.
2056 Ibid at 125.

Pivotal trial

1987 The Pivotal trial required that women read and sign the informed consent form before enrolment. The form provides some background to the device and information about the purpose of the trial. It states that '[t]he STOP device and the procedure to put it in place are experimental'[2057] and that '[r]emoval WILL require surgery and it may be necessary to take out your fallopian tubes and, perhaps, your uterus (a hysterectomy) to get the device out safely'.[2058]

1988 The form includes a section titled 'Possible Risks or Discomforts' which lists a number of risks associated with the procedure and wearing of the device, including:

(a) pain, cramping and vaginal bleeding associated with the placement procedure;

(b) perforation;

(c) pain or discomfort associated with device wearing; and

(d) abnormal bleeding.[2059]

1989 In relation to pain, the form includes:

> Pain and cramping can occur during your menses, during or after sex or other activities. Usually this is short term and not severe. If it becomes a problem, you should talk to the doctor about removal.[2060]

1990 In relation to abnormal bleeding it states:

> Bleeding between your normal menses may occur. Bleeding during your menses may be heavier than normal.[2061]

1991 The form also includes a section with contact details for participant questions in relation to 'the study, the procedures, risks or benefits, the alternatives, or your rights'.[2062]

2057 BAY-ESSURE-0016353 at 819.
2058 Ibid at 826.
2059 Ibid at 824-6.
2060 Ibid at 826.
2061 Ibid.
2062 Ibid at 828.

1992 As with the Phase II study, the PMA application for the Pivotal trial recorded some minor deviations from the informed consent protocol, including a centre where 17 study candidates had pre-procedure lab work performed before signing an informed consent form.[2063]

Submissions

Turner

1993 The Australian PIBs, which were patient-facing documents whose target audience was women seeking or contemplating an effective contraceptive option, did not effectively communicate the presence of the inherent defects, failure defects, risk of adverse events or the removal limitation. Although they vary over time, the PIBs give the impression of a soft, gentle, and worry-free procedure.[2064] The PIBs do not refer to a metal device with sharp edges causing mechanical injury to the fallopian tube and eliciting a persistent inflammatory response.

1994 There are only limited references to risks in the Australian PIBs. The PIBs do not refer to the risk of long-term, severe, chronic or debilitating pain and AUB. The brochures do not include consistent and fulsome references to risks of device migration, breakage or perforation. While the Essure procedure is described as 'not reversible', the fact that a hysterectomy or salpingectomy may be required if adverse events arise is not disclosed.[2065]

1995 The kind of information contained in the PIB attached to the 2017 recall notice should have been included in PIBs throughout the commercial supply period in Australia.[2066]

1996 Padgham and Merrell gave evidence that the PIBs were distributed in Australia. It is reasonable to infer, in the absence of any evidence to the contrary having been produced by the defendants, that one or more of the defendants distributed or caused to be distributed the PIBs to women considering Essure implantation during the

2063 SBM.500.001.0003_2 at 403.
2064 SBM.001.001.0004 at 122 [364].
2065 Ibid at 122 [366].
2066 Ibid at 124 [372].

supply period in Australia.[2067]

1997 Although Merrell referred to refresher training being offered to Australian gynaecologists, she confirmed that there was no mandatory retraining of gynaecologists who had been first trained by a different distributor.[2068] There is no evidence that later PTMs were distributed to gynaecologists trained at an earlier time.

1998 To the extent the distribution and content of IFUs and PTMs is established, they do not contain any or any adequate warnings of the pleaded risks.[2069] It is necessary to consider more than the words used in an IFU or PTM when determining whether adequate information or warnings were given by the defendants about the failure defects, the prominence given to any warning in documents provided by the defendants and information about the gravity of any potential resulting outcome.

1999 The warnings provided in the IFUs were inadequate insofar as they did not relate to the long-term adverse effects of Essure use, and did not make clear that resolution of symptoms could only be achieved through surgery. In summary:

(a) while one Australian IFU identified chronic inflammation, none identified the risk of ongoing chronic inflammation which could persist long-term and lead to CPP or AUB;

(b) reference to risk of breakage and perforation was limited to during the placement procedure;

(c) reaction to nickel was identified for people 'allergic to nickel' — suggesting relevance to an existing (known) allergy;

(d) there is no reference to the leaching or reaction to any other metals;

2067 Ibid at 125; *Blatch v Archer* (1774) 1 Cowp 63 at 65 (Lord Mansfield); *Weissensteiner v The Queen* (1993) 178 CLR 217 at 225 (Mason CJ, Deane and Dawson JJ); *Gill* at [3267] (Katzmann J).

2068 SBM.001.001.0004 at 136 [422].

2069 Ibid at 128 [389].

(e) pain, cramping and bleeding were identified as 'following the placement procedure' and downplayed as 'typically tolerable, transient and successfully treated with medication' when in fact the evidence shows that the risk was longer term, serious and debilitating;

(f) there was a short generic statement that 'abdominal/pelvic pain and cramping may occur', but there was no reference to severe, ongoing or CPP or exacerbation of such;

(g) there was a generic statement that 'intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced' — but there was no reference to serious, ongoing or AUB or exacerbation of such;

(h) the following statement was included in a number of IFUs: 'as with currently available methods of mechanical permanent contraception (ie clips and rings), if the Essure micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required' — when in fact if the Essure micro-insert was to be removed, salpingectomy or hysterectomy would almost always be required and after more than three months would inevitably be required. The word 'possibly' is inaccurate.[2070] Surgical removal of clips and rings is also generally a far less serious operation and, therefore, also a misleading comparison;[2071]

(i) device removal by salpingectomy was generally only referred to in the context of improper placement;

(j) there was no true disclosure of the link between the risk of symptoms such as CPP and AUB leading to a hysterectomy as the only means of resolving the symptoms;

2070 T2028 (TRA.500.021.0001_2 at 0006_7-24).
2071 T2031-2 (TRA.500.021.0001_2 at 0009-10).

(k) there is no section related to patient counselling or warnings which is clearly set out to draw attention to these factors; and

(l) none of the warnings were identified prominently such as to reinforce the need for these matters to be drawn to the attention of the patient by the doctor.[2072]

These deficiencies can be compared and contrasted to the contents of the proposed 2017 IFU, and to the IFUs used in the US from 2002 to 2016.

2000 While there is greater variation in language between the PTMs relied on by the defendants, in those documents:

(a) references to nickel reaction are generally related to known allergies;

(b) references to perforation are generally related to the risk with placement procedure;

(c) references to pain are generally focused on post-procedural pain or during the first year of reliance rather than a long-term risk of CPP;

(d) references to bleeding are generally focused on post-procedural bleeding or first year of reliance rather than a long-term risk of AUB;

(e) there were limited references to the need for salpingectomy or hysterectomy in the event of CPP and AUB, for example. Hysterectomy was only noted as 'possible' or that it 'may be required'.[2073]

2001 In 2016, the FDA imposed a requirement on Bayer to improve its Essure warnings. Carney said that she treated the draft guidance document as binding when it was first issued by the FDA in March 2016.[2074] Despite those improved warnings in the US, the defendants did not amend the warnings or patient checklist in the IFU in Australia

2072 Ibid at 138 [429](a)–(g), (i)–(m).
2073 SBM.001.001.0004 at 141.
2074 SBM.001.001.0004 at 142 [440].

until after May 2017 when a decision was made to stop distribution.

Defendants

2002 At all times, Turner bore the onus of proving that:

(a) Essure had a defect/safety defect or suffered from a want of merchantable/acceptable quality by reference to all of the information provided in relation to it; and

(b) there was a warning which, if provided, would have made a difference in outcome to her or a group member.

This onus extends to identifying the information and warnings available and the study, training and expertise of medical practitioners who consulted with group members and performed the Essure procedure.[2075]

2003 Essure was accompanied by detailed IFUs which set out, among other matters, the mechanism of action of the device; indications and contraindications for use; warnings; precautions; and possible adverse effects. Additional material that may reasonably be expected to be within the knowledge of specialist medical practitioners includes the Essure PTMs, other materials made available at training programs, practical training, general medical knowledge and clinical experience, conferences and literature more generally.[2076]

2004 The text and context of the IFUs showed they were intended to be read by specialists, informed by their existing knowledge and expertise. Save for IFU 1, each of the IFUs make explicit that '[t]he Essure procedure should only be performed by skilled hysteroscopists who have completed the Conceptus training program for this procedure'.[2077] The text, context and content of IFU 1 is consistent with this

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2075 SBM.500.001.0003_2 at 365 [5.2].
2076 Ibid at 380 [8.2].
2077 BES.001.001.0033 at 2.

proposition. The proposition is further supported by the PTMs.[2078]

2005 Bayer specifically indicated that gynaecologists had to be familiar with and trained in the Essure procedure, and provided the means by which that could occur. It was entirely reasonable in those circumstances for Bayer to expect medical practitioners, acting reasonably, to seek guidance or clarification should they not understand a statement in an IFU.[2079]

2006 Turner has sought to make much of the PIBs, alleging that they did not contain an exhaustive statement of the risks associated with the Essure device, and that as a result inadequate warnings of those risks were given. Strikingly, Turner has not adduced evidence of any person who has been provided with, read or relied upon any PIB.[2080]

2007 No finding can be made that any PIB was intended to be a substitute for the IFUs or, importantly, relevantly affect the discussion and process at consultation that each patient would have with her medical professional. It is unrealistic, and inconsistent with the evidence, that a patient would access a PIB and proceed to have Essure devices implanted without there being any further discussion with the medical professional who performed the procedure to ensure that the patient understood the risks and benefits, including relative to other means of contraception and sterilisation.

2008 To the extent that the defendants are criticised for a failure to update warning statements in line with the changes implemented in the US, despite repeated communications from the TGA, the defendants submit the following:

(a) Turner's pleaded case in relation to failure to update 'marketing materials' relates to the PIBs. This aspect of her claim has not been particularised in relation to a failure to update the warnings included in the IFUs or PTMs.

2078 SBM.500.001.0003_2 at 380 [8.3].
2079 Ibid at 381 [8.5].
2080 Ibid at 367 [5.11].

(b) Much of the 'delay' in updating the warnings included in the Australian PTMs after communication from the TGA, was during a period of time when the updated warnings had not yet been approved for the US PIBs. Taken at its highest, the delay could only be said to have been between November 2016 and August 2017, which should not be characterised as 'unreasonable'.

(c) The Court should not form the view that any 'delay' was unreasonable unless the existence of the actual risks subject of the proposed warning are also established.

(d) The FDA expressed a concern in 2016 that some women were not 'receiving or understanding information regarding the risks and benefits of permanent, hysteroscopically-placed tubal implants that are intended for sterilisation'. There is no evidence that a similar concern in relation to Australian warnings was expressed.

(e) Even if the PIB was immediately updated, the warnings made available to patients would not have changed as these were provided in combination with information available to physicians including their specialist training, knowledge and experience.

(f) There are complex regulatory interactions between the TGA and other regulatory bodies including the NSAI which affected the ability to implement labelling changes in Australia quickly.[2081]

Analysis

2009 For the following reasons I reject Turner's submissions that would, if accepted, effectively limit the information and warnings provided by the defendants to women who underwent the Essure procedure to the content of the PIBs.

2010 First, in Australia the Essure procedure was performed by gynaecologists who had

[2081] SBM.500.001.0003_2 at 340 [4.7].

completed the Essure training conducted in accordance with the PTMs. I infer it is likely that gynaecologists had access to the PTMs as part of the training programs.

2011 Second, gynaecologists had access to IFUs that were contained in every box in which Essure devices were supplied in Australia.

2012 Third, the Essure procedure was performed in an operating theatre setting under anaesthetic.[2082]

2013 Fourth, it is reasonable to expect in these circumstances that gynaecologists consulted with patients before the Essure procedure was performed. Further, it is reasonable to expect that in that consultation gynaecologists involved discussion with their patients matters including contraceptive options, the Essure procedure, the mechanism by which Essure operates, and relevant risks and contraindications. It is reasonable to expect that the source of information conveyed by gynaecologists to patients was their own specialist skill, expertise and experience, and information they obtained from the Essure training, PTMs and IFUs. These conclusions are consistent with Rosen's evidence about his own practice as a gynaecologist and the relatively limited evidence of Turner's consultation with Thalluri. Turner chose not to call Thalluri, Weatherill or any other doctor who performed the Essure procedure. I infer that Rosen's evidence about the patient consultation process, and the consistent evidence in Thalluri's clinical note and confirming letter, reflect a general practice by gynaecologists when consulted about contraceptive options.

2014 Fifth, there is limited evidence about the role of the PIBs. The evidence indicates that PIBs were provided to gynaecologists. I infer this was done so that the PIBs would be available to women who were considering the Essure procedure. However, there is no evidence about whether and in what circumstances the PIBs were provided to or read by women. The defendants did not distribute the PIBs directly to women. Turner did not call evidence from any gynaecologist about the practice of making PIBs

2082 Rosen at 9 [2.3] (EXP.001.002.0002_2).

available to patients. Turner herself did not receive a PIB.

2015 Sixth, while the PIBs were designed to market Essure to women, they were clearly not designed to be the principal source available to women of medical information about the device. The brochures themselves state that women would receive advice from their doctors about whether the Essure procedure was appropriate for them. I accept the defendants' submission that the PIBs were not designed as a substitute for medical information provided to women by their gynaecologist, informed by the Essure training, PTMs and IFUs.

2016 Seventh, I accept the defendants' submission that Turner bore the onus of establishing the information and warnings that were made available to women who underwent the Essure procedure. I am more confident in reaching the conclusions I have about the physician training, PTMs, IFUs and the gynaecologists' consultation with women before the Essure procedure because of Turner's failure to lead evidence about these matters.

2017 I reject Turner's criticism of the PIBs and IFUs by reference to versions of those documents used in the US, or versions that were prepared in 2016 and 2017 in response to regulatory concerns. The adequacy of information provided to gynaecologists and available to women needs to be assessed in the Australian context. That context includes the Essure procedure only being performed in Australia by gynaecologists who had successfully completed Essure training, were provided with IFUs, and performed the procedure in an operating theatre setting under anaesthetic. More comprehensive information included in an IFU or PIB used in the US may reflect differences in the regulatory regime and practices for performing the Essure procedure in that jurisdiction. The defendants could have acted more quickly in response to regulatory concerns by introducing more comprehensive IFUs and PIBs before commercial supply ceased in 2017. However, the adequacy of the IFUs and PIBs that were in use is to be assessed against the risks that have been proven in this case.

Ongoing chronic inflammation causing CPP, dysmenorrhea or AUB

2018 The IFUs and PTMs describe the tissue response to Essure as benign, fibrotic and occlusive in nature. The mechanism of action is described in IFU 9 as follows:

> When the Essure micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[2083]

Each of the IFUs conveys equivalent information. Similar information is also conveyed by each PTM. The anchoring of the Essure device within the fallopian tube and tissue in-growth elicited by the device are further confirmed by descriptions in the IFUs and PTMs of the process for removal.

2019 Each of the PTMs refers to chronic inflammation as part of the response to the Essure device leading to tubal occlusion. For example, PTM 5 states (original emphasis):

> **The efficacy of Essure is believed to be due to a combination of the space-filling design of the micro-insert and a local, occlusive, benign tissue response to the PET fibres.**
>
> - The tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibres. It is believed that the tissue in-growth into the micro-insert caused by the PET fibres results in both micro-insert retention and pregnancy prevention. PET fibres have had widespread use in the clinical setting.[2084]

This information is consistent with the mechanism of action described in each IFU.

2020 Korda agreed that any Australian surgeon qualified to perform hysteroscopic procedures would know that the Essure device was 'intended to result in an inflammatory response, which is the foreign body response'.[2085]

2021 I conclude that Australian gynaecologists who performed the Essure procedure would be aware from their own skill and expertise, and from information conveyed in the IFUs, PTMs and training programs, that the foreign body response to the Essure

2083 AID.500.001.0002 at 1.
2084 AMS.001.001.5420 at 9.
2085 T2458 (TRA.500.027.0001_2 at 0016_31).

device included a chronic inflammatory phase that was intended to result in fibrosis and tubal occlusion. However, the IFUs and PTMs do not inform surgeons that there was a risk that the chronic inflammatory phase of the foreign body response would not resolve and could cause CPP and AUB.

2022 The defendants accepted that they did not inform women contemplating the Essure procedure via the IFUs, PTMs, Essure training or PIBs that there was a risk the devices could cause ongoing chronic inflammation resulting in CPP or AUB. The defendants accepted that if Turner had succeeded in establishing general causation in respect of this aspect of her case, they did not give adequate warning of the risk.

Pain and bleeding disturbance

2023 The defendants' concession did not extend to *any* pelvic pain or *any* alteration in the pattern of uterine bleeding. The defendants submitted that the IFUs and PTMs, either alone or together with other information provided, gave adequate warning of pain or bleeding disturbance that could be caused by Essure in the acute phase following implantation, associated with any of the failure defects where causation was established, or in any other way.

2024 The IFUs and PTMs contained information and warnings about pain. The warning about the risk of immediate pain during and following the Essure procedure in IFU 9 is set out at [1861]-[1865] above. Similar warnings were included in each of the IFUs and PTMs. The IFUs warn about the risk of abdominal/pelvic pain associated with the menstrual period, sexual intercourse and other activity. The PTMs also communicate the risk of menstrual pain, ovulatory pain and other abdominal/pelvic pain.[2086]

2025 The IFUs did contain information about the risk of bleeding and menstrual disturbance as a result of the Essure procedure, perforation and migration. The IFUs warned that wearing the Essure device involved the risk of 'inter menstrual bleeding

2086 AID.500.001.0004 at 29.

or heavier than normal menstrual bleeding'. Similar information was contained in the PTMs, which also set out clinical data of reports in studies of AUB.

2026 I conclude that Turner has not established any inadequacy in the information provided by the defendants to gynaecologists about the risks of pain and altered bleeding following Essure device implantation.

Migration and expulsion

2027 I have set out at [1864] above the information conveyed in IFU 9 about the risk of migration and expulsion. Surgeons were informed that device migration or expulsion could cause pain, menstrual disturbance and other adverse events, that surgery may be required to remove devices, and that this may include salpingectomy and hysterectomy. Information is displayed prominently under a heading 'Possible adverse events' and a sub-heading dealing with risks associated with wearing Essure. The causal link between pain and altered bleeding and the possible need for removal surgery is clearly made. The IFU also describes the need for a confirmation test at three months to evaluate retention and location of the Essure devices, which further emphasises the possibility of migration and expulsion. The process of radiological examination to confirm device location is described in detail. Each of the IFUs contains similar information and warnings.

2028 Each of the PTMs also deals with migration and expulsion. For example, PTM 5 states (original emphasis):

> There is a risk that the Essure® micro-insert could move out of the fallopian tubes. This movement could be 1) expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body), or 2) migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity).
>
> Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events. Migration to the abdominal cavity can also occur without tubal perforation. Confirmatory radiological testing with abdominal x-ray, transvaginal ultrasound (TVU) or hysterosalpingogram (HSG), according to local protocols, is mandatory to establish satisfactory device placement and/or tubal occlusion.
>
> *Reports of expulsion or migration*

> In the 7-year retrospective study that evaluated complications of tubal sterilisation with Essure in 4306 women, 2 cases (0.04%) of asymptomatic migrations into the abdominal cavity where detected. Both women with abdominal migration of one device underwent another placement, retaining the migrated devices in the abdominal cavity.
>
> Malpositionings not otherwise specified were also reported in the MAUDE database[.]
>
> *Management of expulsion or migration*
>
> Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s).[2087]

There is further information in the PTM discussing radiology required for confirmation of device location, and the need for surgery if device removal is required.

2029 In the gynaecology JER, Korda and As-Sanie agreed that migration and expulsion are intrinsic risks associated with the implantation of a foreign body, and that increased surgeon skill and experience in Essure placement would decrease the risk. Korda said that any Australian surgeon qualified to perform hysteroscopic procedures would be aware of the risk of device migration. He said that the risks were low.[2088] The experts also agreed that laparoscopic tubal ligation can be associated with the migration of Filshie clip or Falope ring laparoscopic sterilisation devices.[2089]

2030 I have accepted the evidence of Korda and As-Sanie as to the frequency of migration and expulsion events.[2090] The information conveyed in the IFUs and PTMs is consistent with this evidence. Both documents refer to the need for laparotomy or laparoscopy surgery if removal is required, and more specifically to salpingectomy and hysterectomy. Turner has not established that the magnitude of the risk is greater than conveyed in the IFUs and PTMs. Further, as Korda said, Australian surgeons would be aware of these intrinsic risks. I reject Turner's submission that the migration and expulsion warnings in the IFUs and PTMs were inadequate because they did not convey the degree or gravity of the risk of these adverse events.

2087 AMS.001.001.5420 at 80 (end notes omitted).
2088 T2458-9 (TRA.500.027.0001_2 at 0016–7).
2089 Korda at 5 [15.1]-[15.2] (EXP.001.002.0011).
2090 See Chapter XVII.

Breakage, fragmentation and fatigue

2031 The IFUs and PTMs convey the possibility that an Essure device may break or fragment during attempted removal, and that this may be associated with adverse effects.[2091] The IFUs and PTMs do not say there is a risk the device will fatigue, break or fragment during the period of wear. However, for reasons set out in Chapter XVIII, I have concluded Turner has not established the existence of that risk. Turner has not established any inadequacy in the information provided in the IFUs and PTMs about the risks of breakage, fragmentation and fatigue.

Corrosion

2032 There was a risk that corroded nickel ions from an Essure device in vivo would cause some women to experience a DTHR/allergy reaction. Eiselstein said that nickel was the focus of the corrosion testing required for FDA approval and commercial supply because the risks associated with nickel were known. Sokol said that while DTHR to nickel are rare, the associated symptoms can be severe. The evidence of the experts supports the conclusion that a warning should have been given about the risk of an allergic reaction to nickel from the device.

2033 Each of the IFUs and PTMs, apart from IFU 1 and PTM 1, identify the risk of an allergic reaction to nickel released from the Essure device under headings such as 'Contraindications' or 'Warnings'. There is no merit in Turner's criticism that the warning was only directed to women with a known allergy to nickel. The warning was sufficient to raise the possibility of an allergic reaction that could be discussed by a treating gynaecologist with their patient in consultation. Turner has not established any inadequacy in the information or warnings given to gynaecologists about the risk of an allergic/hypersensitivity reaction to nickel from the time IFU 2 and PTM 2 were in use.

2034 Rosen gave the following uncontradicted evidence:

> Known Nickel allergy – patients are asked about Nickel allergy due to the presence of Nickel in the nitinol coil. A skin reaction to inexpensive jewelry is

[2091] BAG.001.001.2362 at 28, 31; AMS.001.001.5420 at 35, 84.

> a useful entry question. Known hyper-sensitivity to Nickel is recorded as a contraindication to the Essure procedure in the Physician Training manual. On review of my records, I commenced routinely asking patients about Nickel allergy from June 12, 2001 and continued to do so with every patient throughout my career as a surgeon performing the Essure procedure, and as part of the training and preceptorship of my gynaecological colleagues. My consent process including risk factors and specific warnings did not change in this respect during the following 16 years during which I performed the Essure procedure.[2092]

Rosen did not give any further explanation for why he began asking patients about nickel allergy and included that issue as part of his training and preceptorship of gynaecologists from June 2001. IFU 2 listed known nickel allergy as a contra-indication for use of Essure. It is possible IFU 2 was in use earlier than March 2002 when it was mentioned in correspondence, or that another document that identified the risk of nickel allergy was in circulation. That may explain Rosen raising the matter during training and in his clinical practice from mid-2001.

2035 The first shipments of Essure to Australia for the purposes of commercial supply commenced in the second quarter of 2001. It is not clear precisely when the commercial supply of Essure devices to gynaecologists and hospitals first occurred. It is possible that this was after the risk of nickel allergy became part of physician training.

2036 I am not positively satisfied on this evidence that the defendants failed, during the first months of the commercial supply period, to provide an adequate warning to gynaecologists about the risk of nickel allergy/hypersensitivity associated with Essure.

2037 Turner has not established a risk that corrosion of Essure devices in vivo could cause other adverse events or injuries.

Perforation

2038 The IFUs and PTMs identified the risk of perforation associated with the Essure procedure. Korda said that this was the most likely time at which perforation

2092 Rosen at 16 [5.1.10] (EXP.001.002.0002_2).

occurs.[2093] He said that perforations are rare when the placement procedure is performed correctly; that the uterus and fallopian tubes are the most common structures that are perforated; and that in the majority of cases, perforation at the time of placement would be diagnosed at the Essure confirmation test. Korda said that the more skilful and experienced the surgeon is, the lower the risk of perforation will be.[2094]

2039 The IFUs and PTMs also identified the risk that a device may migrate out of the fallopian tube into the peritoneal cavity. Korda said that 'perforations can be exacerbated following placement due to tubal peristalsis which could cause migration of the micro-insert'.[2095] He said that the perforations of the bowel or bladder by a migrated device which result in damage to those organs can be very serious. However, there are no documented cases of such a risk eventuating in the case of Essure.

2040 The IFUs state that perforation during the placement procedure may result in injury to the bowel, bladder and major blood vessels; pain and/or menstrual disturbance or other adverse event; and that surgical intervention may be required. The IFUs also warn about the risk of adverse events associated with migration. The risk of perforation, the complications that may arise, and the possible need for surgery is described in very similar terms in the PTMs. Clinical data as to the rate of recorded tubal perforations is set out in each IFU except for IFU 2.

2041 Korda and As-Sanie agreed that surgeons would be aware of the intrinsic risk of perforation associated with placement of a biomedical device such as Essure.

2042 I conclude it is likely that Australian gynaecologists performing the Essure procedure would have been aware from their own skill, expertise and experience, and from information provided by the defendants including the IFUs, PTMs and training

2093 Korda at 16 [6.1.6])(EXP.001.001.0025).
2094 T2454 (TRA.500.027.0001_2 at 0012_23).
2095 Korda at 36 [123.1] (EXP.001.002.0011).

programs, of the risk of perforation associated with the Essure procedure or subsequent migration of an Essure device; the possible consequences of perforation including pain, AUB and damage to other internal organs; and the possible requirement for surgery to resolve those adverse outcomes. Turner has not established any inadequacy in the information and warnings provided by the defendants to gynaecologists about the risks of perforation or associated adverse outcomes.

Damage to internal organs

2043 The IFUs warned of the risk of uterine perforation and possible injury to the bowel, bladder and major blood vessels associated with the Essure procedure. Further, the IFUs warned of the risk of the Essure device migrating from the fallopian tube into the peritoneal cavity and the associated risk of pain/menstrual disturbance or other adverse events. The PTMs contained similar information.

2044 Turner has not established that the degree or magnitude of the risk of damage to internal organs meant that the warnings contained in the IFUs and PTMs were insufficient or that more was required.

2045 I conclude that there was no inadequacy in the warnings and information in the IFUs and PTMs about the risk of damage to internal organs associated with Essure.

Removal limitation

2046 The IFUs and PTMs describe the mechanism of action of Essure as involving tissue in-growth resulting in it being firmly anchored in the fallopian tube. The documents clearly state that device removal will require surgery, and that salpingectomy and hysterectomy may be required.

2047 Turner criticised the removal information on the basis that it did not convey that salpingectomy or hysterectomy would almost inevitably be required more than three months after device placement. I reject that criticism. The IFUs and PTMs gave considerable information about the requirement for surgical removal in a number of

circumstances. The only circumstance identified where removal could be attempted without surgery was if the device was placed too proximally in the fallopian tube and 18 or more coils remained visible in the uterus during the Essure procedure. The documents identified that laparotomy or laparoscopy would be required, and that surgery could be by way of salpingotomy, salpingectomy, cornual resection and hysterectomy. The choice of surgery would necessarily depend on the circumstances requiring removal. This information was being conveyed to specialist gynaecologists who would understand the mechanism of action of Essure. It is notable that Turner did not call evidence about the adequacy of the removal limitation and warnings from Korda or any Australian gynaecologist who had performed Essure procedures.

2048 There was no inadequacy in the information provided to gynaecologists about the removal limitation associated with Essure.

Clinical trial period

2049 I accept the defendants' evidence that informed consent protocols were used for each clinical trial participant in Australia.

2050 Information and warnings given to participants in clinical trials would necessarily differ from what was provided as part of commercial supply. Each consent protocol described the Essure device as experimental, and indicated it was associated with unknown risks. The protocols did give information and warnings about certain risks that were known to exist. Participants were provided with an opportunity to ask questions about possible risks associated with participation in a trial.

2051 Turner did not advance submissions about the adequacy of the clinical trial informed consent protocols.

2052 Turner has not established that the information and warnings communicated to clinical trial participants were inadequate.

XXI. POST-MARKET SURVEILLANCE

2053 While Turner did not frame her case as a regulatory one, she did rely on a number of alleged deficiencies in the defendants' PMS systems and pleaded regulatory events as relevant to the foreseeability of harm and the question of knowledge.

2054 The defendants were obliged to comply with the regulatory requirements under the *TG Act* for the period of Essure supply in Australia. The TGA relied heavily on a 'conformity assessment', which in essence was a form of mutual recognition of the CE mark.[2096] From 2002, the ARTG required compliance with 'Essential Principles' which were modelled off the European 'Essential Regulations'.[2097]

2055 Brandwood said that in his experience, the TGA interpreted and enforced the Essential Principles as follows:

> a) TGA required that safety was considered in design and construction, appropriate Risk Management was applied in device development and that device clinical benefit was required to outweigh any risks associated with device use. As noted at 54) above, it is important to understand that this balance of risk and benefit was the core definition of safety under the regulations and that no device was required to be absolutely safe. Instead known risks were required to have been considered in context of clinical benefit. (Essential Principles 1-2,6)
>
> b) It was required that the device meet the manufacturers Intended Purpose as embodied in labelling claims. (Essential Principle 3)
>
> c) It was required that the device continued to perform safely for its use life and not be adversely affected by conditions of transport and storage. (Essential Principles 4-5)
>
> d) It was required that the device safety considerations were addressed in the design and construction including ensuring, where applicable: electrical, mechanical, and biological safety, radiation safety, cleanliness and sterility, and appropriate software validation. (Essential Principles 7-12)
>
> e) It was required that the device Labelling must include Manufacturer and sponsor details and sufficient information to allow the safe use of the device including instructions for use and identification [of] known potential adverse effects. (Essential Principle 13)

2096 Brandwood at 49 [192]-[193], 51 [201] (EXP.001.002.0009_2).
2097 Ibid at 45.

> f) TGA required that clinical trials complied with Good Clinical Practice standards to ensure protection of trial subjects and integrity of trial data. (Essential Principle 14)[.][2098]

2056 Following the grant of a CE mark to Essure in 2001 and registration on the ARTG, Bayer was required to conduct PMS during the supply period to capture, track and trend Essure safety, performance and conformity.[2099]

2057 Dent and Brandwood agreed that the manufacturers had primary responsibility for the conduct of risk management and PMS throughout the device life cycle. They agreed that Bayer had the following PMS obligations in relation to Essure:

> a. Ensuring that satisfactory arrangements were in place for the collection of postmarket feedback. This included ensuring the Australian sponsor had appropriate arrangements and competency to collect such information and promptly make it available to the manufacturer.
>
> b. Conduct of review and analysis of postmarket feedback from all sources.
>
> c. Taking appropriate actions in response to postmarket feedback including:
>
> i. conducting follow up investigations where required,
>
> ii. preparation of Adverse Event Reports for submission to TGA by the sponsor,
>
> iii. conducting analyses including trend analyses and using this information to inform other activities including in risk assessment and clinical evaluation and in further product design and development, and
>
> iv. based on postmarket feedback and any subsequent investigations carried out, the raising of [corrective and preventative actions] and subsequent corrective actions including postmarket actions such as hazard alerts or recalls where required.
>
> …
>
> e. The manufacturer was required to ensure that the Australian sponsor had appropriate systems and capabilities to:
>
> i. receive reports and to transmit these to the manufacturer for assessment in a timely fashion,
>
> ii. file promptly with TGA any Adverse Event reports prepared by the Manufacturer,

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2098 Ibid.

2099 Dent at 19 (EXP.001.001.0547).

iii. conduct any other necessary communications with TGA on behalf of the manufacturer.[2100]

2058 The regulatory experts agreed that the Australian sponsors had no responsibility for risk management, but said that the sponsors:

> … were, at times, unable to fully meet their obligations to TGA because of delays in the provision of timely and complete information by the manufacturer. This included the manufacturer:
>
> i. Not promptly updating warning statements on labelling in line with the changes previously implemented in the USA (refer to TGA communications referenced in section 3.11.3 of Ms Dent's reply report).
>
> ii. Potentially not reporting Adverse Events as fully as expected by TGA.[2101]

2059 According to Carney, the Bayer PMS processes involved the regular preparation of:

(a) the annual PMA reports;

(b) clinical evaluation reports;

(c) PMS reports;

(d) various risk management file materials;

(e) pharmacovigilance reports;

(f) risk analysis reports; and

(g) discussion of issues and risks relevant to PMS activities relating to Essure at certain regular review meetings.[2102]

Carney's evidence in relation to these PMS processes is further summarised in Chapter X.

2060 The annual PMA report from 2017 is 782 pages in length. It includes a review of the published scientific literature, unpublished reports of data from clinical

2100 Regulatory JER at 6 (EXP.500.001.0002).
2101 Ibid at 9.
2102 Carney at 5 (LAY.500.001.0008_2).

investigations, reports on unsatisfactory device locations and summary and analysis of Essure device removal cases for the year 2017.[2103] The report concludes that:

> Overall, the data from post-marketing cases (especially those that are medically confirmed), analyses of databases, observational study, and the clinical trials provide similar results regarding the reasons for Essure removal and the procedures used.[2104]

2061 The 2017 Clinical Evaluation Report ('2017 CEUR') is 1075 pages in length. It includes a review of Manufacturer Complaint Data:

> A review of the manufacturer's complaint data includes all cases created from 01 JAN 2017 to 31 DEC 2017. The data were analyzed as retrieved from the manufacturer's global safety database (ARGUS) and the product technical complaint database (Deva@com). Furthermore, the results of other pertinent analyses of post-marketing safety data on several safety topics are also included under the respective topics in Section 4.7.[2105]

The report contains analyses of available data from all sources. In relation to post-market reporting, it summarises that:

> Evidence suggests that for the past few years, Essure has been subject to stimulated post-marketing reporting, both through social media and through legal sources. Post-marketing reports are an important way of monitoring the ongoing safety of devices and improvements to the system are warranted. The current wave of reports, however, are often vague, contain limited information, with many reporting the same event multiple times. In reports that come from litigation, currently the majority of reports, there is a financial incentive to declare complications.
>
> Regardless of the source or motivation for these reports, they represent an important avenue to gathering data about Essure. Along with data from clinical trials and scientific publications, these data are incorporated into the evaluation of every potential risk of the product.[2106]

2062 Bayer handled complaints using two systems. The 'Dev@com' system was used for entry and initial assessment of complaints, while the ARGUS database was used for management of reportable events. 'Pegasus' was a data tool used to compile and study data from both systems. This was a complex system which was multilocational

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2103 BAY-JCCP-3798228 at 1-2.
2104 Ibid at 189.
2105 BAY-JCCP-1120549 at 43.
2106 Ibid at 110.

and involved inputs from various teams.[2107]

2063 The experts agreed that the following audits were conducted of the manufacturers' PMS systems:

(a) An audit to ensure that the quality management systems of the manufacturer complied with the applicable standards and were being maintained before certification was provided.[2108]

(b) Surveillance audits every 12 months.[2109]

(c) A special follow-up audit which followed after category one non-compliance had been identified in a previous audit to assess whether the non-compliance had been rectified.[2110]

(d) Audits performed as part of the recertification process which occurred every three to five years.[2111]

2064 Dent and Brandwood agreed that the primary non-compliances in risk management and PMS systems during the relevant period were:

(a) non-compliance in complaint handling processes at Conceptus, identified in a mock FDA audit in August 2008 ('2008 mock audit'). The following external NSAI audit in October 2009 recorded that the process was compliant, indicating that the manufacturer had carried out actions to correct the non-compliance; and

(b) internal and external audits from 2013 to 2015 which showed that Bayer PMS systems were not compliant with reasonable practice.[2112]

2107 Brandwood at 80 [331] (EXP.001.002.0009_2).
2108 T3875 (TRA.500.038.0001_2 at 0058_10-13).
2109 T3875 (TRA.500.038.0001_2 at 0058_26-7).
2110 T3876 (TRA.500.038.0001_2 at 0059_10-11).
2111 T3876 (TRA.500.038.0001_2 at 0059).
2112 Regulatory JER at 9-10 (EXP.500.001.0002).

The experts agreed that these PMS non-compliances 'arose from considerable difficulties experienced with integration of post-market surveillance systems into the Bayer [pharmacovigilance] systems'.[2113] They further agreed that these audit non-conformances were closed by the time of a June 2016 NSAI audit.[2114]

2065 The June 2016 NSAI audit found that 'the threshold analysis for complaints in TD-03457 does not ensure that all changes in risk that could impact the risk rating would be determined'.[2115] The experts said that there remained some disagreements between the regulators and Bayer as to the regulators' expectations for reporting practices which were finally resolved in January 2017.[2116]

2066 Dent and Brandwood differed in their opinions about the consequences of the non-compliances. Dent said that inappropriate and extremely limited complaint criteria and return processes resulted in Bayer failing to comprehensively understand the extent of issues where Essure was linked to or had caused perforations, migration including breakages, pain, bleeding and/or allergies/hypersensitivity. Brandwood said that there were separate processes in place at Bayer that adequately captured post-market trends and provided further analysis as an input to clinical evaluation. Brandwood said that no regulatory body had found that there had been a systemic major non-compliance with requirements for risk management by Bayer.

2067 Dent said that Bayer's underreporting between 2001 and 2017 of issues relating to pain, perforation or bleeding requiring micro-insert removal; ectopic pregnancy; infection requiring medical intervention; and nickel allergy requiring micro-insert removal contributed to ongoing compliance issues.[2117] She said that this had a flow-on effect resulting in misinterpretation of Essure safety, performance and risk-benefit analysis. She said that significant compliance issues were identified for an extended

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2113 Ibid at 11.
2114 Ibid at 10.
2115 BAY-EDPA-2046085 at 22.
2116 Regulatory JER at 11 (EXP.500.001.0002).
2117 Dent at 12 (EXP.001.002.0013).

period and were not fully addressed.

2068 Dent said that:

> … inappropriate and extremely limited complaint/[corrective and preventative action] criteria and return processes resulted in the manufacturer failing to comprehensively understand the extent of issues where the Essure device were linked to/causing perforation, migration including breakages, pain, bleeding, and allergies/hypersensitivity… specific examples such as:
>
> i. When no device was returned, the manufacturers related processes stated no investigation was possible, the classification used was "unconfirmed quality defect or device malfunction" and no [corrective and preventative action] was required/completed. This specific issue was identified as a major non- compliance during NSAI Audit completed in December 2015, which further evidences the manufacturers compliance challenges.
>
> ii. If an adverse event that was identified on IFU was reportable.
>
> iii. Post Market Surveillance Report dated January 2017 stated, "the benefit-risk profile remains unchanged, there has been a decline in implants and in some regions an increase in the number of requests to remove the Essure device", which was consequently dismissed by the manufacturer due to the "extensive coverage by media and social media groups."[2118]

2069 Dent agreed this did not mean that incidents were not included in the pharmacovigilance database maintained by Bayer.[2119] She said, however, that there was 'clear evidence of information not being included into trending and post-market data due to the classification of [the] reports being non-reportable.'[2120]

2070 Brandwood said there was sufficient redundancy in the post-market monitoring, review and reporting to ensure adequate detection of safety signals.[2121]

2071 He said that although Bayer's complaint handling processes may have initially been deficient in raising corrective and preventative action and making individual risk categorisations of single reports, it was evident that:

a) the receipt of reports from customers, and onwards reporting to Competent

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2118 Ibid at 16.
2119 T3899 (TRA.500.038.0001_2 at 0082_22).
2120 T3899 (TRA.500.038.0001_2 at 0082_28-31).
2121 Brandwood at 83 (EXP.001.002.0009_2).

> authorities was functioning as required;
>
> b) the deficiencies identified in audits were all successfully corrected and
>
> c) there were separate processes in place for direct trend analysis as input to periodic updates of clinical evaluation. The Witness statement of Patricia Carney describes extensive processes at Bayer for preparation of clinical evaluation reports and for analysis of postmarket data including trend analysis and risk management reviews.[2122]

2072 He disagreed with Dent's evidence that PMS systems were deficient in reporting adverse outcomes and that this ultimately led to a misrepresentation of post-market performance in clinical evaluation reports. He said:

> Although Bayer had not provided copies of Adverse Event reports to NSAI under contractual obligations, there was no finding of failure to submit these reports to competent Authorities in compliance with regulatory requirements. The batch submission to NSAI of copies of the Competent Authority reports include multiple examples of reports relating to significant clinical findings such as pain, bleeding, or allergic reactions.[2123]

2073 Brandwood said, in relation to the deficiencies identified in the 2013-2015 audits, that 'the audit findings present a picture of considerable challenges in this migration of systems which took approximately two years to resolve[,] where the March 2015 NSAI special audit found all postmarket complaint handling and reporting to be compliant'.[2124]

2074 He said that the 2016 NSAI surveillance audit 'reviewed complaint handling in depth'. He said that despite the utilisation of post-market information in 'Risk Management' activities being identified as a category one major non-conformance, 'no re-audit was required and the nonconformance was rapidly addressed by documentation and recorded as successfully closed in the June 2017 audit record'.[2125]

2075 Brandwood said that he was not aware that a very large backlog of open complaints were identified in the 2008 mock audit report when he formed the views expressed in

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2122 Ibid at 82.
2123 Ibid at 83.
2124 Ibid at 79.
2125 Ibid at 80.

his primary report.[2126] He said these results did not alter his view that Conceptus' post-market and risk management controls were well designed, complete and properly integrated because the company itself had identified and addressed the problem and the notified body external auditor later found no problem.[2127]

Submissions

Turner

2076 The deficiencies associated with the PMS systems demonstrate that the defendants were not adequately informing themselves of problems and safety signals associated with Essure. Brandwood conceded in the regulatory JER that the Bayer surveillance systems were 'not compliant with reasonable practice'. Carney accepted the general proposition that deficiencies in PMS can potentially impact on the ability of a company to properly assess the risk-benefit profile of a medical device.[2128]

2077 From at least as early as mid-2016 through to about September 2017, the NSAI had ongoing substantive concerns in relation to the biocompatibility and safety profile of Essure. The concerns in relation to the safety profile of Essure were not satisfactorily addressed in the timeframe provided by the NSAI to Bayer in the context of CE Mark re-certification.

2078 The Court should accept that there were significant deficiencies in the defendants' PMS system which impacted on their ability to recognise safety signals associated with the device.

Defendants

2079 It is ultimately for the Court to determine the questions as to whether or not the pleaded safety risks and defects actually exist, and to then construe the relevant warnings and information available in the context of the pleaded case. Turner repeatedly said that this is not a regulatory case. As such, the approach taken by

2126 T3906 (TRA.500.038.0001_2 at 0089_8-10).
2127 T3907-8 (TRA.500.038.0001_2 at 0090-1).
2128 SBM.001.001.0004 at 206-42.

regulators (and any concerns that they voiced) in relation to Essure are tangential to ultimate questions of liability. Turner has not established that any regulatory issues made any relevant difference in favour of the case she brings. [2129]

2080 To the extent that there were deficiencies in Bayer risk management and PMS systems, these were remedied within the required regulatory timeframes and subsequently found to be compliant by the NSAI. A commercial decision was made to cease supply of Essure in Australia. Dent's subjective opinions as to inadequacies of dealings Bayer had with regulators are therefore not relevant.

2081 There was sufficient redundancy in the post-market monitoring, review and reporting of Essure to ensure adequate detection of any safety signals. The defendants regularly reviewed complaints and adverse events in respect of Essure, including clinical evaluation reports. The plaintiff has not proved how a different process would have caused a different result in relation to any alleged inadequacy.

2082 Non-compliances found in the 2008 FDA mock audit and the later NSAI audits were all remedied within required timeframes. The defendants' PMS systems were subsequently found to be compliant.

2083 The defendants engaged in rigorous PMS of Essure. Those systems and processes in place at the time Essure was in commercial supply took data from the ARGUS database into account which included the Essure-related health and safety information from clinical trials, literary sources, and reports of adverse events.

Analysis

2084 I accept the defendants' submission that evidence as to the regulatory approach to Essure is peripheral to the critical issues requiring determination in this case.

2085 Turner relied on Dent's criticism that Bayer did not report certain adverse events to the regulators. However, those adverse events were not excluded from the data

[2129] SBM.500.001.0003_2 at 328-52.

systems maintained by Bayer, or the trend analyses that it performed. I accept Brandwood's evidence that redundancies in the PMS systems meant that Bayer adequately captured post-market trends. There is no evidence that a relevant safety signal went undetected by Bayer's PMS systems. I accept the defendants' submission that Turner has not proved how a different PMS process would have resulted in a relevantly different risk-benefit profile for Essure.

2086 Deficiencies in Bayer's PMS systems were identified by the 2008 mock audit and by the later NSAI audits. I accept the evidence that those deficiencies were resolved in a timely fashion. Further, it is not clear to me how the identified deficiencies directly relate to the claims Turner makes in this proceeding.

XXII. LIMITATION PERIODS

2087 Had the general cases advanced by Turner succeeded at the initial trial, any limitations defence raised against a group member would have required individual analysis based on factors including the date of supply of Essure devices to the group member, the timing of any injury sustained, and the date of discoverability. The outcome of analysis of those factors would have varied between group members.

2088 However, there are relevant provisions of the *TPA* that have a common effect on statutory causes of action by group members that arose before 28 June 2007.

2089 The writ commencing this proceeding was filed on 28 June 2019.

2090 The ACL provides that a person may commence a defective goods action or an acceptable quality action within three years of certain matters being discoverable.[2130] There is a long-stop limitation period of 10 years from the supply by the manufacturer of the goods to which the action relates for any defect claim.[2131] That long-stop period had not expired for any claims under the ACL by the time the proceeding was

[2130] ACL s 273.
[2131] Ibid s 143(2).

commenced. Accordingly, any limitation issues that arise on statutory claims under the ACL could only be assessed on an individual basis for group members.

2091 Some group members' defect claims and merchantable quality claims arose under the *TPA*.[2132] For these cases, the limitation period that applies to a group member's claim will depend on whether Essure devices were supplied to the group member before or after 13 July 2004.

2092 The limitation period for defect claims where supply occurred before 13 July 2004 is governed by s 75AO of the *TPA*. For merchantable quality claims, the governing provision is s 74J of the *TPA*. In both cases, the limitation period is three years after discoverability of certain matters, with a long-stop period of 10 years after the supply of the goods to which the action relates. This means that the defect claims and merchantable quality claims of group members in respect of supply of Essure devices that occurred before 13 July 2004 are statute-barred or subject to the defence in s 74J(b) of the *TPA*.

2093 The *TP Amendment Act*, which commenced on 13 April 2004, altered the limitation period that previously applied to claims made under ss 74D and 75AD of the *TPA*.

2094 The basic rule imposed by s 87F(1) of the *TPA*, introduced by the *TP Amendment Act*, is that:

> A court must not award personal injury damages in a proceeding to which this Part applies if the proceeding was commenced:
>
> (a) after the end of the period of 3 years after the date of discoverability for the death or injury to which the personal injury damages would relate; or
>
> (b) after the end of the long-stop period for that death or injury.

2095 The date of discoverability, which is defined by s 87G of the *TPA*, takes into account actual and constructive knowledge of certain matters. The long-stop period is

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2132 *TPA* ss 75AD, 74D.

governed by s 87H, introduced by the *TP Amendment Act*, which provides:

> (1) The ***long-stop period*** for the death or injury of a person is:
>
> (a) the period of 12 years following the act or omission alleged to have caused the death or injury; or
>
> (b) that period as extended by the court.
>
> (2) The court must not extend the period by more than 3 years beyond the date of discoverability for the death or injury.
>
> (3) In considering whether to extend the period, the court must have regard to the justice of the case, and, in particular, must have regard to:
>
> (a) whether the passage of time has prejudiced a fair trial; and
>
> (b) the nature and extent of the person's loss or damage; and
>
> (c) the nature of the defendant's conduct alleged to have caused the death or injury; and
>
> (d) the nature of the defendant's conduct since the alleged act or omission.

2096 As a result, claims under ss 74D and 75AD of the *TPA* by a group member who had the Essure devices supplied between 13 July 2004 and 28 June 2007 will have expired, unless an extension of time is granted pursuant to ss 87H(2) and (3).

XXIII. STATUTORY CLAIMS

2097 Turner brings her Defect claim and Merchantable Quality claim under the *TPA* and ACL.

2098 The ACL is schedule 2 to the *CCA*, which came into operation on 1 January 2011.

2099 The *TPA* is the predecessor legislation to the ACL. The *Trade Practices Amendment (Australian Consumer Law) Act (No. 2) 2010 (Cth)* saves the operation of the *TPA* as in force immediately prior to the commencement of the *CCA*.

2100 This means the statutory claims are made under the *TPA* for the period to 31 December 2010, and pursuant to the ACL for the period from 1 January 2011.

2101 The provisions of the *TPA* and ACL under which claims are made by Turner are in substantially the same form. For the purposes of this case, there is no material difference between them.

Application of the *TPA* and ACL to the defendants

Clinical trial period

2102 Essure devices were imported into Australia from the late 1990s for the purpose of clinical trials. Women implanted with the Essure devices as part of those clinical trials are group members in this proceeding. There was a dispute between the parties about whether the *TPA* applies to the supply of devices for the purposes of clinical trials.

2103 Whether the *TPA* applies to clinical trial supply is moot. For reasons set out in Chapter XXII, I have concluded that the Defect claims and Merchantable Quality claims of group members in respect of supply of Essure devices that occurred before 13 January 2004 are statute-barred. Turner did not seriously contest this outcome. Therefore, it is not necessary to determine whether the provisions of the *TPA* relied on by Turner apply to the supply of Essure devices to women for the purposes of clinical trials. However, I will consider the issue because the parties led evidence and made submissions relevant to it.

2104 The TGA granted approval to Conceptus on or around 20 May 1997 to import the STOP Device into Australia for the purpose of conducting clinical trials.[2133] Handwritten notes tendered in a bundle with the TGA approval letter refer to the process for commercial supply of Essure in Australia. The notes make reference to Medicare, private insurance funds, application for the 'prosthesis benefits list', price lists, funding and the need to establish relationships with hospitals and insurers to show cost effectiveness. The notes refer to being '[a]llowed to sell' the product 'as soon as TGA approves'.[2134] While the notes are not dated and no author is identified, I infer that they originate from Conceptus and were made at around the time the TGA

2133 BAY-EDPA-4197110 at 4.
2134 SBM.001.001.0004 at 14 [31]; BAY-EDPA-4197110 at 3.

granted the clinical trial approval. The notes were clearly directed to the plan for commercial supply of Essure in Australia.

2105 Documents tendered by Turner show that Conceptus managed inventory of the product supplied during the clinical trials[2135] and paid Rosen, who was one of the investigating physicians for the purpose of the clinical trials, a 'gap' fee on a per-patient basis.[2136] In an email sent in September 2000, Conceptus' Director of Clinical Research, Mary Kenney, said that Conceptus had 'some sort of business presence in Australia'.[2137]

2106 'Trade or commerce' is defined in the *TPA* to mean:

> trade or commerce within Australia or between Australia and places outside Australia.[2138]

'Supply' includes:

> in relation to goods—supply (including re-supply) by way of sale, exchange, lease, hire or hire-purchase[.][2139]

2107 The duty under s 74D of the *TPA* is owed to 'the consumer or a person who acquires the goods from … the consumer'.[2140] Under s 74B of the *TPA*, a person shall in certain defined circumstances 'be taken to have acquired particular goods as a consumer'.[2141] Those circumstances relate to the price of the goods and, depending on that price, whether they 'were of a kind ordinarily acquired for personal, domestic or household use or consumption'.[2142] 'Acquire' is defined to include 'purchase, exchange, or taking

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2135 See eg the 'investigational device logs' BAU.001.002.2112; BAY-EDPA-0399163; BAY-EDPA-0399694; BAY-EDPA-0399159; BAU.001.002.2250; BAY-EDPA-0399160; BAY-EDPA-0399695; BAY-EDPA-0399162; BAY-EDPA-4200191; BAY-EDPA-4200197; BAY-EDPA-4200195; BAY-EDPA-4200198; BAY-EDPA-4200201; BAY-EDPA-4200204; BAY-EDPA-0277821; BAY-EDPA-0526330; BAY-EDPA-0526334; BAY-EDPA-0526338; BAY-EDPA-0397318; BAY-EDPA-4200207; BAY-EDPA-0397317; BAY-EDPA-0397319; BAY-EDPA-4200208; BAY-EDPA-4200210; BAY-EDPA-0397320; BAY-EDPA-4200213; BAY-EDPA-0397321; BAY-EDPA-4200216; BAY-EDPA-4200217; BAY-EDPA-0397322; BAY-EDPA-4200220.

2136 BAY-EDPA-4624737 at 7.

2137 BAY-EDPA-4780091 at 1.

2138 *TPA* s 4.

2139 Ibid.

2140 Ibid s 74D(1)(d).

2141 Ibid s 4B(1)(a).

2142 Ibid.

on lease, on hire or on hire purchase'.[2143]

2108 For the supply of goods to be 'in trade or commerce', the relevant conduct must have some identifiable feature of commerciality.[2144] It is enough if the conduct of the corporation is in furtherance of a future commercial endeavour.[2145]

2109 I conclude that the importation and supply of devices to hospitals and doctors for use in clinical trials conducted from 1997 was in furtherance of one of Conceptus' commercial interests, namely the supply and sale of Essure in Australia. The supply of devices as part of the clinical trials was 'in trade or commerce' for the purposes of the *TPA*.

2110 However, there is no evidence the Essure devices were 'supplied' to women who participated in the clinical trials, as that word is defined in the *TPA*. Further, there is no evidence that those women acquired the Essure devices in accordance with s 4B of the *TPA*.

Extra-territorial application

2111 There is a question about whether the *TPA* and ACL apply to the foreign defendant corporations, namely Bayer AG, Bayer HealthCare and Bayer Essure. Bayer AG was at all material times incorporated in Germany, and Bayer HealthCare and Bayer Essure were at all material times incorporated in the US.

2112 There is a general presumption that the territorial operation of a statute is limited to the nationals of the State which enacts it.[2146]

2113 The application of certain parts of the *TPA* is extended to conduct outside Australia by s 5(1), which provides:

> (1) Part IV, Part IVA, Part V (other than Division 1AA), Part VB and Part VC extend to the engaging in conduct outside Australia by bodies corporate

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2143 Ibid s 4.
2144 *Concrete Constructions (NSW) Pty Ltd v Nelson* (1990) 169 CLR 594 at 604.
2145 *Sykes v Reserve Bank of Australia* (1998) 88 FCR 511 at 516 (Heerey, Sundberg and Emmett JJ).
2146 *Meyer Heine Pty Ltd v China Navigation Co Ltd* (1966) 115 CLR 10 at 43 (Windeyer J), 23 (Kitto J), 38 (Menzies J).

> incorporated or carrying on business within Australia or by Australian citizens or persons ordinarily resident within Australia.

2114 This section captures the Merchantable Quality claim under s 74D, which is in Part V of the *TPA*, but not the Defect claim under ss 75AC and 75AD which are located in Part VA.

2115 The equivalent extraterritorial application provision in the *CCA* is also s 5(1), which applies to both the acceptable quality and the safety defect clauses of the ACL.

2116 The application of ss 5(1) of the *TPA* and *CCA* was considered by Merkel J in *Bray v F Hoffman-La Roche Ltd*[2147] ('*Bray*'), where his Honour said:

> [Section] 5 of the TPA is to be accounted for only on the basis that the Act as a whole, including s 5 itself, has been framed on the assumption that when conduct is made a contravention of the Act it is only *conduct in Australia* that is meant unless the conditions set out in s 5 apply.
>
> …
>
> [U]nless expressly provided otherwise, the legislature intended that the Act is only to apply to extra-territorial conduct in the circumstances and subject to the conditions laid down in s 5.[2148]

2117 The defendants submitted that Bayer AG, Bayer HealthCare and Bayer Essure could only be subject to the Defect and Merchantable Quality claims if they fell within the extra-territorial jurisdiction of the legislation. They submitted that this would require the Court to be satisfied that those defendants 'carried on business' for the purposes of s 5(1) of the *TPA* and *CCA*.

2118 The starting point is to consider where the conduct by the Bayer defendants on which the Defect and Merchantable Quality claims are based took place.[2149]

2119 *Vautin v BY Winddown (No 4)*[2150] ('*Vautin*') concerned a claim under the ACL by the Australian purchaser of a motor yacht against a foreign manufacturer. The plaintiff

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2147 (2002) 118 FCR 1 ('*Bray*').

2148 Ibid at [50]-[51] (emphasis added); See also *Bright v Femcare Ltd* (2000) 175 ALR 50 at [77]–[78] (Lehane J).

2149 *Paper Products Pty Ltd v Tomlinsons (Rochdale) Ltd (No 2)* (1993) 44 FCR 485 at 493 (French J); *ACCC v Valve Corporation (No 3)* (2016) 337 ALR 647 at [169] (Edelman J).

2150 362 ALR 702 ('*Vautin*').

submitted that all that was required for the foreign defendant to be subject to the operation of the ACL was that there had been a supply of goods to him in Australia. The plaintiff submitted that the supply did not need to be directly by the manufacturer. Derrington J rejected that submission, and said:

> The question is one of the liability of an overseas manufacturer who has sold goods in the USA to Eagle Yachts and the latter has imported them to Australia and supplied them to Mr Vautin. On a proper construction of the ACL the liability imposed on the manufacturer under s 271(5) does not arise merely by reason of the supply of the goods to a consumer by some third party (such as a retailer). That alone is insufficient and, as was identified in *Bray v Hoffman-La Roche Ltd*, the nexus with Australia must be, at least, conduct by the manufacturer. Moreover, that relevant conduct must be conduct in relation to the relevant contravention and, indeed, it is probably necessary that it relate to the gravamen of the statutory cause of action being pursued.[2151]

However, Derrington J concluded that a warranty given by the manufacturer to the plaintiff in Australia when he purchased the yacht had the effect of attracting the operation of the ACL, rendering the manufacturer liable by reason of a statutorily imposed guarantee.

2120 *Gill v Ethicon Sàrl (No 5)*[2152] ('*Gill*') concerned the supply of urogynaecological medical devices manufactured by foreign corporations to women in Australia. Two of the respondents in that case, who were incorporated overseas and did not have a place of business in Australia, argued that the statutory causes of action under the *TPA* and ACL did not apply to them. Katzmann J said, rejecting that submission:

> …This case is not concerned with the extra-territorial operation of the Act. The statutory claims are concerned with conduct relating to the supply of goods… Supply of the Ethicon devices took place in Australia because the devices were received in Australia by JJM, an Australian company, delivered to Australian hospitals and doctors, and implanted in women in Australia. … Where the relevant conduct occurs in Australia, in *Trade Practices Commission v Australia Meat Holdings Pty Ltd* [1988] FCA 338; (1998)) 83 ALR 299 at 356 Wilcox J described it as "a misuse of language" to speak of the statute being given an extra-territorial effect".[2153]

2151 Ibid at [212].
2152 *Gill*.
2153 Ibid [3129].

2121 The phrase 'carrying on business' is not defined in the *TPA* or the *CCA*. The ordinary meaning of 'carrying on business' is the undertaking of a commercial enterprise as a going concern, which is to say, 'activities engaged in for the purpose of profit on a continuous and repetitive basis'.[2154] The phrase usually connotes some kind of ongoing commercial presence of a corporation. In *Smith v Capewell*,[2155] Gibbs J observed:

> The expression "carry on business", in its ordinary meaning, signifies a course of conduct involving the performance of a succession of acts, and not simply the effecting of one solitary transaction… A single transaction may amount to the carrying on of a business, although no other transaction has so far been effected, if it is proved that there was an intention to carry on a business and that the transaction was undertaken in pursuance of that intention.[2156]

2122 In *Norcast S.ar.L v Bradken Limited (No 2)*,[2157] ('*Norcast*') Gordon J said:

> At general law, carrying on a business generally involves conducting some form of commercial enterprise, systematically and regularly with a view to profit: *Gebo Investments* at [38]. It is unnecessary to restate the "usual elements" of a finding of carrying on business in Australia. It is, however, necessary to point out that a company may be found to carry on business in Australia even though the bulk of its activities are conducted elsewhere (*Gebo Investments* at [38]–[41]) and that it conducts its activities in Australia by reason of its control over or connection with an Australian company: *Adams v Cape Industries Plc* [1990] Ch 433 at 530 and *Bray v F Hoffman-La Roche Ltd* (2002) 118 FCR 1 at [60]–[63].[2158]

2123 In circumstances where a foreign company is allegedly carrying on business by virtue of the conduct of an Australian subsidiary, 'the question is whether the business was carried on by the Australian subsidiaries on their own account, or on behalf of, the […] parent'.[2159] It is usually not enough that a foreign company operates a subsidiary within Australia. In *Bray*, Merkel J said:

> The difficulty with the sweeping assertion that the Australian subsidiaries, being directed and controlled by an overseas parent as part of the parent's global enterprise, carried on the business of the parent, is that that alone is not

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2154 Ibid [3133], referring to *Hope v Bathurst City Council* (1980) 144 CLR 1 at 8–9 (Mason J).
2155 (1979) 142 CLR 509.
2156 Ibid at 517, 519.
2157 (2013) 219 FCR 14 ('*Norcast*').
2158 Ibid at [255].
2159 *Bray* at [64].

sufficient to pierce the corporate veil.[2160]

2124 In *Gill*, Katzmann J found that the two foreign companies were carrying on business in Australia:

> Here, the evidence establishes that the two Ethicon companies were engaged in a systematic course of conduct in Australia. This is not a case involving a small number of isolated transactions. They were selling their products in Australia over a number of years through a related company and promoting them jointly with that company. Supplying goods on a regular basis to an Australian company for the purpose of sale to Australian consumers is "carrying on business" in Australia. The respondents admitted in their defence that both companies supplied their goods to JJM for sale in Australia throughout the period covered by the statement of claim. In the ordinary course, the seller would profit from such an enterprise. In the absence of evidence to the contrary, I infer, based on the principle in *Blatch v Archer* (1774) 1 Cowp 63; [1774] 98 ER 969, that both Ethicon Inc. and Ethicon Sàrl derived profit from the sales.[2161]

Submissions

Turner

2125 The primary position is that the extra-territorial provisions are not relevant to the defendants' impugned conduct under the ACL and *TPA*. It is not correct to assert, as the defendants do, that a foreign corporation must 'carry on business' in Australia in order for any of their impugned conduct to be caught by the relevant provisions of the *TPA* or the *CCA*. The conduct of foreign corporations within Australia is captured by the ordinary territorial operation of the *TPA* and the *CCA*, irrespective of whether they carry on business in Australia.[2162] The relevant conduct at issue — the supply and marketing to Australian consumers of a product that was not of acceptable quality or had a safety defect — occurred in Australia.[2163]

2126 As in *Gill*, Essure was received by Australian distributors in Australia, delivered to Australian hospitals and doctors, and implanted in women in Australia. Similarly,

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2160 Ibid at [72].
2161 *Gill* at [3144].
2162 SBM.001.001.0004 at 272 [904].
2163 Ibid at 272 [906].

any information and warnings about Essure was necessarily provided to Australian women in Australia or by Australian doctors to Australian women in Australia.[2164]

2127 Alternatively, if it is necessary to establish that the three foreign Bayer defendants were carrying on business in Australia, the evidence overwhelmingly shows that they were.[2165]

2128 The defendants admit that Conceptus (which became Bayer Essure) and Bayer HealthCare engaged a number of third-party distributors from about 1 December 1999 until about August 2017. The purpose of the engagement of the distributors was plainly for these defendants to sell the device into Australia for profit.[2166]

2129 In addition to the distribution agreements, there are other indicia which demonstrate that Conceptus and Bayer HealthCare were carrying on business in Australia. Each company assumed reporting obligations with the TGA and was registered with the TGA as manufacturer of the Essure device at different points during the commercial supply period; Conceptus organised the handover of inventory from a prior distributor to Gytech in around August 2010; and logos and names of the Bayer companies were registered as trademarks in Australia.

2130 Bayer AG has, since the acquisition of Conceptus, been the 'pure holding company' of each of the other Bayer defendants. It follows that Bayer AG must therefore have acted — and carried on business — through its subsidiaries. The use of Bayer trademarks owned by Bayer AG by subsidiaries was expressly authorised in the distribution agreements with AMSL and Gytech.[2167]

2164 Ibid at 273 [908].
2165 Ibid at 273 [910].
2166 Ibid at 274 [916].
2167 Ibid at 277 [926]-[928].

Defendants

2131 Each of the second, third, and fourth defendants was not 'carrying on business' in Australia, and were therefore not subject to the obligations imposed by the consumer protection legislation.

2132 There is no evidence proffered by Turner of Bayer AG conducting any form of commercial enterprise in Australia, systematically or regularly with a view to profit or engaging in Australia in any repetition of acts in the nature of commercial activities which possess something of a permanent character. The mere existence of an Australian subsidiary is insufficient to satisfy the test.[2168]

2133 There is clear evidence that, at all material times, Bayer HealthCare appointed an independent distributor to market Essure in Australia.[2169]

2134 Bayer Essure sold its assets and liabilities to Bayer HealthCare effective 1 July 2013. Bayer Essure does not presently actively carry on any part of Bayer's business.[2170]

Analysis

2135 I accept Turner's submission that the alleged marketing and supply of Essure devices by the foreign Bayer defendants occurred within Australia, such that the extra-territorial provisions in the *TPA* and CCA do not apply. Unlike in *Vautin*, the Essure devices were not purchased from the foreign defendants by an independent third party retailer outside Australia, then imported for supply to women in Australia. The Bayer defendants imported Essure devices into Australia for distribution by companies engaged for that purpose.[2171] The information and warnings about Essure communicated in the physician training, PTMs, IFUs and PIBs was provided by the foreign companies. The foreign Bayer defendants imposed obligations on the distributors to conduct physician training, distribute product information and engage in marketing in accordance with their requirements. The content of the information

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2168 SBM.500.001.0003_2 at 97 [5.2].
2169 Ibid at 101 [6.3].
2170 Ibid at 101 [7.1], [7.2](e).
2171 BHC.001.001.1122; AMS.001.002.0098.

and warnings is central to the statutory claims made by Turner on behalf of group members.

2136 I conclude that in the circumstances of this case, the provisions of the *TPA* and ACL relied on by Turner apply to Bayer AG, Bayer HealthCare and Bayer Essure, without the need to consider whether each of those corporations was 'carrying on business' in Australia for the purposes of s 5(1) of the *TPA* and *CCA*.

2137 Had it been necessary, I would also have concluded, for the following reasons, that the foreign Bayer defendants were 'carrying on business' in Australia.

2138 First, it is not in issue that Conceptus (later as Bayer Essure) and Bayer HealthCare engaged various third-party Australian distributors from around December 1999 to August 2017 to sell Essure in Australia.

2139 Second, Bayer's trademark registration history suggests it has carried on business in Australia for substantial periods of time. Bayer AG has been the registered owner of Australian trademarks protecting the Bayer Cross logo and the word 'Bayer' since 1970.[2172] Bayer AG registered different versions of the Bayer Cross logo in March 2008 and December 2017.[2173] Schalk said these were the most important trademarks to the company. He explained that maintaining the trademarks in Australia involved engaging a local attorney to represent Bayer AG before the Australian IP office and paying required fees. He said that trademarks need to be registered for each jurisdiction. He said that registration of the trademarks in Australia was a conscious decision by Bayer AG to mark out its intellectual property, because of its desire to do business in Australia. He said that the intention when registering a trademark was to use it for marketing of goods and services.

2140 Schalk said that Bayer AG was the parent company of a number of subsidiaries that included Bayer HealthCare, Bayer Essure and Bayer Australia. Bayer AG owned 100%

2172 MSC.001.002.0028.
2173 Schalk at 2 (LAY.500.001.0004).

of the shares in Bayer Essure, Bayer HealthCare and Bayer Australia.[2174] Bodesheim said that Bayer AG was a 'pure holding company' and did not have employees of its own.[2175]

2141 The 'Bayer Cross Logo' and 'Bayer' trademarks were used on some items and documents relevant to Essure in Australia. The agreements between Bayer HealthCare and distributors Gytech and AMSL granted a royalty-free licence to the distributors to use the Bayer trademarks 'to promote, market, distribute, use and sell' Essure.[2176] The agreements recorded that Bayer HealthCare was 'a member of the Bayer AG group of companies'.[2177] It defined 'Bayer Trademark' as:

> … any registered and unregistered trademark (including applications for registrations) owned by or licensed to Bayer or its Affiliates including its parent company Bayer AG or to Bayer Intellectual Property GmbH, Germany.[2178]

Schalk said that upon his review of relevant records, he had not found any licence or approval for use of the Bayer trademarks direct to Gytech or AMSL, or any license to Bayer HealthCare authorising it to sub-license use of the trademarks in connection with Essure. Schalk also said he had not found any record of any request by Bayer HealthCare for authorisation to sub-license the trademarks.[2179] However, in cross-examination, Schalk conceded that the distribution agreements expressly authorised AMSL and Gytech to use the Bayer trademarks;[2180] that Bayer AG would not sue subsidiaries such as Bayer HealthCare in respect of unlicensed use of the trademarks;[2181] and that as far as he was aware, no action had been taken by Bayer to enforce its trademark rights against Gytech or AMSL in respect of their use of those trademarks.[2182] He agreed that the distribution agreement with AMSL authorising use of the Bayer trademarks was missing from the database of trademark

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2174 SBM.001.001.0004 at 423.
2175 T2078 (TRA.500.021.0001_2 at 0056).
2176 BAY-EDPA-0938454 at 18.
2177 BAY-EDPA-0938454 at 3.
2178 BAY-EDPA-0938454 at 4.
2179 Schalk at 3 (LAY.500.001.0004).
2180 T1997 (TRA.500.020.0001_2 at 0082_27).
2181 T1983 (TRA.500.020.0001_2 at 0068_16).
2182 T2001 (TRA.500.020.0001_2 at 0086_27).

authorisation agreements maintained by Bayer.[2183] He agreed, at least at a conceptual level, that there could be acquiescence to use of a trademark absent any formal agreement.[2184]

2142 There were repeated acts by Bayer AG in Australia to register and maintain the Bayer trademarks. The company's business purpose was advanced by use of the Bayer trademarks in connection with the marketing and sale of Essure. While there is no evidence of an express licence from Bayer AG authorising use of its trademarks by AMSL, I infer that the authorisation for that use provided by Bayer HealthCare was given on behalf of Bayer AG. Bayer AG, as a holding company, carried on business through its subsidiaries. I conclude that the evidence establishes that Bayer AG was carrying on business in Australia during the period Essure was supplied, for the purposes of s 5(1) of the *TPA* and *CCA*.

2143 Conceptus had trademarks 'Conceptus' registered in Australia in 1996 and 'Essure' in 2001.[2185] Those trademarks were assigned to Bayer HealthCare in December 2015. Bayer HealthCare has also been the long-term owner of many trademarks registered in Australia including the trademark for 'Alka-Seltzer', a pharmaceutical product trademarked in Australia since 1935.[2186]

2144 Third, Bayer Essure (as Conceptus) was registered as manufacturer of Essure with the TGA in 1999 and again in 2010.[2187] Bayer HealthCare became the registered manufacturer for Essure on the ARTG from January 2015.[2188]

2145 For these reasons, I conclude that Bayer AG, Bayer HealthCare and Bayer Essure carried on business in Australia for the purposes of s 5(1) of the *TPA* and ACL.

2183 T1997 (TRA.500.020.0001_2 at 0082_16).
2184 T1986 (TRA.500.020.0001_2 at 0071).
2185 MSC.001.002.0029; MSC.001.002.0030.
2186 MSC.001.002.0022; MSC.001.002.0100.
2187 BAU.001.001.0180; BAU.001.001.0182.
2188 AMS.001.001.5677.

Defendants as 'manufacturers'

2146 The obligations created by the *TPA* and ACL that Turner relies on are imposed on corporations that are 'manufacturers' or that 'manufactured' goods. Turner alleges that for the purposes of the *TPA* and/or the ACL, each defendant is a manufacturer of, or manufactured Essure devices supplied in Australia.

2147 'Manufactured' is defined in s 74A(1) of the *TPA* and:

> includes grown, extracted, produced, processed and assembled.

The meaning of 'manufacturer' is also governed by s 74A of the *TPA*:

> (3) If:
>
> > (a) a corporation holds itself out to the public as the manufacturer of goods;
> >
> > (b) a corporation causes or permits the name of the corporation, a name by which the corporation carries on business or a brand or mark of the corporation to be applied to goods supplied by the corporation; or
> >
> > (c) a corporation causes or permits another person, in connexion with the supply or possible supply of goods by that other person, or in connexion with the promotion by that other person by any means of the supply or use of goods, to hold out the corporation to the public as the manufacturer of the goods;
>
> the corporation shall be deemed, for the purposes of this Division, to have manufactured the goods.
>
> (4) If:
>
> > (a) goods are imported into Australia by a corporation that was not the manufacturer of the goods; and
> >
> > (b) at the time of the importation the manufacturer of the goods does not have a place of business in Australia;
>
> the corporation shall be deemed, for the purposes of this Division, to have manufactured the goods.
>
> (5) For the purposes of paragraph (3)(b):
>
> > (a) a name, brand or mark shall be deemed to be applied to goods if it:
> >
> > > (i) is woven in, impressed on, worked into or annexed or affixed to the goods; or
> > >
> > > (ii) is applied to a covering, label, reel or thing in or with which

the goods are supplied; and

(b) if the name of a corporation, a name in which a corporation carries on business or a brand or mark of a corporation is applied to goods, it shall be presumed, unless the contrary is established, that the corporation caused or permitted the name, brand or mark to be applied to the goods.

(6) The reference in subsection (5) to a covering includes a reference to a stopper, glass, bottle, vessel, box, capsule, case, frame or wrapper and the reference in that subsection to a label includes a reference to a band or ticket.

(7) If goods are imported into Australia on behalf of a corporation, the corporation shall be deemed, for the purposes of this Division, to have imported the goods into Australia.

The meaning of 'manufacturer' in s 74A applies to Division 2A of Part V of the *TPA*, which contains the provisions relevant to the Merchantable Quality claim. The same definitions of 'manufactured' and 'manufacturer' apply to the Defect claim by operation of ss 75AA and 75AB of the *TPA*.

2148 The meaning of 'manufacturer' is contained in s 7 of the ACL:

(1) A ***manufacturer*** includes the following:

(a) a person who grows, extracts, produces, processes or assembles goods;

(b) a person who holds himself or herself out to the public as the manufacturer of goods;

(c) a person who causes or permits the name of the person, a name by which the person carries on business or a brand or mark of the person to be applied to goods supplied by the person;

(d) a person (the ***first person***) who causes or permits another person, in connection with:

(i) the supply or possible supply of goods by that other person; or

(ii) the promotion by that other person by any means of the supply or use of goods;

to hold out the first person to the public as the manufacturer of the goods;

(e) a person who imports goods into Australia if:

(i) the person is not the manufacturer of the goods; and

(ii) at the time of the importation, the manufacturer of the goods does not have a place of business in Australia.

(2) For the purposes of subsection (1)(c):

(a) a name, brand or mark is taken to be applied to goods if:

(i) it is woven in, impressed on, worked into or annexed or affixed to the goods; or

(ii) it is applied to a covering, label, reel or thing in or with which the goods are supplied; and

(b) if the name of a person, a name by which a person carries on business or a brand or mark of a person is applied to goods, it is presumed, unless the contrary is established, that the person caused or permitted the name, brand or mark to be applied to the goods.

(3) If goods are imported into Australia on behalf of a person, the person is taken, for the purposes of paragraph (1)(e), to have imported the goods into Australia.

Bayer Australia

2149 Bayer Australia was the registered sponsor of Essure on the ARTG and under the TGA from about 29 January 2018 until 9 February 2018. The defendants admit that during the period between about 1 July 2013 and August 2017, some material published in Australia regarding Essure (PIBs in particular) included the name of Bayer Australia Ltd. PIB 13 from 2015 bears the Bayer Cross logo on the front page, and on the final page the following appears:[2189]

[2189] BAU.001.001.0040 at 7.

2150 The name 'Bayer Australia Ltd' does not appear on Essure IFUs or PTMs used in Australia. Those documents carry the Bayer Cross logo and state that Essure is manufactured by Bayer HealthCare.

2151 Turner submitted that the extended definition of 'manufacturer' means that it is sufficient for Bayer Australia's name to have been used 'in relation to' Essure.[2190] That submission appears to rely on the following statement by Katzmann J in *Gill*:

> At all relevant times Ethicon Sàrl and Ethicon Inc. were "manufacturers", at least because they manufactured the Ethicon devices and used their brand name in relation to them, and JJM was a "manufacturer" because it imported them into Australia.[2191]

2152 The defendants submitted that Bayer Australia played a very limited role in the marketing and supply of Essure in Australia, and the appearance of its name on PIBs did not constitute Bayer Australia holding itself out to the public as the manufacturer of Essure.

2153 I reject Turner's submission. A corporation does not come within the extended

2190 SBM.001.001.0004 at 268 [888].
2191 *Gill* at [3121].

definition of manufacturer merely because its name, brand or mark is applied to goods. There is no evidence that Bayer Australia supplied Essure. The limited use of Bayer Australia's name on some PIBs did not constitute holding the corporation out to the public as the manufacturer of the goods. There is no evidence Bayer Australia imported Essure into Australia. The position of Bayer Australia is clearly distinguishable from the circumstances considered by Katzmann J in *Gill*.

Bayer AG

2154 The Essure box that was tendered in evidence and the items it contained were all marked with the Bayer Cross Logo.

2155 Three of the IFUs used in Australia had the Bayer Cross trademark on the front and final pages.

2156 I infer that in the period after Bayer purchased Conceptus, the Bayer Cross trademark was regularly affixed to documents and items relating to Essure and with which Essure was supplied in Australia. I infer it is likely that this included the trademark being affixed to the box in which Essure devices were supplied in Australia, and items in the box including the bag holding the Essure devices.

2157 There is no evidence that Bayer AG was named as a corporate entity on the supply box or any of the items it contained. The most recent IFU contains the following on one of the final pages:[2192]

[2192] AMS.001.001.0010 at 87.

Manufactured by:
Bayer Healthcare LLC
1011 McCarthy Boulevard
Milpitas, CA 95035
USA
essure.com

This consistently appears on each IFU during the commercial supply period.

2158 The Bayer Cross Logo was on the front page of PIBs used during the commercial supply period. The final page had the Bayer Cross Logo and the Bayer trademark, followed by the names and details of Bayer Australia and AMSL. Bayer AG was not named in any of the PIBs.

2159 It was not alleged that Essure was supplied or imported by Bayer AG. The question is whether Bayer AG was held out to the public as the manufacturer of Essure. The PIBs were the most public facing Essure documents. While the Bayer Cross Logo and Bayer trademark were on the PIBs and other Essure documents, Bayer AG was not named, much less identified directly or inferentially as manufacturer of Essure. Other Bayer companies were named in the PIBs and other Essure documents. For example, in PIB 15, Bayer HealthCare was named in association with an IFU that was referred to. The Bayer Cross Logo and trademark would have been associated by the public with Bayer corporations named in the PIBs, not with Bayer AG.

2160 Turner has not established that Bayer AG was a manufacturer of Essure for the purposes of the ACL.

Bayer HealthCare

2161 Bayer HealthCare admits that it was a manufacturer of Essure within the meaning of s 7 of the ACL from 5 June 2013 to 9 February 2018.

Bayer Essure

2162 Bayer Essure admits that it was a manufacturer within the meaning of s 74A of the *TPA* and s 7 of the ACL from about 1999 to about 1 May 2014.

Gytech

2163 Gytech admits it was a manufacturer of Essure for the purposes of s 7 of the ACL between 19 August 2010 and 31 December 2014.

AMSL

2164 AMSL admits it was a manufacturer of Essure for the purposes of s 7 of the ACL between 1 January 2015 and 1 August 2017.

Supply in trade or commerce

2165 'Trade or commerce' is defined in the *TPA* to mean 'trade or commerce within Australia or between Australia and places outside Australia'.[2193] The term has the same meaning in the ACL, and is further extended to include 'any business or professional activity (whether or not carried on for profit)'.[2194]

2166 It is uncontroversial that Essure was manufactured outside Australia and supplied to Australian distributors. The defendants admit that the supply of devices during the commercial supply period was in trade or commerce.

2167 Had it been relevant, I would have concluded that supply as part of the clinical trials conducted in the late 1990s and early 2000s was for the purpose of furthering Conceptus' commercial interests. On that basis, the clinical trial supply was also in trade or commerce.

2168 Essure was supplied by Bayer Essure and then Bayer HealthCare to various Australian distributors, including Gytech and AMSL, for distribution in Australia. The Australian distributors in turn supplied the Essure devices to treating hospitals and physicians for resupply to consumers. Accordingly, each of Bayer Essure, Bayer HealthCare, Gytech and AMSL supplied Essure devices for the purposes of the *TPA*

2193 *TPA* s 4.
2194 ACL s 2.

and/or ACL.

Defect claim

2169 Sections 75AC and 75AD of the *TPA* provide as follows:

> **75AC Meaning of goods having defect**
>
> (1) For the purposes of this Part, goods have a defect if their safety is not such as persons generally are entitled to expect.
>
> (2) In determining the extent of the safety of goods, regard is to be given to all relevant circumstances including:
>
> (a) the manner in which, and the purposes for which, they have been marketed; and
>
> (b) their packaging; and
>
> (c) the use of any mark in relation to them; and
>
> (d) any instructions for, or warnings with respect to, doing, or refraining from doing, anything with or in relation to them; and
>
> (e) what might reasonably be expected to be done with or in relation to them; and
>
> (f) the time when they were supplied by their manufacturer.
>
> (3) An inference that goods have a defect is not to be made only because of the fact that, after they were supplied by their manufacturer, safer goods of the same kind were supplied.
>
> (4) An inference that goods have a defect is not to be made only because:
>
> (a) there was compliance with a Commonwealth mandatory standard for them; and
>
> (b) that standard was not the safest possible standard having regard to the latest state of scientific or technical knowledge when they were supplied by their manufacturer.
>
> **75AD Liability for defective goods causing injuries—loss by injured individual**
>
> If:
>
> (a) a corporation, in trade or commerce, supplies goods manufactured by it; and
>
> (b) they have a defect; and
>
> (c) because of the defect, an individual suffers injuries;

then:

(d) the corporation is liable to compensate the individual for the amount of the individual's loss suffered as a result of the injuries; and

(e) the individual may recover that amount by action against the corporation; and

(f) if the individual dies because of the injuries—a law of a State or Territory about liability in respect of the death of individuals applies as if:

(i) the action were an action under the law of the State or Territory for damages in respect of the injuries; and

(ii) the defect were the corporation's wrongful act, neglect or default.

These provisions are replicated in ss 9 and 138 of the ACL, save for the change from 'defect' to 'safety defect'. For convenience in these reasons, I will refer only to the *TPA* provisions except where it becomes necessary for some reason to separately consider the ACL provisions. A reference in these reasons to 'defect' includes 'safety defect'.

Principles and authorities

2170 The test for whether goods have a defect is objective. The standard is what the public at large is entitled to expect, not the expectations of the plaintiff.[2195]

2171 All relevant circumstances, including the matters set out in s 75AC(2) of the *TPA*, must be considered in determining the extent of the safety of goods. Other matters that may be relevant include the nature of the goods, community knowledge of those goods, the use made of the goods, the degree and magnitude of risks associated with that use, the extent to which there is community knowledge of those risks and general acceptance that they cannot be avoided, and benefits that may flow from use of the goods.[2196]

2172 The role played by intermediaries in the supply of goods to consumers may also need to be taken into account to determine whether goods are defective.[2197] This is

2195 *Merck* at 53–54 [191]–[192] (Keane CJ, Bennett and Gordon JJ).
2196 Ibid at [191]-[192].
2197 Ibid at [191].

particularly so where the claimed defect relates to information and warnings provided with the goods.

2173 The provisions do not require that goods be free of risk.[2198] It will be relevant to the determination of whether goods have a defect to consider the degree of any risk to safety to consumers of the goods, and the magnitude of that risk if it eventuates.[2199]

2174 What the manufacturer has said about the goods may affect public expectations of safety.[2200] Goods that present a risk of injury may be found to have a defect because the manufacturer failed to provide 'sufficient information, advice or warning in relation to that risk'.[2201] In *Ethicon Sàrl v Gill*[2202] '(*Gill appeal*'), the Court said:

> It follows that although a product presents a risk of injury, it may nevertheless not have a defect under s 75AC if the manufacturer provides appropriate information, advice or warnings about that risk in its marketing or product information. That is, the fact that goods present a risk of injury does not, of itself, establish the existence of a defect.[2203]

2175 A product may have a defect even if the risk to safety associated with the goods is one which only affects some people.[2204]

2176 In *Batchelder & Anor v Holden Ltd*,[2205] Beach J held that the defect or defects need not be identified with any particular level of precision.[2206] Further, it is not necessary to prove the mechanism by which the defect occurred or could have occurred.[2207]

2177 Turner alleges that Essure has the following defect:

> By reason of all or any of the Inherent Defects, the Failure Defects, the Adverse Events and the Removal Limitation, along with the Marketing Conduct, the safety of the Essure Devices acquired by the Plaintiff and group members was

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2198 Ibid.
2199 Ibid at [201]; *Gill* at [3175] (Katzmann J); *Gill appeal* at [601] (Jagot, Murphy and Lee JJ).
2200 *Gill* [3172].
2201 *Gill appeal* at [597] (Jagot, Murphy and Lee JJ), citing *Merck* at [201] (Keane CJ, Bennett and Gordon JJ).
2202 *Gill appeal*.
2203 Ibid at [598].
2204 *Merck* at [201] (Keane CJ, Bennett and Gordon JJ); *Gill* at [3174] (Katzmann J); *Gill appeal* at [600].
2205 [2009] VSC 29.
2206 Ibid at [14].
2207 *Merck* at [201] (Keane CJ, Bennett and Gordon JJ).

not such as persons generally are entitled to expect.[2208]

2178 The community cannot expect goods that are inherently dangerous or known to carry a risk of harm to be risk free. Issues that may require particular consideration where the goods are biomedical devices to be implanted within a patient's body include community knowledge of the product; information provided to doctors by the manufacturer; reasonable expectations about information to be provided by doctors to patients before the devices are implanted; and in that context, what is known about the risk of harm and side effects associated with the device that cannot be avoided.[2209] The safety profile and relative benefits of available alternative treatment options may be a relevant consideration.[2210]

2179 In the *Gill appeal* the Court considered the relevance of the role played by medical intermediaries in relation to implanted biomedical devices. The Court explained:

> Having regard to the [Explanatory Memorandum] it is clear that Parliament intended that, in relation to medical goods supplied to doctors rather than directly to patients, manufacturers provide doctors with sufficient information, advice and warnings about any material risk of harm presented by goods so as to properly inform the doctor about the risk, in order that the doctor can appropriately inform or warn his or her patient. The [Explanatory Memorandum] explains that:
>
> (1) where goods are marketed and supplied to professionals for use (which we interpolate includes medical devices supplied to doctors for use in relation to their patients) a manufacturer can assume a "certain amount of pre-existing knowledge on the part of the purchaser". But that "is not to suggest that professional products require no warnings or instructions, merely that the type and pitch of any instructions and warnings will necessarily be different": at [17];
>
> (2) it is expected that "detailed product information is provided to doctors…by the manufacturer so *these learned intermediaries are sufficiently informed* to be able to decide whether or not it is appropriate to dispense pharmaceuticals [and we interpolate other medical goods] to particular consumers": at [24];
>
> (3) information and warnings are provided by the manufacturer to doctors and pharmacists in "the expectation that *it will be used to properly inform the consumer* about the product as the

2208 PLE.001.002.0001 at [58].
2209 *Merck* at [191]–[192] (Keane CJ, Bennett and Gordon JJ).
2210 *Gill* at 857–858 [3207] (Katzmann J); *Gill appeal* at 123 [582] (Jagot, Murphy and Lee JJ).

doctor…sees fit": at [50]; and

(4) a product that causes injury cannot be considered to be defective "due to the failure of the intermediary to properly inform the consumer, provided that *the proper information is provided by the manufacturer to the intermediary*: at [50].

(Emphasis added).

This approach is consistent with Jessup J's finding in *Peterson* at [917] as follows, which was not disturbed on appeal:

> Persons generally are, in my view, entitled to expect that, to the extent that a drug is known or believed to have side-effects, or to carry the potential for side-effects (particularly of a serious nature), practitioners will, in whatever terms, and by whatever means, are appropriate, be furnished by the drug supplier with information or warnings sufficient to permit a balanced, cautious and informed judgment to be made.

We take the same view.

The statement in *Peterson* concerned prescription drugs but the same can be said in relation to medical devices and accompanying IFUs supplied to doctors and hospitals and not directly to patients. We consider that persons generally are entitled to expect that to the extent that a medical device is known or believed to present a risk of harm, particularly significant harm, the manufacturer of the device will furnish doctors with sufficient information, advice and warnings to permit a balanced, cautious and informed judgment to be made by the doctor and an informed choice by the patient.[2211]

2180 The Court in the *Gill appeal* summarised the position of the medical intermediary as follows:

> The role of a doctor in deciding whether to recommend use of a medical device (whether or not for implantation) is relevantly analogous to that of a doctor deciding whether to recommend use of a prescription drug. In both settings the manufacturer supplies the goods and any accompanying product information or instructions for use to the doctor, not to the patient. The goods will be used by the patient only upon receipt of medical advice and a recommendation, which can be expected to include an appropriate warning about any risks associated with the goods. In both settings the doctor is required to exercise medical expertise and professional judgment in providing medical advice and a recommendation, which can be expected to be tailored to the patient's individual circumstances and may in some circumstances take into account the doctor's personal preferences.[2212]

2211 *Gill appeal* at [608]–[610].
2212 Ibid at [621].

'State of scientific knowledge' defence

2181 Section 75AK(1)(c) of the *TPA* provides that:

> (1) In a liability action, it is a defence if it is established that:
>
> …
>
> > (c) the state of scientific or technical knowledge at the time when they were supplied by their actual manufacturer was not such as to enable that defect to be discovered[.]

2182 In the trial judgment in *Merck*, Jessup J found that while there had been an hypothesis to the effect that Vioxx materially increased the risk of suffering the pleaded cardiovascular conditions when the medication was supplied to the plaintiff, the scientific evidence did not rise 'to the level of scientific knowledge required to enable a defect to be discovered during the relevant period', and that 'it was not until September 2004 that that increase in risk could be 'discovered' in the sense of established at the scientific level'.[2213] On appeal, the plaintiff argued that Jessup J had misconstrued s 75AK(1)(c):

> … as requiring that for a defect to be discovered, it had to be established at a scientific level rather than when it is known that there is a real and serious risk that it exists, notwithstanding that it may only be later that the defect can be positively proved to exist at the scientific level.[2214]

The Court on appeal dismissed the plaintiff's complaint, and said:

> … the state of scientific knowledge at the time Mr Peterson took Vioxx was such that it was not demonstrated that Vioxx caused an increased risk of MI. As the primary judge said at [929]:
>
> > Section 75AK(l)(c) contemplates the existence of a defect capable of being discovered by reference to the current state of scientific or technical knowledge. It is not concerned with the kind of contextual circumstances referred to in s 75AC(2). … The defect was something inherent in Vioxx as a matter of composition. I consider that the intent of s 75AK(1)(c) is that if *that* defect could not be discovered according to the state of scientific or technical knowledge, the defence should be available, notwithstanding that enough was suspected about the product to activate an implied obligation to give warnings of the kind mentioned in s 75AC(2)(d).

That is, the state of scientific or technical knowledge at the time when Vioxx

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2213 *Peterson* at [927].

2214 *Merck* at [207] (Keane CJ, Bennett and Gordon JJ).

> was supplied by MSDA to Mr Peterson was not such as to enable the defect to be discovered. We refer to [35] to [46] above. We agree with these conclusions.[2215]

2183 In *Gill*, Katzmann J observed in respect of the defence:

> The clear intention of Parliament was to limit the relevance of any deficiency in the state of scientific or technical knowledge at the time of supply to that which was unable to be discovered and to impose an onus on the manufacturer to prove the deficiency. The onus imposed by s 75AK(1)(c) is a legal onus, not merely an evidentiary one as the respondents submitted in closing argument. The applicant bears no onus in this regard.[2216]

Katzmann J went on to conclude that the focus of inquiry was the objective state of knowledge that existed at the time of supply of the particular good, and not the subjective knowledge of the manufacturer, or what the manufacturer could reasonably be expected to have discovered. The Court in *Merck*, and Katzmann J in *Gill*, set out the following description of the defence contained in the explanatory memorandum:

> It is the objective state of scientific and technical knowledge, not the subjective knowledge of the individual manufacturer, which is to be taken into account. **It is only if the defect could not have been discovered by anybody that the manufacturer will be able to succeed.** A manufacturer must expect that there may be further scientific or technical advances during the period of testing and production. The manufacturer should therefore satisfy itself that there have been no further technical advances which affect the safety of the goods before putting them into circulation.
>
> Similarly, a manufacturer must keep up to date with advances in knowledge after it first puts a product into circulation to ensure that new information is taken into account in the manufacture of subsequent goods, as new information may expose defects in goods. **The crucial time is therefore when the alleged defective good which caused the injury was supplied by the manufacturer, not the time at which the manufacturer first supplied goods of that type.**
>
> (Emphasis added)[.] [2217]

2215 Ibid at [208].
2216 *Gill* at [3358].
2217 Ibid [3504]; *Merck* at [204] (Keane CJ, Bennett and Gordon JJ).

Submissions

Turner

2184 By reason of the inherent defects, failure defects, the adverse events and the removal limitation, along with the marketing conduct, the safety of the Essure devices acquired by Turner and group members was not such as persons are generally entitled to expect.[2218] This means that Essure had a defect within the meaning of s 75AC of the *TPA* and/or a safety defect within the meaning of s 9 of the ACL.[2219]

2185 Essure did not have the level of safety persons generally were entitled to expect, and was therefore defective. The device posed a heightened risk of catastrophic consequences for a proportion of women. These significant consequences could not, unlike in the case of other medical devices such as heart stents or pacemakers, be justified by or balanced against any capacity on the part of Essure to offer any life-saving or significant medical treatment to the recipient. Given the availability of safe alternative contraceptive methods, the public was generally entitled to expect that Essure would not carry with it a risk of persistent chronic inflammation resulting in CPP or AUB (or the exacerbation of these symptoms) in a proportion of women, or the risk of breakage and perforation leading to the prospect of organ damage and possible organ removal.

2186 The purpose of Essure was to prevent pregnancy through implantation of a mechanical device that could be left permanently in the body. If Essure could not safely be left in the body for the lifetime of the patient because of the risks of adverse events and the removal limitation, even if it was effective at permanent contraception, then this points to the device being defective.[2220]

2187 The contents of the PIBs and websites, which were directly patient facing, were entirely inadequate to communicate the true risks associated with Essure.

2218 PLE.001.002.0001 at [58].
2219 SBM.001.001.0004 at 284.
2220 Ibid at 287 [968].

State of scientific knowledge defence

2188 The defence in s 75AK(1)(c) of the *TPA* is narrow, and requires the defendants to allege and prove that they *could not* have discovered the defects. Here, all the defendants have asserted is that certain studies and tests were conducted which did not discover the defects in respect of which the defence is invoked. They have not identified any objective lacunae in the state of scientific knowledge — which has since been addressed by scientific developments — so as to preclude the discovery of the defects by anyone when Essure was supplied in Australia.[2221]

2189 The tests and studies particularised by the defendants do not support the proposition that the defendants could not have discovered the defects. In fact, the studies identify aspects of those defects or 'red flags' associated with them.[2222] The studies relied on by the defendants were not designed to capture the true state of affairs with respect to the risks posed by Essure.

2190 The evidence shows that the defendants knew or ought to have known of the relevant risks.

2191 The regulatory evidence shows that there were significant deficiencies in the defendants' PMS systems, such that the true extent of adverse events did not properly emerge.

2192 The evidence of Robertson and Chrzanowski shows that Essure was obviously a bad idea from the start. The potential for the device to cause chronic inflammation leading to chronic pain and bleeding ought to have been identified at the outset. It is a matter of first principles and not of new science.

Defendants

2193 Turner has not established that any observation of CPP and AUB after Essure implantation, or any incidence of those conditions at a similar rate to laparoscopic tubal ligation, can support the suggestion that there is an association (let alone

2221 Ibid at 302 [1007]-[1008].
2222 Ibid 304 [1011].

causative relationship) between the conditions and Essure. Turner's failure to establish a statistical association between Essure and any increased incidence of CPP and AUB means that the Court should not conclude that any defect exists by reason of a risk of such outcomes.

2194 Matters said to amount to statutory defects are, in truth, normal and expected consequences of the ordinary operation and effect of Essure. The initial injury caused to the fallopian tube upon implantation of Essure is local, transient and minor; not unique to Essure, but a function of the placement of any medical device in the body; and contributes to the commencement of the body's normal wound healing response. Inflammation is a necessary part of this foreign body response. Turner's attempt to characterise this inflammation as 'chronic' should not be accepted.

2195 The risks associated with Essure were known to medical practitioners and/or were the subject of appropriate information accompanying supply of the devices.

2196 It is not disputed that removal of Essure, unless it occurred within a relatively short time after placement, would in the ordinary course require some form of surgery typically requiring (at a minimum) removal of part or all of the fallopian tubes. Fixation in the fallopian tubes is inherent to the mode of operation and effect of the device. The information provided about the device made clear that it was an 'irreversible' procedure, which was enough to alert physicians (and patients who read the PIB or who were informed of these matters) that Essure was not intended to be removed from their bodies and, by extension, that doing so would not necessarily be straightforward. During the relevant period, the IFUs and PTMs expressly warned that the device, once placed, may not be capable of removal without surgery. As-Sanie and Korda agreed that this would be obvious to a gynaecologist. The Court should not find that an inherent property of Essure, being the permanence of the contraception, its embedding in the fallopian tube and resultant need for surgery and/or organ removal to remove it (which were both obvious to the gynaecologists who placed it and the subject of information provided to surgeons and patients)

constituted a defect or safety defect.

State of scientific knowledge defence

2197 It will be apparent to the Court that the state of scientific knowledge has changed between the time at which the Essure device was first designed, developed and manufactured, and the knowledge available today.[2223] First, the mere fact that Turner's expert witnesses have, for the specific purpose of this proceeding, 'brainstormed' a number of hypotheses (wholly or largely unsupported by direct evidence) about ways in which Essure might be capable of causing harm, does not, without more, mean that those hypotheses form part of the scientific and technical knowledge base during the relevant period.[2224]

2198 The Full Court in *Merck* approved the reasoning of the primary judge in respect of the meaning of the statutory phrase 'could not have been discovered by anybody', to the effect that the word 'discovered' is to be understood as 'established at the scientific level'.[2225] It is not sufficient, for the purpose of showing that something was 'discoverable', to simply point to a hypothesis (which lacks proper scientific evidence in support). In this case, there has been no study carried out that has at any time rendered 'discoverable' any of the hypotheses of the Turner's experts. All of the tests and studies required by various regulators were undertaken as part of the approval process for Essure. Those tests, including the further tests mandated by the various regulators, did not detect the defects Turner alleges.[2226]

2199 Second, just like in *Merck*, the knowledge and testing carried out by Conceptus (and later Bayer) ought to be taken to represent the height of the state of scientific and technical knowledge during the relevant period. The Court should assess what the scientific and technical knowledge was during the relevant period through the 'prism' of the testing conducted by (and therefore, the knowledge of) Conceptus and later

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2223 Ibid at 66 [5.7].
2224 Ibid at 181 [1.17](e).
2225 *Merck* at [206] (Keane CJ, Bennett and Gordon JJ).
2226 SBM.500.001.0003_2 at 181 [1.17](e).

Bayer.[2227]

2200 Third, if the hypotheses devised by Robertson and Chrzanowski are the basis upon which Essure is found by the Court in this proceeding to have had a statutory defect, those hypotheses rest on the knowledge that those experts have gained and 'synthesised' over a significant period. Having regard to the broad range of disciplines and subjects underpinning the hypotheses on which Turner's statutory defects case is predicated, it would be an error to 'fix' one or more of the defendants with the 'knowledge' of these hypotheses at a particular time that predates the synthesis and articulation of these hypotheses by Turner's experts in this proceeding. Further, they remain scientific hypotheses, not scientific knowledge.

2201 The alleged defects are particularised in many different ways which draw on many different scientific disciplines and hypotheses. To the extent that specific causal mechanisms are denied by the defendants, they were not discoverable during the relevant period for the purpose of this defence.

Analysis

Defect

2202 Turner has not established that Essure caused ongoing chronic inflammation in some women resulting in CPP, dysmenorrhea and AUB. This central part of Turner's defect case can be dismissed.

2203 Turner has not established that Essure devices could break or fragment during the period of wear because of corrosion and/or fatigue. There was a risk that Essure could break or fragment during surgical removal. Information and a warning about that risk was communicated to gynaecologists in the IFUs and PTMs.

2204 There was a risk of perforation, migration (including expulsion), and damage to internal organs caused by Essure. The eventuation of one or a combination of those risks could result in pain, abnormal bleeding and the need to surgically remove the

[2227] Ibid.

device. Information and warnings about those matters were communicated to gynaecologists in the physician training, PTMs and IFUs.

2205 Incorrect placement of a device or the experience of an adverse event may result in the need for surgical removal by a salpingectomy or hysterectomy. Information about those risks was communicated to gynaecologists in the training material, PTMs and IFUs.

2206 There was a risk that a woman might experience a DTHR to nickel ions that leached from an Essure device. From the time IFU 2 came into use and, in respect of training conducted by Rosen, from mid-2001, information about that risk was communicated to gynaecologists. Turner has not established a risk of DTHR to any other metals contained in the device.

2207 For the reasons set out in Chapter XX, information and warnings given by the defendants about the established risks were adequate to properly inform gynaecologists so that they could appropriately inform or warn their patients about those matters. It is reasonable to expect that specialist gynaecologists armed with the warnings and information provided by the defendants would, in consultation with their patients, provide relevant information about the comparative risk-benefit profile of Essure. It is reasonable to expect that, insofar as the pleaded risks have been established, information would be conveyed about those matters by gynaecologists to their patients taking into account the warnings communicated by the defendants and the gynaecologists' specialist training, skill and experience.

2208 Having regard to these matters, and to the findings that I have made about the degree and magnitude of the risks associated with Essure, Turner has not established that the device had a defect.

State of scientific knowledge defence

2209 This defence potentially applied to risks that Turner has failed to prove existed. Accordingly, the defence has no work to do.

2210 Had Turner succeeded in proving that Essure could cause CPP, dysmenorrhea or AUB it may have been on the basis of one or more of the theories proposed by Robertson. Whether the state of scientific knowledge defence could succeed in those circumstances would necessarily depend on the facts that were found. The issue cannot be considered as a hypothetical.

Merchantable Quality claim

2211 Section 74D of the *TPA* provides as follows:

> **74D Actions in respect of goods of unmerchantable quality**
>
> (1) Where:
>
> (a) a corporation, in trade or commerce, supplies goods manufactured by the corporation to another person who acquires the goods for re supply;
>
> (b) a person (whether or not the person who acquired the goods from the corporation) supplies the goods (otherwise than by way of sale by auction) to a consumer;
>
> (c) the goods are not of merchantable quality; and
>
> (d) the consumer or a person who acquires the goods from, or derives title to the goods through or under, the consumer suffers loss or damage by reason that the goods are not of merchantable quality;
>
> the corporation is liable to compensate the consumer or that other person for the loss or damage and the consumer or that other person may recover the amount of the compensation by action against the corporation in a court of competent jurisdiction.
>
> …
>
> (3) Goods of any kind are of merchantable quality within the meaning of this section if they are as fit for the purpose or purposes for which goods of that kind are commonly bought as it is reasonable to expect having regard to:
>
> (a) any description applied to the goods by the corporation;
>
> (b) the price received by the corporation for the goods (if relevant); and
>
> (c) all the other relevant circumstances.

Clause 54 of the ACL is to the same effect, save that it replaces 'merchantable quality'

with 'acceptable quality'. For the purposes of this proceeding there is no material difference between the provisions. For convenience I will refer to the *TPA* provisions. References in these reasons to 'merchantable quality' include 'acceptable quality'.

Principles and authorities

2212 The test is objective, and involves consideration of the expectations of a reasonable consumer in the position of the actual consumer.[2228] That assessment is made on the circumstances at the time of supply.[2229] In *Medtel Pty Ltd v Courtney*[2230] ('*Medtel*'), Branson J explained:

> The test contained in s 74D(3) is a test that requires the making of a comparison. It calls for the fitness for purpose of the goods in question to be measured against what it was objectively reasonable to expect, in terms of fitness for purpose, in all the relevant circumstances. Those circumstances include the description applied to the goods by the manufacturer and the price received by the manufacturer for the goods. What it is objectively reasonable to expect in terms of fitness for purpose of goods of one description may be quite different from what it would be reasonable to expect of goods of another description. What it would be reasonable to expect in terms of fitness for purpose of an inexpensive product might be quite different from what it would be reasonable to expect of an expensive product of the same kind.[2231]

2213 The standard is not of perfection, but what a reasonable consumer would regard as acceptable given the relevant circumstances.[2232] The expectations of a reasonable consumer of a medical device may be informed by the expectations of specialist medical practitioners, upon whose advice consumers may be heavily dependent.[2233] Goods may not be of acceptable quality if the evidence shows there is a risk they may fail.[2234]

2214 In *Capic v Ford Motor Company of Australia Pty Ltd*,[2235] Perram J said:

2228 *Graham Barclay Oysters Pty Ltd v Ryan* (2000) 102 FCR 307 at [533]–[534] (Lindgren J), [69] (Lee J), [611] (Kiefel J) ('*Graham Barclay Oysters*'); *Courtney v Medtel Pty Ltd* (2003) 126 FCR 219 at [216] (Sackville J).

2229 *Medtel Pty Ltd v Courtney* (2003) 130 FCR 182 at [64], [70] (Branson J) ('*Medtel*'); *Merck* at [180] (Keane CJ, Bennett and Gordon JJ).

2230 *Medtel*.

2231 Ibid at [64].

2232 *Dwyer v Volkswagen Group Australia Pty Ltd t/as Volkswagen Australia* [2021] NSWSC 715 at [22]; *Australian Competition and Consumer Commission v Jayco Corporation Pty Ltd* [2020] FCA 1672 at [27].

2233 *Courtney v Medtel Pty Ltd* (2003) 126 FCR 219 at [216] (Sackville J).

2234 *Medtel* at [72]–[74] (Branson J).

2235 (2021) 154 ACSR 235.

> I accept that not every inherent risk of failure will have the consequence that goods are not of acceptable quality. The conclusion in any particular case will be a function of the nature of the feared failure and the extent of the risk of its occurrence, measured against the consumer's reasonable expectations of how the product ought to behave. Sometimes the failure will be trivial or the risk insubstantial and in such cases the claim may fail. Further than this, at least in principle, seems dangerous to go.[2236]

Submissions

Turner

2215 By reason of all or any of the inherent defects, the failure defects, the risk of adverse events and the removal limitation, the Essure devices acquired by Turner and group members:

(a) were not as fit for the purpose of Essure;

(b) were not as free from defects; and/or

(c) were not as safe,

as would be expected by a reasonable consumer.[2237]

2216 The evidence shows that Essure was not of merchantable or acceptable quality, for the reasons identified above in relation to the Defect claim.[2238]

2217 The defendants also plead in the alternative that the reasons why Essure was not of merchantable quality or acceptable quality were specifically drawn to the attention of Turner and group members by the information and risk warnings (being the PIBs, IFUs and PTMs identified by the defendants), or in the process of consultation or advice. The defendants rely on s 74D(2)(b) of the *TPA* and s 54(4) of the ACL. Again, this defence has not been specifically pleaded with respect to Turner. Again, no evidence was adduced as to any matters that were specifically brought to Turner's attention either by way of the process of consultation or otherwise. It was never put

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2236 Ibid at [612].
2237 PLE.001.002.0001 at [55].
2238 SBM.001.001.0004 at 309 [1033].

to her in cross-examination that any such matters were drawn to her attention.

Defendants

2218 The assessment of the reasonableness of an expectation in relation to a particular good is objective,[2239] and is determined by reference to a reasonable consumer in the position of the plaintiff.[2240] No reasonable consumer could expect that a manufacturer would supply goods that are held to an unobtainable standard (such as one that exceeded the limits of current scientific or technical capability). Equally, a reasonable consumer could not expect that a manufacturer would avoid a defect in a product where the prevailing state of scientific or technical capability did not permit such avoidance. So much is clear from the Full Court's statement in *Merck* that '[t]he time at which the goods are assessed is the time of supply'.[2241] This necessarily means that the reasonableness of any expectation in relation to a good is to be assessed as at the time of supply. The time of supply will be different for Turner and each of the group members in this proceeding.[2242]

2219 The design and manufacture of medical devices is inherently complex given the nature of the devices themselves, their purpose and the ongoing development of the state of scientific capability. In the context of medical devices, manufacturers are faced with the task of developing products that improve upon previous devices and treatment options, including by using and relying on the experience of constituent parts of a device. In turn, this development of new products contributes to the development of scientific knowledge and capability. The testing undertaken by Bayer was comprehensive, satisfying the requirements of the relevant regulatory bodies and based on scientific knowledge and capability available at the time of manufacture and supply.[2243]

2220 The fact that a product is included in a hazard alert or recall notice alone is not

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2239 *Medtel* at [43] (Moore J), [64] (Branson J).
2240 Ibid at [43]; *Graham Barclay Oysters* at [534] (Lindgren J).
2241 *Merck* at [180] (Keane CJ, Bennett and Gordon JJ).
2242 SBM.500.001.0003_2 at 73 [6.14].
2243 Ibid at 74 [6.16].

sufficient to render that product of unmerchantable quality.[2244]

Analysis

2221 For the reasons outlined above in respect of the Defect claim, Turner has not demonstrated that the Essure device was not of merchantable quality.[2245]

2222 The Essure training and material provided by the defendants informed gynaecologists about each of the pleaded risks that have been established. Based on the information provided by the defendants and their own specialist training, experience and skill, gynaecologists would expect Essure to carry the risks of migration, perforation, damage to internal organs, and associated symptoms of pain and altered menstrual bleeding. Further, gynaecologists would expect that removal of Essure devices would require surgery and may involve salpingectomy or hysterectomy. Turner has not established that the degree and magnitude of these risks, or the circumstances in which they may eventuate, was not sufficiently communicated by the defendants to gynaecologists or was not otherwise within their expectation.

2223 The evidence establishes that risks of harm are associated with every contraceptive choice. A reasonable consumer who is considering the option of Essure permanent sterilisation would have consulted with her treating gynaecologist. It is reasonable to expect information conveyed in that consultation to include the risk-benefit profile of different contraceptive options, including Essure. I accept the defendants' submission that a woman considering Essure could not reasonably expect the devices to reach an unobtainable standard of safety. The mere fact that a device may fail or cause harm is insufficient to establish that it is not of merchantable quality.

XXIV. NEGLIGENCE

2224 Turner put her negligence case in two ways:

a. Bayer Essure and Bayer Healthcare designed, developed,

2244 Ibid at 74 [6.17].
2245 Ibid at 184.

manufactured and distributed and supplied the device with the Inherent Defects, Failure Defects, risk of Adverse Events and the Removal Limitation (**the Design Failure**); and/or

b. Bayer Essure, Bayer Healthcare, Gytech, AMSL and Bayer Australia:

i. promoted or marketed the Essure Device to the Plaintiff and group members without warning or without adequate warning about the Inherent Defects, the Failure Defects, the risk of Adverse Events and the Removal Limitation (Failure to Warn); and/or

ii. failed to make available to the Plaintiff and group members who had already received the Essure Device information disclosing the Inherent Defects, Failure Defects and/or the risk of Adverse Events (Failure to Inform).[2246]

Duty

2225 It is not in dispute that a manufacturer owes a duty to take reasonable care to avoid reasonably foreseeable risks of harm to the users of its products. In *Graham Barclay Oysters Pty Ltd v Ryan*,[2247] McHugh J explained:

> The duty of care owed by a manufacturer or producer to a consumer is a duty to take reasonable care to avoid injury to the consumer. To formulate the duty in more specific terms invites error because it is likely to mix a question of law (whether a duty existed) with a question of fact (whether a breach occurred). If the duty is formulated in specific terms, the issue on breach is whether the duty has been performed in accordance with the terms of the duty as formulated. But, as *Wyong Shire Council v Shirt* shows, the question of breach is far more complex than an affirmative or negative answer to the question whether the defendant carried out the duty as formulated. It involves evaluating and weighing a number of competing considerations. Both the trial judge and the majority judges in the Full Court did not attempt to evaluate and weigh the competing considerations. In failing to do so, they erred in law.[2248]

2226 The defendants admit that Bayer Essure (as Conceptus) designed, developed and manufactured Essure, and supplied Essure for importation into Australia, from about 1999 to 1 July 2013.

2227 The defendants admit that Bayer HealthCare:

2246 SBM.001.001.0004 at 312 [1044].
2247 (2002) 211 CLR 540.
2248 Ibid at [106] (citations omitted).

(a) was responsible for design and development of Essure between 5 June 2013 and about 1 January 2016;

(b) was responsible for limited manufacturing and assembly of Essure between 1 July 2013 and about 1 January 2016;

(c) supplied Essure for importation into Australia for distribution by Gytech and then AMSL from about 1 July 2013 until about 31 May 2017; and

(d) was the registered manufacturer of Essure on the ARTG under the *TG Act* from May 2014 to 9 February 2018.[2249]

The defendants also admit that some material published in Australia regarding Essure during the period 1 July 2013 and August 2017 included the name of Bayer HealthCare.

2228 Bayer Essure was a manufacturer of Essure from 1999 until 1 July 2013. Bayer HealthCare was a manufacturer of the device from about 5 June 2013. As manufacturers, Bayer Essure and Bayer HealthCare owed a duty to take reasonable care to avoid reasonably foreseeable risks of harm to the users of Essure.

2229 Turner alleges that:

(a) it was reasonably foreseeable to each of Bayer Essure, Bayer HealthCare, AMSL, Gytech and Bayer Australia that individuals who were considering a procedure to implant Essure devices may suffer harm arising from Essure if they were not warned or adequately warned about the inherent defects, the failure defects, the risk of adverse events and the removal limitation. Turner alleged that accordingly the defendants owed a duty to warn group members about those matters;

[2249] SBM.500.001.0003_2 at 100 [6.2].

(b) it was reasonably foreseeable to each of Bayer Essure, Bayer HealthCare, AMSL, Gytech and Bayer Australia that individuals may suffer harm or further harm arising from Essure after undergoing the procedure, if information disclosing the inherent defects, failure defects and/or the risk of adverse events was not made available to them. Turner alleged that accordingly the defendants owed group members who had already undergone the Essure procedure a duty to inform them about those matters ('duty to inform').

2230 Each of the defendants deny the existence of this alleged duty to inform. They submitted that the alleged duty was incoherent with well-established principles as to the duty owed by doctors to patients; and was inconsistent with the notion of informed consent which, by its very nature, requires an assessment of the individual patient's needs by their treating doctor. The defendants submitted that any 'duty to inform' imposed on a manufacturer cannot involve individualised assessment.[2250]

2231 However, the defendants accepted as trite that in certain circumstances, the discharge of a manufacturer's duty to the end user of their product may require that the manufacturer provide information to the end user, or to an intermediary who will advise the end user about the use of the product. The defendants accepted that such was the case with Essure, where access to the product could only be obtained through an appropriately trained doctor.[2251]

2232 Turner relied on the following excerpt from the reasons of Katzmann J in *Gill* in support of her 'duty to inform' pleading:

> In the context of the present case, the manufacturers had a duty to take reasonable care in the design, testing, evaluation, supply, and marketing of the devices. That duty extended to providing accurate information about the performance and safety of the devices, including warnings about potential complications and contraindications. The duty was not confined to the period before the devices were made or placed on the market, it was a continuing obligation to evaluate their safety and keep abreast of information about the nature and extent of potential complications and to convey that information to

2250 Ibid at 76 [7.8].
2251 Ibid at 82 [7.24](a).

users of the devices.[2252]

Clearly her Honour was not identifying different duties of care owed by a manufacturer to users of its product. Rather, Katzmann J was identifying, on the facts of the case before her, the content of the duty and what reasonableness required of the manufacturers in order to satisfy the duty to persons supplied with their product.

2233 The central issue on the question of breach was whether Turner had established a foreseeable risk that Essure could cause an ongoing chronic inflammatory response resulting in CPP or AUB. If that risk was established and found to be non-insignificant, the question would become what, if any, precautions a reasonable person in the position of the defendants would have taken. Arguably, those precautions may have extended to informing women who had already undergone the Essure procedure so that they could obtain medical advice and treatment to ameliorate the risk. Considered in this way, the 'duty to inform' is not a separate or additional duty, but is an allegation that is potentially relevant to the content of the duty owed by Bayer Essure and Bayer HealthCare as manufacturers, and to the precautions that reasonableness required they take in response to the risk.

2234 Turner submitted that the duty owed by Gytech and AMSL was 'a duty to provide accurate information as to the safety of [Essure]'. The duty pleaded by Turner against the distributor defendants is premised on the allegation that they knew or ought to have known that Essure had the pleaded inherent defects, failure defects, risk of adverse events and removal limitation.

2235 Whether a vendor of goods owes a duty to a purchaser to take reasonable care may depend on the nature of the goods sold, the risks involved with those goods, and whether the vendor had actual or imputed knowledge of the risks. *Laundess v Laundess*[2253] ('*Laundess*') concerned a claim against the vendor of a second-hand vehicle by a passenger who was injured when a door flew open and her foot was

2252 *Gill* at [3627]; SBM.001.001.0004 at 313.
2253 (1994) MVR 156 ('*Laundess*').

dragged along the road. Mahoney JA, with whom Meagher and Powell JJA agreed, observed:

> In my opinion a vendor of goods does not, as such, have a duty in negligence to a purchaser. There must be something more than a mere relationship of vendor and purchaser. The problem is to define what more is necessary and when the duty arises.[2254]
>
> …
>
> I do not think that that additional factor can be stated in a simple formula of words. The circumstances in which a duty of care will be imposed upon a vendor of goods must in my opinion depend upon the nature of the goods, the risk involved, and the circumstances of the case.[2255]

2236 In *J & V Pesl Pty Ltd v Ray Smith Tractors Pty Ltd*[2256] ('*Smith*'), a claim was made against the respondent to the appeal relating to a grass slasher supplied by it to the appellant. A 'U' shaped steel strap was bolted to the slasher and described in the Owners Manual published by the manufacturer as a 'lifting bracket'. A worker employed by the appellant suffered serious harm while servicing the slasher, which was lifted above him, when the lifting bracket gave way and the slasher fell. Some years after the slasher was sold to the appellant but before the incident occurred, the respondent received a service bulletin from the manufacturer containing a warning that the lifting bracket was not designed to lift the slasher and should not be used for that purpose. The respondent did not communicate this warning to the appellant. Tobias JA, with whom Beazley and Ipp JJA agreed, said:

> Accordingly, the issue before her Honour as to the existence of a duty of care needed to focus upon whether the Smith companies knew or should have known that it was dangerous for the slasher to be lifted off the ground by using only the lifting bracket attached to its gearbox housing. Absent actual knowledge of such a danger, then on Ipp JA's formulation in *McPherson*, a duty to take reasonable care arose if in the circumstances of the case there should be imported to the Smith companies knowledge that lifting the slasher by the lifting bracket could be dangerous in that there was a reasonably foreseeable risk of harm to a person who was working underneath it. The answer to that question may depend upon whether it was reasonably foreseeable that that risk, unless investigated, researched or warned against, might materialise.

2254 Ibid at 160.
2255 Ibid at 161.
2256 (2007) Aust Torts Reports 81-883 ('*Smith*').

> As I have indicted, the existence of such a duty of care on the part of the Smith companies depended upon their actual or imputed state of knowledge with respect to the use of the lifting bracket for the purpose of supporting the slasher at a 45 angle to the ground to enable access beneath it to the cutting blades.
>
> If the duty did exist then its scope or content must be determined in the light of that knowledge. Whether there was a breach of the duty depended on the considerations referred to in the judgment of Mason J in *Wyong Shire Council v Shirt* (1980) 146 CLR 40 (*Shirt*) at 47-48.[2257]

2237 The Court in *McPherson's Ltd v Eaton*[2258] *('Eaton')* reviewed the authorities relevant to the question of whether a 'general duty of care arise[s] merely because a retailer sells to the public'.[2259] Many of the authorities to which Ipp JA referred focused on the nature of the goods and the particular risks associated with the goods, about which the vendor was duty-bound to know. However, it is clear from what was said by Mahoney JA in *Laundess*, and from some of the authorities reviewed by Ipp JA in *Eaton*, that the matters relevant to whether the vendor of goods owes a duty to the purchaser or end consumer are not limited to the vendor's actual or constructive knowledge of particular risks associated with the product. Relevant matters include whether the vendor's role extends beyond being 'a mere retailer'.[2260] For example, in *Eaton*, Ipp JA said:

> It is important that McPhersons was solely a retailer, in effect, a conduit, of the millboard.[2261]

2238 Neither Gytech nor AMSL was 'solely a retailer' acting as a conduit of Essure from the manufacturer to the doctors and hospitals who purchased it and the women who underwent the Essure procedure. Gytech and AMSL were listed as 'sponsors' of Essure on the ARTG, and therefore had significant regulatory responsibilities.[2262] Both suppliers played an active role in marketing, promoting and distributing Essure. This included engaging with the Bayer defendants to learn about Essure and its comparative risks and benefits; conducting Essure training courses for medical

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2257 Ibid at [40]-[42].
2258 (2005) 65 NSWLR 187 ('*Eaton*').
2259 Ibid at [58]-[59] (Ipp JA).
2260 Ibid at [66]–[67], [76], [79]–[80].
2261 Ibid at [59].
2262 BES.001.001.0125; AMS.001.001.5677.

specialists; supervising the first Essure procedures performed by each medical specialist before that specialist was approved; conducting refresher courses for specialists; receiving and processing reports of adverse events; and supplying the PTMs, IFUs and PIBs which contained details of the benefits and risks of Essure, and in many cases were marked with Gytech's or AMSL's details. Gytech and AMSL were not general retailers of goods. They were specialist suppliers of medical devices and equipment.

2239 On any view, there are significant risks associated with Essure. Gytech and AMSL engaged with the Bayer manufacturers to learn about and understand those risks. Gytech and AMSL assumed the responsibility of providing information, instruction, training and supervision about those matters to medical experts. In the circumstances of this case, the relationship between Gytech and AMSL, the doctors and hospitals to which Essure was supplied, and the women who received the devices, was clearly more than a mere relationship of vendor and purchaser or vendor and end consumer.

2240 I conclude that each of Gytech and AMSL owed a duty to take reasonable care to avoid injury to the users of Essure. The content of that duty, and questions of breach, must take into account the position occupied by Gytech and AMSL in relation to the supply of Essure. They were not the manufacturers of a complex biomedical device, and were to a very significant degree dependent on scientific information about Essure supplied by the Bayer defendants. A risk that was foreseeable to the manufacturers of the device may not have been foreseeable to Gytech and AMSL. The assessment of what precautions were reasonable may also have differed.

2241 Bayer Australia played a far more limited role in relation to Essure than either Gytech or AMSL. Bayer Australia did not supply Essure to purchasers or consumers. Although its name appeared on some of the PIBs, it was not directly involved in the distribution of the PIBs, IFUs or PTMs. Bayer Australia did not play a direct role in the marketing or promotion of Essure or in the training, instruction and supervision of the specialists who performed the Essure procedure. Bayer Australia only became

a sponsor of Essure on the ARTG on 28 January 2018, after the end of the commercial supply period in Australia.[2263] I conclude that Bayer Australia did not owe a relevant duty of care to group members.

Breach

2242 A manufacturer breaches its duty if, by exercising reasonable care, it should have foreseen and avoided the consumer's loss.[2264] Whether the duty has been breached must be assessed prospectively and not retrospectively.[2265]

2243 The common law has been modified by statute in each Australian State.[2266] The parties agreed that the *Wrongs Act* applies to determination of Turner's negligence cause of action, and focused their submissions on the provisions of that Act.

2244 The general principles applicable to breach are set out in s 48 of the *Wrongs Act* as follows:

> (1) A person is not negligent in failing to take precautions against a risk of harm unless—
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> (a) the risk was foreseeable (that is, it is a risk of which the person knew or ought to have known); and
>
> (b) the risk was not insignificant; and
>
> (c) in the circumstances, a reasonable person in the person's position would have taken those precautions.
>
> (2) In determining whether a reasonable person would have taken precautions against a risk of harm, the court is to consider the following (amongst other relevant things)—
>
> (a) the probability that the harm would occur if care were not taken;
>
> (b) the likely seriousness of the harm;
>
> (c) the burden of taking precautions to avoid the risk of harm;
>
> (d) the social utility of the activity that creates the risk of harm.

2263 AMS.001.001.4365.

2264 *Dovuro Pty Ltd v Wilkins* (2003) 215 CLR 317 at [30] (McHugh J) ('*Dovuro*').

2265 *Vairy v Wyong Shire Council* (2005) 223 CLR 422 at [125]–[129] (Hayne J).

2266 *Wrongs Act* s 48(1). *Civil Liability Act 2002* Pt 2 (NSW) s 5B; *Civil Liability Act 1936* (SA) s 32; *Civil Liability Act 2002* (Tas) s 11; *Civil Liability Act 2002* (WA) s 5B; *Civil Liability Act 2003* (Qld) s 9.

(3) For the purposes of subsection (1)(b)—

(a) **insignificant risks** include, but are not limited to, risks that are far-fetched or fanciful; and

(b) risks that are **not insignificant** are all risks other than insignificant risks and include, but are not limited to, significant risks.

2245 The first step in the analysis of breach requires the appropriate identification of the risk of harm.[2267] Turner formulates the relevant risk as follows:

a. the risk of an ongoing inflammatory response consequent to the placement of the Essure Device and/or associated symptoms of pain and bleeding (including exacerbation thereof) resulting in injury in some cases requiring organ removal; and/or

b. the risk of disruption of tissue and damage to internal organs and associated injury including organ removal.[2268]

2246 The statutory requirement that the identified risk is not insignificant 'is more demanding, for a plaintiff, than the common law test, although "… not by very much"'.[2269]

2247 The content of the standard of reasonableness that applies to a manufacturer will necessarily depend on the factual circumstances of each case. In that regard, Turner relied on the following statement by Katzmann J in *Gill*:

> It is well established that the standard of care is determined by what a reasonable person in the position of the respondent or respondents would do in response to the reasonably foreseeable risk: *Graham Barclay Oysters (HC)* at [192] (Gummow and Hayne JJ). The response will be affected, amongst other things, by the nature of the product, the gravity of the risk and the severity of the consequences should the risk eventuate. In the case of an inherently dangerous product or a product designed for human consumption or implantation, particularly permanent implantation, the level of caution required of a reasonable manufacturer (and of a supplier in the position of JJM) will necessarily be high.[2270]

2248 The defendants emphasised that Essure was supplied to specialist surgeons who

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2267 *Erickson v Bagley* [2015] VSCA 220 at [33] (Kyrou and Kaye JJA) ('*Bagley*'); *Roads and Traffic Authority (NSW) v Dederer* (2007) 234 CLR 330 at [60] (Gummow J).

2268 SBM.001.001.0004 at 317 [1065].

2269 *Bagley* at [36] (Kyrou and Kaye JJA); *Shaw v Thomas* [2010] NSWCA 169 at [44] (Macfarlan JA).

2270 *Gill* at [3646].

assessed whether a patient was a suitable candidate for implantation of the devices. The surgeons themselves were subject to professional obligations, including duties to exercise due care and skill in treating patients and undertaking the informed consent process. The knowledge and skill of the expert treating surgeon and the duty of care they owed was a relevant circumstance in determining whether the relevant Bayer defendants, as manufacturers, had discharged their duty of care. The defendants reiterated that no evidence was given by Turner's treating surgeon or any other medical professional that there was a deficiency in the information provided with the Essure device, or that they were not aware of a specific risk associated with the device.

2249 The defendants submitted that the standard of reasonableness and whether it has been discharged is also informed by the statutory and regulatory framework within which Essure was manufactured and distributed. In Australia, the TGA is responsible for regulating therapeutic goods pursuant to the *TG Act*. The objects of the *TG Act* include establishing a system of controls relating to the quality, safety and efficacy of therapeutic goods used in Australia.[2271]

2250 In the US, Essure was approved by the FDA for commercial supply after undergoing the PMA process. Brandwood said that this was the most stringent pre-market review process applied by the FDA, and that it required 'a full first principle scientific and clinical submission demonstrating safety and clinical performance of the device'.[2272]

2251 The defendants submitted that the systems by which medical devices are regulated are carefully calibrated and comprehensive, balancing the public's need for such devices with the need to protect the public from risks associated with them.[2273] The TGA and FDA are the regulators charged with the responsibility of scrutinising the testing of medical devices, approving or declining the devices for commercial supply, and monitoring their safety and efficacy. The defendants submitted that the Court should be slow to find there was a breach of a duty of care owed to group members

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2271 *TG Act* s 4(a).
2272 Brandwood at 58 [248], 59 [253] (EXP.001.002.0009_2).
2273 SBM.500.001.0003_2 at 80 [7.19].

in circumstances where Essure was approved by the FDA.[2274] The defendants relied on the following statement of McHugh J in *Dovuro Pty Ltd v Wilkins*[2275]:

> If negligence law is to serve any useful social purpose, it must ordinarily reflect the foresight, reactions and conduct of ordinary members of the community or, in cases of expertise, of the experts in that particular community. To hold defendants to standards of conduct that do not reflect the common experience of the relevant community can only bring the law of negligence, and with it the administration of justice, into disrepute. That is not to say that a defendant will always escape liability by proving that his or her conduct was in accord with common practice. From time to time cases will arise where, despite the common practice in a field of endeavour, a reasonable person in the defendant's position would have foreseen and taken steps to eliminate or reduce the risk that caused harm to the plaintiff. But before holding a defendant negligent even though that person has complied with common practice, the tribunal of fact had better first make certain that it has not used hindsight to find negligence. Compliance with common practice is powerful, but not decisive, evidence that the defendant did not act negligently. And the evidentiary presumption that arises from complying with common practice should be displaced only where there is a persuasive reason for concluding that the common practice of the field of activity fell short of what reasonable care required.[2276]

2252 In final submissions, Turner clarified that her central case was that in some women, Essure caused ongoing chronic inflammation resulting in CPP, dysmenorrhea and AUB, and the possible need to remove the devices by salpingectomy or hysterectomy. For reasons set out in Chapter XVIII I have concluded that Turner has not established the existence of that risk. In the circumstances, Turner's negligence case based on the first limb of the risk of harm she identified must fail.

2253 My conclusion about general causation is based in part on the finding that Turner has not established a causal relationship between the inflammatory process observed on histological analysis in Hoogendam 2020 and Essure. If this finding is wrong, then Hoogendam 2020 would be evidence that, in a rare case, Essure might be associated with ongoing chronic inflammation resulting in CPP.

2274 Ibid at 81 [7.20].

2275 *Dovuro*.

2276 Ibid at [34] (McHugh J); see also *Sibley v Kais* (1967) 118 CLR 424 at 4 (Barwick CJ, McTiernan, Kitto, Taylor and Owen JJ).

2254 For the following reasons, that finding is not sufficient to establish breach.

2255 First, the evidence does not establish the mechanism by which ongoing chronic inflammation resulting in CPP was caused in Hoogendam 2020. If Essure was a cause, it may not have been by reason of any of the mechanisms for which Turner contended. Robertson said it was possible the Hoogendam 2020 granulomas were caused by bacterial infection associated in some unexplained way to Essure. Further, it is possible that unidentified subjective factors associated with the patient in Hoogendam 2020 affected the kinetics of the foreign body response to the device so that it failed to successfully resolve.

2256 Second, if Hoogendam 2020 was accepted as a case where the risk of harm proposed by Turner eventuated, it would stand alone as the only example identified in all of the evidence. In those circumstances, Turner would have established no more than that there was a rare risk of ongoing chronic inflammation resulting in adverse health outcomes associated with Essure that was no different than with any other biomedical device. As Badylak said, there will be cases like that in Hoogendam 2020 with any medical device. In those circumstances, I would have found that Turner had not established that the risk was 'not insignificant'.[2277]

2257 Third, reasonableness must be assessed in the context of all of the steps taken by Bayer Essure (as Conceptus) and other Bayer entities, both pre- and post-FDA approval, in relation to the design, development, safety assessments and monitoring of Essure.

2258 Fourth, relevant context also includes the process of approval of Essure for commercial supply and the ongoing regulatory oversight by the FDA, TGA and other regulatory bodies set out in Chapter X of these reasons.

2259 Fifth, I take into account the training, information and warnings provided by the defendants to gynaecologists who were approved to perform the Essure procedure,

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2277 *Ultra Thoroughbred Racing Pty Ltd v Those Certain Underwriters* [2011] VSC 589 at [285] (J Forrest J).

set out in Chapter XX of these reasons.

2260 Sixth, it was reasonable for the defendants to expect that gynaecologists consulting with women who were considering permanent sterilisation and the Essure procedure would warn their patients about potential risks associated with the device and relevant contraindications. That would include gynaecologists warning patients about inherent risks associated with implantation of biomedical devices. Turner did not lead evidence to show that a rare outcome such as that in Hoogendam 2020, being the eventuation of a risk associated with implantation of any biomedical device, was outside the knowledge of gynaecologists who performed the Essure procedure.

2261 Seventh, there was clearly social utility in providing women a choice for permanent sterilisation which enjoyed some advantages compared to the available alternatives on a risk-benefit analysis.

2262 Eighth, the burden of taking precautions on the design failure case advanced by Turner was very considerable. Turner's case was, in effect, that Essure was 'a bad idea from the start' and that the device should never have been commercially supplied. Turner submitted that Essure 'was poorly conceived and poorly designed and should not have been put on the market without proper long-term safety testing'.[2278] The extensive process undertaken to design and obtain approval for commercial supply of Essure is set out in these reasons. I infer that the cost of re-conceiving and re-designing Essure in order to minimise the risk of an outcome like in Hoogendam 2020 would have been very considerable.

2263 I conclude that even if the case reported by Hoogendam 2020 was accepted as being an eventuation of the risk of harm identified by Turner, a reasonable person in the position of Bayer Essure or Bayer HealthCare would not have taken the precaution of reconceptualising and re-designing Essure.

2264 For similar reasons, had I found causation in relation to Hoogendam 2020, I would

[2278] T41 (TRA.500.001.0001_2 at 0042_19).

conclude that Turner had failed to establish breach on her 'failure to warn/failure to inform' case. While the burden on the defendants of taking precautions on that case would have been lower, it is not clear what further warning or information should have been provided to take account of the rare occurrence described in Hoogendam 2020. It is also unclear why a warning framed to take account of that possible eventuation of the risk would be more effective than the information already provided by the defendants in the training, PTMs, IFUs and PIBs, considered in the context of the skill of doctors who performed the Essure procedure and the duties they owed to their patients. Turner did not call Weatherill or any other gynaecologist who had performed the Essure procedure in Australia. Turner has not established that Bayer Essure, Bayer HealthCare, Gytech or AMSL breached their duty of care to group members by failing to give a warning or information about the possibility of a Hoogendam 2020 outcome.

2265 To establish the probability of harm, Turner relied on the following evidence. First was Robertson's opinion that Essure would cause persistent chronic inflammation in a small but not insignificant proportion of women; that persistent chronic inflammation has a 'very high likelihood' of triggering or exacerbating CPP;[2279] and that she expected it to cause AUB in a not insignificant proportion of women.[2280] Robertson based her opinion on her theories as to biological plausibility and the findings of chronic inflammation recorded in the Essure histological studies.[2281] She said the adverse events recorded in the MAUDE database and the outcomes of the causation studies aligned with and corroborated her opinion.[2282]

2266 Second was Korda's opinion that Essure 'often' caused pain and increased or worsened heavy menstrual bleeding, dysmenorrhea and damage to internal organs.[2283]

2279 Robertson at 118 (EXP.001.002.0015_2).
2280 Robertson at 181 (EXP.001.001.0127_2).
2281 Ibid at 14.
2282 Ibid at 171–181.
2283 Korda (EXP.001.001.0025).

2267 Third, Turner submitted that the 2015 FDA report[2284] prepared for the 2015 OGDAP meeting which summarised the reports of adverse events and information from the ARGUS database[2285] was 'further evidence of the prevalence of the harms associated with the device' for which she contended. Turner submitted that the 2023 interim results of the 522 study, 'while not conclusive of incidence of Adverse Events[,] further [support] a finding that the incidence is not insignificant'.[2286]

2268 Had I found that there was a risk that Essure would cause ongoing chronic inflammation resulting in CPP and AUB in some women, Turner's submissions and the evidence upon which she relied could not form the basis of a positive conclusion as to the degree of that risk. The quantifications expressed by Robertson in terms of 'not insignificant proportion of women' and 'very high likelihood' are based largely, if not entirely, on her theories of biological plausibility. There is no path of reasoning from any quantitative evidence identified by Robertson that makes her expression of opinion meaningful. Attribution of causation must be considered in the context that complaints of CPP and AUB are common in reproductive age women, that there are a large range of potential causes of those complaints, a number of which are themselves common, and that frequently no pathological cause is found for symptoms of CPP and AUB. In this context, the mere fact that complaints of this nature are frequently recorded in the MAUDE database, the 2015 FDA report and the ARGUS database means nothing in terms of attributing causation.

2269 The opinions of Robertson and Korda about the probability of harm are untethered to any quantitative evidence or clinical evidence of instances in which the identified harm has eventuated and is causally linked to Essure. In the circumstances, I attribute little weight to these opinions about the probability of harm.

2270 The defendants admit that Essure did cause some of the pleaded 'failure defects' and 'adverse events'. It is not reasonable to expect that a biomedical device such as Essure

2284 BAY-EDPA-0934554.
2285 TUR.002.001.0067_2.
2286 SBM.001.001.0004 at 319 [1072].

will be risk free. The established risks were the subject of adequate warnings by the defendants, and were in the nature of adverse outcomes that surgeons would expect to be associated with implantable devices and procedures such as the Essure procedure. Turner has not established that Bayer's design, testing or manufacture of the device was in some way deficient such that it fell below the reasonable standard of care. Reasonableness did not require that Bayer Essure, Bayer HealthCare, Gytech or AMSL provide further information or warnings to group members about those risks, or take any other step as a precaution against evaluation of a risk.

2271 I conclude that Turner has failed to establish any breach of the duty owed to her and group members by Bayer Essure, Bayer HealthCare, Gytech and/or AMSL.

XXV. ANSWERS TO COMMON QUESTIONS

Question 1: Over what time period was the Essure Device supplied in Australia and by which Defendants?

Bayer Essure supplied Essure from about 1999 to about 1 July 2013. Bayer HealthCare supplied Essure from about 1 July 2013 to 28 August 2017. Gytech supplied Essure from 19 Augst 2010 to 31 December 2014. AMSL supplied Essure from 1 January 2015 to around 28 August 2017.

Question 2: Were the Essure Devices goods within the meaning of sections 4 and 74A(2) of the Trade Practices Act and section 2 of the Australian Consumer Law?

Yes.

Question 3: Which, if any, of the Defendants were 'manufacturers' of the Essure Device within the meaning of section 74A of the *Trade Practices Act* and/or section 7 of the *Australian Consumer Law* (and, if any, during what time periods)?

Bayer HealthCare from 5 June 2013 to 9 February 2018. Bayer Essure from about 1999 to about 1 May 2014. Gytech between 19 August 2010 and 31 December 2014. AMSL between 1 January 2015 and 28 August 2017.

Question 4: Which, if any, of the Defendants promoted and marketed the Essure Device in Australia (and, if any, during what time periods)?

Bayer Essure from about 1999 to 2014. Bayer HealthCare from about July 2013 to 28 August 2017. Gytech from 19 August 2010 to 31 December 2014. AMSL from 1 January 2015 to 28 August 2017.

Question 5: Which, if any, of Bayer Australia Ltd, Gytech Pty Ltd and/or AMSL were a 'sponsor' of the Essure Device for the purposes of the *Therapeutic Goods Act* (and, if any, during what time period)?

Bayer Australia from about 29 January 2018 until 9 February 2018. Gytech from 19 August 2010 to 31 December 2014. AMSL from around 23 January 2015 to 28 January 2018.

Question 6: Was the Essure Device supplied for importation into Australia and, if so, by whom and during what time periods?

Yes. Bayer Essure from about 1999 to 1 July 2013. Bayer HealthCare from about 1 July 2013 to about August 2017.

Was the supply of the Essure Device into Australia:
(a) for resupply to consumers; and
(b) in trade or commerce between Australia and places outside of Australia;
and, if so, by whom and during what time periods?

(a) Yes, (b) Yes. Essure was supplied by Bayer Essure, and then Bayer HealthCare, to various Australian suppliers, including Gytech and AMSL, for distribution in Australia from around 1997 to 1 August 2017.

Was the Essure Device imported into and supplied to treating hospitals or doctors (the Intermediary Suppliers) for resupply to consumers and, if so, by whom and during what time periods?

Yes. Bepen Pty Ltd between about 1 December 1999 and about 6 November 2000. Conceptus (Australia) Pty Ltd between about 6 November 2000 and about January 2005. N Stenning & Co Pty Ltd between about January 2005 and about August 2010. Gytech between about August 2010 and about January 2015. AMSL between about January 2015 and August 2017.

Was the supply of the Essure Device to Intermediary Suppliers and to the Plaintiff and Group Members in trade or commerce in Australia?

Yes.

Question 7: In respect of the Essure Device micro-insert (the Essure Insert):
(a) Was it comprised of any (and if so, which) of the following?
(i)A 316L stainless steel 'inner coil';
(ii) A chromium-doped nitinol (nickel titanium alloy) 'outer coil';
(iii) Polyethylene terephthalate fibres;
(iv) "platinum-iridium bands and bump";
(v) silver-tin solder?
(b) Was it a spring-like device that:
(i) was wound down, in the disposable delivery system, to approximately 4 cm in length and 0.8 mm in diameter;
(ii) expanded, once deployed, to approximately 2.0 mm in diameter?
(c) Was a cross-section of the chromium- doped nitinol (nickel-titanium alloy) 'outer

coil' of the micro-insert "rectangular with sharp corners"?

(a) Yes, (b) Yes, (c) No.

Question 8: Was the purpose of the Essure Device:

(a) to prevent pregnancy through implantation of a mechanical insert that could be left permanently in the body; or

(b) to provide patients with permanent birth control (contraception) by bilateral occlusion of the fallopian tubes?

Yes to both.

Question 9: Is the Essure Device designed to operate in any (and if so, which) of the following ways:

(a) via its initial presence, by triggering an acute inflammatory response in the fallopian tubes and/or endometrium?

(b) via its continued presence, by triggering a foreign body response in the fallopian tubes and/or endometrium?

(c) by disrupting the soft tissue in the walls of the fallopian tube once anchored?

(d) via its continued presence, by triggering a chronic inflammatory response in the fallopian tubes and/or endometrium?

(e) via the acute inflammatory response and/or chronic inflammatory response and/or foreign body response, by resulting in tissue in-growth into the coils of the Essure Insert and around the PET fibres?

(f) to the extent that the answer to the previous question is 'yes', by occluding the fallopian tube in which the Essure device was located?

(g) to the extent that the answer to the previous question is 'yes', by preventing pregnancy?

(h) by operating as an intrauterine device?

(a) Yes in the fallopian tubes, no in the endometrium, (b) Yes in the fallopian tubes, no in the endometrium, (c) Yes, (d) Yes in the fallopian tube, no in the endometrium, (e) Yes, (f) Yes, (g) Yes, (h) No.

Question 10: By reason of any of the matters alleged in ASOC to [17], did the Essure Insert cause any of the following:

(a) Disruption of the inner layers of the uterine horn and/or the fallopian tubes?

(b) Initial acute inflammation in the fallopian tubes and/or endometrium?

(c) Ongoing chronic inflammation in the fallopian tubes and/or endometrium?

(d) A foreign body response in the fallopian tubes and/or endometrium and/or uterine cavity?

(the Inherent Defects).

(a) Yes in the fallopian tubes, no in the uterine horn, (b) Yes in the fallopian tubes, no in the endometrium, (c) Yes in the fallopian tubes, no in the endometrium, (d) Yes in the fallopian tubes, no in the endometrium, no in the uterine cavity.

Question 11: By reason of any of the matters alleged in ASOC to [17], was there a risk that the design and composition of the Essure Insert would, following implantation, do any of

the following:

(a) migrate;
(b) be expulsed from the fallopian tube and/or uterus;
(c) break or fragment;
(d) corrode;
(e) fatigue;
(f) perforate the fallopian tube, uterus or other organs such as the bowel;
(g) leach nickel or other metals into the body of the recipient;

(the Failure Defects).

(a) Yes, (b) Yes, (c) Yes, in the context of implantation or explantation of the device, (d) Yes, (e) No, (f) Yes, (g) Yes.

Question 12: To the extent that they are made out, did any one of the Failure Defects and/or the Inherent Defects (including in any combination) give rise to a risk that the Essure Insert would:

(a) cause or exacerbate pelvic pain (including dysmenorrhea, being intense uterine cramping and pain);
(b) cause or exacerbate serious continuing chronic and/or recurring pain;
(c) cause or exacerbate menorrhagia (being heavy menstrual bleeding);
(d) cause damage to internal organs;

(the Adverse Events).

(a) Yes, (b) No, (c) No, (d) Yes.

Question 13: Once the Essure insert is anchored into the fallopian tube(s):

(a) was it designed to be removed;
(b) was it unlikely to be able to be removed without surgery; and
(c) could it likely only be removed by:
(i) a salpingectomy; Or
(ii) a hysterectomy?

(a) No, (b) Yes, (c) Yes.

In the event that a woman experienced Adverse Events or other complications associated with the Essure Insert, would she be unable to resolve the Adverse Events or other complications through removal of the Essure Insert without abdominal surgery and likely the removal of one or more organs (the Removal Limitation)?

Yes.

Question 14: What information was provided about risks associated with the Essure Device, during what time periods and was this information provided to:

(a) recipients of the Essure Device in Australia (consumers); and/or
(b) users of the Essure Device in Australia (healthcare practitioners and healthcare institutions);

and if so, by which Defendants?

(a) Consumers:

(i) Fifteen PIBs were published in Australia during the commercial supply period.
(ii) Webpages were published in Australia during the commercial supply period.
(iii) Information conveyed by gynaecologists in consultation with consumers.
(iv) Informed consent protocols were used as part of clinical trials conducted from about 1997.

(b) Healthcare practitioners and institutions:

(i) Eleven IFUs were distributed to gynaecologists in Australia in the period March 2001 to October 2017.
(ii) At least three PTMs were distributed to physicians in Australia during the period 2000 to 28 August 2017.
(iii) Training was provided to gynaecologists during the commercial supply period.

The clinical trial protocols were provided by Bayer Essure. The PIBs, IFUs, PTMs and physician training programs were provided to the Australian distributors by Bayer Essure from about 1999 to 1 July 2013, and by Bayer HealthCare from 1 July 2013 to 28 August 2017. It is unclear which entity published the webpages. Gytech and AMSL provided the PIBs, IFUs, PTMs and the training to gynaecologists from 19 August 2010 to 31 December 2014, and 1 January 2015 to 28 August 2017 respectively.

Question 15: Were the Plaintiff and Group Members each 'consumers' within the meaning of section 4B of the *Trade Practices Act* and/or section 3 of the *Australian Consumer Law*?

No for those group members who received Essure as part of the clinical trials. Otherwise yes.

Question 16: Were the Essure Devices:

(a) not of 'merchantable quality' within the meaning of section 74D(1) and 74D(3) of the *Trade Practices Act*; and/or

(b) not of 'acceptable quality' within the meaning of sub-sections 54 (2) and (3) of the *Australian Consumer Law*;

by reason of any or all of the Inherent Defects, the Failure Defects, the risk of Adverse Events and/or the Removal Limitation?

No.

Question 17: Did the Essure Device have:

(a) a 'defect' within the meaning of s 75AC of the *Trade Practices Act*; and/or

(b) a 'safety defect' within the meaning of section 9 of the *Australian Consumer Law*;

by reason of any or all of the:

(c) Inherent Defects, the Failure Defects, the risk of Adverse Events and/or the Removal Limitation; and/or

(d) relevant matters identified in s 9(2) of the *Australian Consumer Law* or s 75AC(2) of the *Trade Practices Act*?

No.

If the answer to any part of this question is "yes", for what time period was this the case?

Not necessary to answer.

Question 18: Having regard to the answers to the preceding question, are any of the Defendants (and if so, which and in respect of which defects / safety defects, and for what time periods) not liable for damages to the Plaintiff and/or Group Members pursuant to the statutory causes of action alleged against them under s 75AC of the *Trade Practices Act 1974*, and/or s 9 of the *Australian Consumer Law*, because of the defences in:

(a) s 75AK(1)(a) of the *Trade Practices Act* and/or s 142(a) of the *Australian Consumer Law*, that any defect or safety defect in the Essure Device did not exist at the time when it was supplied by its actual manufacturer;

(b) s 75AK(1)(c) of the *Trade Practices Act* and/or s 142(c) of the *Australian Consumer Law*, that the state of scientific or technical knowledge at the time when the Essure Device was supplied by its manufacturer was not such as to enable that defect or safety defect to be discovered?

Not necessary to answer.

Question 19: Was it reasonably foreseeable (and if so, to which Defendant/s, and during which time period/s) that loss or damage would be suffered by the Plaintiff and Group Members as a result of the Inherent Defects, the Failure Defects, the risk of Adverse Events and/or the Removal Limitation?

(a) Inherent defects – No, (b) Failure defects – Yes, in relation to perforation, migration, expulsion, corrosion and leaching to the extent of delayed type hypersensitivity reaction to nickel, and breakage and fragmentation in the process of surgical removal. No, in relation to the other failure defects, (c) Risk of adverse events – Yes, to the extent that pain or increased pain, altered bleeding, and damage to internal organs may be associated with incidents of expulsion, migration, perforation, breakage and fragmentation with surgical removal or DTHR to nickel, (d) Removal limitation – Yes.

Question 20: Was it reasonably foreseeable (and if so, to which Defendant/s, and during which time period/s) that:

(a) Individuals who were considering a procedure to implant the Essure Device or Devices may suffer harm arising from the Essure Device or Devices if they were not warned (or not adequately warned) about the Inherent Defects, the Failure Defects, the risk of Adverse Events and the Removal Limitation; and/or

(b) Individuals who had a procedure to implant the Essure Device or Devices may suffer harm (or further harm) arising from the Essure Device or Devices if information disclosing the Inherent Defects, Failure Defects and/or the risk of Adverse Events was not made available to those individuals?

(a) Yes, to the extent the risks existed.

(i) For Bayer Essure from at least 1 December 1999.
(ii) For Bayer HealthCare from at least 1 July 2013.
(iii) For Gytech from 19 August 2010.
(iv) For AMSL from 1 January 2015.

(b) No.

Question 21: Did any one or more of the Defendants know or ought they to have known that the Essure Device had the Inherent Defects, the Failure Defects, the risk of Adverse Events and/or the Removal Limitation (and if so who and in what time periods?)

Yes, to the extent the risks existed.

(a) For Bayer Essure from at least 1999.
(b) For Bayer HealthCare from at least 1 July 2013.
(c) For Gytech from 19 August 2010.
(d) For AMSL from 1 January 2015.

Question 22: In the period between about 1999 and about 2018, what duty did Bayer Essure Inc owe to the Plaintiff and each Group Member?

As a manufacturer, Bayer Essure owed a duty to take reasonable care to avoid reasonably foreseeable risks of harm to the users of Essure, which included the plaintiff and group members.

Question 23: In the period between about 2014 and about 2018, what duty did Bayer Healthcare LLC owe to the Plaintiff and each Group Member?

As a manufacturer, Bayer HealthCare owed a duty to take reasonable care to avoid reasonably foreseeable risks of harm to the users of Essure, which included the plaintiff and group members.

Question 24: In the period from about 2010 onwards, what duty did Gytech Pty Ltd owe to the Plaintiff and each Group Member?

Gytech owed a duty to take reasonable care to avoid injury to the users of Essure, which included the plaintiff and group members.

Question 25: In the period from about 2015 onwards, what duty did Australasian Medical and Scientific Limited owe to the Plaintiff and each Group Member?

AMSL owed a duty to take reasonable care to avoid injury to the users of Essure, including the plaintiff and group members.

Question 26: In the period from about 2014 onwards, what duty did Bayer Australia Limited owe to the Plaintiff and each Group Member?

None.

Question 27: If any duty is identified in the answers to questions 35-36, did Bayer Essure Inc and/or Bayer Healthcare LLC breach and if so on and from what dates did they breach that duty in:

(a) designing, developing, manufacturing; and/or
(b) distributing in Australia and supplying for sale in Australia,

the Essure Device with the Inherent Defects, the Failure Defects, the risk of Adverse events and the Removal Limitation?

No.

Question 28: If any duty is identified in the answers to questions 35-39, did Bayer Essure Inc, Bayer Healthcare LLC, Gytech Pty Ltd, Australasian Medical and Scientific Limited and/or Bayer Australia Ltd breach and if so on and from what dates did they breach that duty in:

(a) promoting or marketing the Essure Device without warning or adequate warning of the Inherent Defects, the Failure Defects, the risk of Adverse Events and/or the Removal Limitation; and/or

(b) failing to make available to the Plaintiff and Group Members who had already received the Essure Device information disclosing the Inherent Defects, Failure Defects and/or the risk of Adverse Events?

No.

Question 29: Are the claims of group members under s 74D of the *Trade Practices Act* who had their devices supplied on a date between 13 July 2004 and 28 June 2007 statute barred under s 74J(3), 87F(1)(b), 87H(1) of the *Trade Practices Act*, unless they obtain an extension of the long-stop period under s 87H(1)(b)?

Yes.

Are the claims of group members under s 75AD of the *Trade Practices Act* who had their devices supplied on a date between 13 July 2004 and 28 June 2007 statute barred under s 75AO and 87F(1)(b), 87H(1) of the *Trade Practices Act*, unless they obtain an extension of the long-stop period under s 87H(1)(b)?

Yes.

Are the claims of group members under s 74D of the *Trade Practices Act* who had their devices supplied on a date before 13 July 2004 statute barred under s 74J(3)?

No, but they are subject to the defence in s 74J(3).

Are the claims of group members under s 75AD of the *Trade Practices Act* who had their devices supplied on a date before 13 July 2004 statute barred under s 75AO(2)?

Yes.

Question 30: Did Bayer Essure Inc and/or Bayer Healthcare Inc design, develop and/or manufacture the Essure Device and, if so, during what time periods?

Yes. Bayer HealthCare designed, developed and manufactured Essure from around 5 June 2013. Bayer Essure, as Conceptus, designed, developed and manufactured Essure from 1997 to 1 May 2014.

Question 31: Did Bayer Australia, Bayer Essure, Bayer HealthCare LLC, Gytech and/or AMSL (and if so which) make available to the Plaintiff and Group Members who had

already received the Essure Device information disclosing the Inherent Defects, the Failure Defects and/or the risk of Adverse Events and, if so, when?

Yes. On 30 August 2017, AMSL in consultation with the TGA issued a hazard alert referring to symptoms including chronic bleeding, perforation, migration and the requirement for abdominal surgery or hysterectomy for device removal.

CERTIFICATE

I certify that this and the 744 preceding pages are a true copy of the reasons for Ruling of the Honourable Justice Keogh of the Supreme Court of Victoria delivered on 10 December 2024.

DATED this 10th day of December 2024.

Associate

SCHEDULE 1

RESULTS OF CONCEPTUS BIOCOMPATIBILITY STUDIES[1]

Table II.3: Biocompatibility Studies of the Essure **Micro-insert**
Category: Implant Device
Contact: Tissue/Bone
Duration: Permanent (>30 days)

Table II.3: Biocompatibility Studies of the Essure **Micro-insert**				
Biocompatibility Study	**Study Description**	**Study Criteria**	**Results**	**Data Location**
Cytotoxicity using the ISO Elution Method in the L-929 Mouse Fibroblast Cell Line. Protocol # • MG064-100 • V0014-130	A rapid, standardized, and sensitive means to determine whether a material contains significant quantities of biologically harmful extractables. The cell or tissue culture method is a good predictor of biocompatibility when used together with other appropriate tests.	•Negative controls have 0 reactivity •Positive controls have 3-4 reactivity •Test Samples have 2 or less reactivity	**Pass** – Non-cytotoxic Both negative controls and test samples rated 0.	Appendix 1 Appendix 2 Appendix 3 Appendix 21 Appendix 22
ISO **Sensitization** Study in Guinea Pig with Saline and Cotton Seed Oil Extract Protocol # • T1261-300 • T1261-301	Magnusson-Kligman Maximization Method: Dermal sensitization is performed to demonstrate the potential of the device to elicite [sic] an immunological response through its contact with the skin. This reaction is primarily due to substances that could leach out of a material. Guinea pigs are used because they have been shown to be the best animal model for human allergic contact dermatitis.	•Compare dermal irritation of controls to test article. •If controls have irritation >1 use worst-case control for comparison.	**Pass** – no evidence of delayed dermal contact sensitization All Test Samples and Controls have 0 rating	Appendix 4
ISO Subchronic **Vaginal**	Assessment of the material under test to	•Microscopic evaluation of	**Pass** – Non-irritant	Appendix 5

[1] BAY-ESSURE-0006158 at 30–33

Irritation in Rabbit with Histopathology. (prolonged exposure) Protocol # • T1265-802/S	produce irritation of the vaginal tissue. Extracts applied to the vaginal mucosa remain in contact with the tissue for an extended time, exaggerating exposure; the vaginal epithelium of the rabbit is only one cell thick and thus particularly sensitive to irritants; and a microscopic scoring system is available, providing a cellular basis for judging the irritant potential of a material.	vaginal tissue compared to controls. •Irritation rating value <8 acceptable.	• Test Samples rating average = 5 • Control rating average = 4	
ISO **Acute Systemic Toxicity** Study in the Mouse Protocol # • T1264-500	Determines the harmful effects of either single or multiple exposures to materials and/or extracts within a short time after exposure. Mice are injected with two extracts (saline and cottonseed oil) and observed for 3 days to determine toxic effects of any leachables present in the extracts.	•Compare reaction of mice injected with extract from micro-insert and the control extract.	**Pass** – no evidence of systemic toxicity No evidence of systemic toxicity from controls or micro-insert.	Appendix 6
26 week **Sub-Chronic Toxicity** with Intramuscular Implant in Rabbits Protocol # • 7176-102	Determines the harmful effects that can occur as a result of repeated daily dosing of a substance to experimental animals over a portion of their life span. 20 rabbit[s] tested with control at each subcutaneous site.	•Histopathology evaluation of tissue at implant sites. •Necroscopy of external features of animals •Macroscopic evaluation of organs. •Organ-to-body weight %	**Pass** – No evidence of systemic toxicity or irritancy. Expected response to PET fibers in micro-insert.	Appendix 7
Genotoxicity •In Vitro Chromosomal Aberration Study in Mammalian Cells Protocol #: MG016-130 •Mouse Lymphoma Assay Protocol #: L5178Y TK $^{+/-}$ •Bacterial Reverse Mutation Study	Tests apply to mammalian cells to determine gene mutations changes in chromosonal [sic] structure, or other DNA or gene changes that are caused by the test materials.	•Comparison of % cell aberration between controls and micro-insert. •Comparison of mutation of the mouse lymphoma cells to positive controls, negative controls and the micro-insert. •Mouse Bone Marrow Toxicity compared polychromatic erythrocytes	**Pass** – Non-genotoxic •Pass cell aberration. •No induction of mutations of the mouse lymphoma cells •Not mutagenic under Reverse Mutation test condition •Not genotoxic to the mouse •Positive and negative	Appendix 8 Appendix 9 Appendix 10 Appendix 11

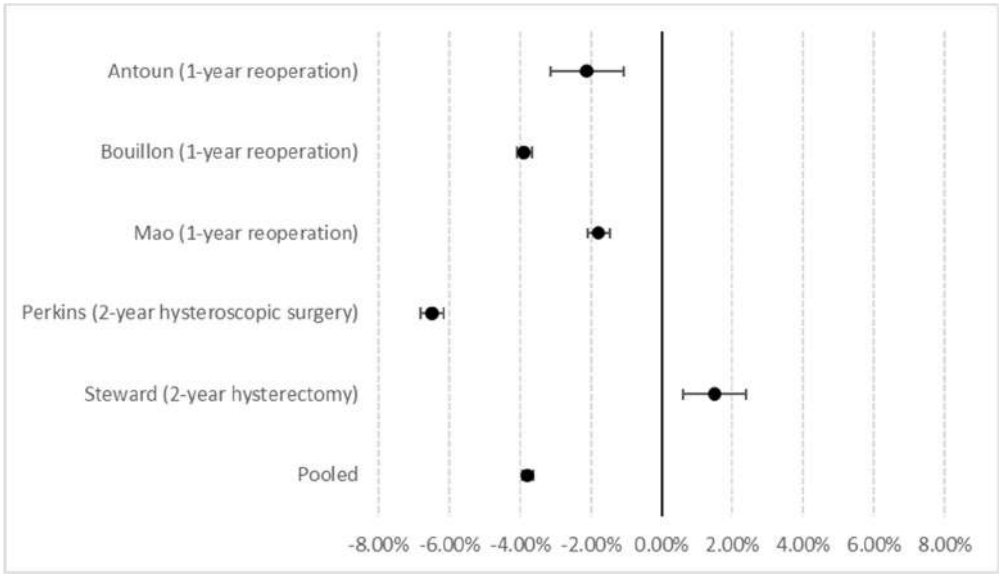
Protocol #: MG114-211, MG114-212		(PCEs) to total erythrocytes.	controls performed as anticipated.	
12-week **Mutagenicity** study of Essure Implanted Subcutaneously in Female *p53–/-cll* Double Transgenic Mice Protocol # • G128-01	Determine the potential in vivo mutagenicity of the test article following subcutaneous implantation into mice containing a knockout of one copy of the *p53* tumor suppressor gene, and a lambda-shuttle vector containing the *cll* mutagenesis target gene.	•Palpation at implant site to note presence of masses. •Mortality comparison •50% or less increase in mutant frequency (mf). •Positive control fails mf.	**Pass** – Non mutagenic •No adverse toxicological effects •No increase in gene mutations at the site of implantation	Appendix 12
ISO Surgical **Muscle Implantation** in the Rabbit with Histopathology at 1 week, 4 weeks and 12 weeks Protocol # • T1247-801 • T1247-804 • T1247-812 • TH035-800	Evaluates the local pathological effects on living tissue at both the gross level and microscopic level, to a material that is surgically implanted into the muscle of rabbits. 1-week: 3 test rabbits /3 control rabbits 4-week: 3 test rabbits /3 control rabbits 12-week: 3 test rabbits /3 control rabbits	• Macroscopic scoring of test implant compared to negative controls. •Microscopic scoring of implants and negative controls. •Histological evaluation of test implants for adverse host reaction (foreign body reaction with evidence of encapsulation or necrosis) at 12 weeks. •Expected tissue response to PET fibers	**Pass** •Rating of 0 for macroscopic evaluation of implant and controls at all time points. •Implant rated a slight irritant as compared to controls at 1 week. •Implant rated a moderate irritant as compared to controls at 4 weeks. •Implant rated a severe irritant as compared to controls at 12 weeks. •No adverse host reaction.	Appendix 13 Appendix 14 Appendix 15
ISO **Vaginal Irritation** in Rabbit with Histopathology, (repeat exposure) Protocol # • T1265-801	Assessment of the material extracts under test to produce irritation of the vaginal tissue. Saline (SC) and Cotton Seed Oil (CSO) extracts were used.	•Microscopic evaluation of vaginal tissue compared to controls. •Irritation rating value <8 acceptable for solutions.	**Pass** – Non-irritant •Test Samples rating average – 4 (SC) and 4 (CSO) •Control rating average= 4 (SC) and 5 (CSO)	Appendix 18

Table II.4: Biocompatibility Studies of the Essure **Delivery System**
Category: Surface Device
Contact: Mucosal Membrane
Duration: Limited (≤ 24 hours)

Table II.4: Biocompatibility Studies of the Essure **Delivery System**				
Biocompatibility Study	**Study Description**	**Study Criteria**	**Results**	**Data Location**
Cytotoxicity Protocol # • MG064-100 • V0014-130	See description in Implant Category. Cytotoxicity test methods are useful for screening materials that may be used in medical devices because they serve to separate reactive from nonreactive materials, providing predictive evidence of material biocompatibility	•Negative controls have 0 reactivity •Positive controls have 3-4 reactivity •Test Samples have 2 or less reactivity	**Pass** – Non-cytotoxic •Negative controls rated 0. •Positive controls rated 4. •Delivery Catheter samples rated 2. •Introducer samples rated 0.	Appendix 16 Appendix 20 Appendix 2
Sensitization Protocol # • T1261-300 • T1261-301	Magnusson-Kligman Maximization Method: Dermal sensitization is performed to demonstrate the potential of the device to elicite [sic] an immunological response through its contact with the skin. This reaction is primarily due to substances that could leach out of a material. Guinea pigs are used because they have been shown to be the best animal model for human allergic contact dermatitis.	•Compare dermal irritation of controls to test article. •If controls have irritation >1 use worst-case control for comparison.	**Pass** – no evidence of delayed dermal contact sensitization •All Test Samples and Controls have 0 rating	Appendix 17 Appendix 4
ISO **Vaginal Irritation** in Rabbit. (repeat exposure) Protocol # • T1265-801	Assessment of the material under test to produce irritation of the vaginal tissue.	•Microscopic evaluation of vaginal tissue compared to controls. •Irritation rating value <8 acceptable for solutions.	**Pass** – Non-irritant •Test Samples rating average = 1 and 3 •Control rating Average = 2 and 3.	Appendix 18 Appendix 19

SCHEDULE 2

Pooled analysis for reoperation - applying methodology as set out in Gebski primary report, Appendix 1



	laparoscopic			hysteroscopic			difference				
Author	N	events	rate (%)	N	event	rate (%)	%	lower 95% CI	upper 95% CI	weight (inv. var. method)	weight* diff
Antoun (1-year reoperation)	2400	8	0.33%	902	22	2.44%	-2.11%	-3.14%	-1.07%	36017	-758
Bouillon (1-year reoperation)	34054	601	1.76%	71303	4032	5.65%	-3.89%	-4.11%	-3.67%	795346	-30938
Mao (1-year reoperation)	44278	99	0.22%	8048	162	2.01%	-1.79%	-2.10%	-1.48%	399811	-7154
Perkins (2-year hysteroscopic surgery)	42391	302	0.71%	27724	1998	7.21%	-6.49%	-6.81%	-6.18%	387749	-25182
Steward (2-year hysterectomy)	2673	94	3.52%	2673	54	2.02%	1.50%	0.62%	2.38%	49755	745
Pooled							**-3.79%**	**-3.94%**	**-3.64%**	**1668677**	**-63288**

SCHEDULE 3

Australian Essure class action

Aide Memoire - Australian IFU Warnings (clean)

The documents which are summarised in this aide memoire have the following document ID numbers:

Document ID	Pinpoint
BES.001.001.0029	Entire document
BES.001.001.0033	Entire document
BAY-EDPA-3576314	[3576353] to [3576376] / Pages 40 to 63
BAY-EDPA-2425528	[2425571] to [2425594] / Pages 44 to 67
GYT.001.001.3669	[3696] to [3699] / Pages 28 to 31
GYT.001.001.4299	[4326] to [4329] / Pages 27 to 30
BAU.001.001.4133	[0027] to [0030] / Pages 28 to 31
BAU.001.001.0174	Entire document
BAG.001.001.2362	[0027] to [0030] / Pages 28 to 31
BAU.001.001.5676	[0027] to [0030] / Pages 28 to 31
AMS.001.001.0010	[0083] to [0086] / Pages 84 to 87

TABLE 1: MECHANISM OF ACTION - ASOC 18

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
I. Device Description/Mechanism of Action … When the STOP micro-coil expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the device elicits an intended benign tissue response, resulting in tissue in-growth into the device that anchors the device firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[1]	**I. Micro-insert Description/Mechanism of Action** … When the Essure micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[2]	**I. Micro-insert Description/Mechanism of Action** … When the Essure Micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[3]	**II. Mechanism of Action** … When the Essure Micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[4]	**II. Mechanism of Action** … When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors in the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[5]	**II. Mechanism of Action** … When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[6]	**II. Mechanism of Action** … When the Essure micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[7]	**II. MECHANISM OF ACTION** … When the Essure micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[8]	**II. Mechanism of Action** … When the Essure micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[9]	**II. Mechanism of Action** … When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[10]	**II. Mechanism of Action** … When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert into firmly into the fallopian tube. This benign tissue response is local fibrotic and occlusive in nature.[11]

[1] [BES.001.001.0029] at [0001] / page 2.
[2] [BES.001.001.0033] at [0001] / page 2.
[3] [BAY-EDPA-3576314] at [3576353] / page 40.
[4] [BAY-EDPA-2425528] at [2425571] / page 44.
[5] [GYT.001.001.3669] at [3696] / page 28.
[6] [GYT.001.001.4299] at [4326] / page 27.
[7] [BAU.001.001.4133] at [0027] / page 28.
[8] [BAU.001.001.0174] at [BAU.001.001.0174] to [0001] / pages 1 to 2.
[9] [BAG.001.001.2362] at [0027] / page 28.
[10] [BAU.001.001.5676] at [0027] / page 28.
[11] [AMS.001.001.0010] at [0083] / page 84.

TABLE 2: MIGRATION - ASOC 19(a)(i)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	2. ~ Mar 02 - Sept 04 **BES.001.001.0033** (Entire document)	3. ~ Sept 04 - Mar 06 **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	4. ~ Mar 06 - Sept 09 **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	5. ~ Sept 09 - Oct 10 **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	6. ~ Sept 11 - Sept 12 **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	7. ~ Sept 12 - Feb 13 **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	8. ~ Feb 13 - Nov 13 **BAU.001.001.0174** (Entire document)	9. ~ Nov 13 - Dec 14 **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	10. ~ Dec 14 - 2015 **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	11. ~ 2015 - Oct 17 **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
VII. Possible Adverse Effects … **C. Risks Associated with STOP Device Wearing** There is a risk that the STOP device could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the device(s), and surgery may be required to remove the device(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events.[12] … **X. Device Removal** … A STOP device that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingostomy or salpingectomy accomplished via laparoscopy or laparotomy.[13]	**VI. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-Insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events.[14] … **XII. Micro-Insert Removal** … A Essure micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingostomy or salpingectomy accomplished via laparoscopy or laparotomy.[15]	**VI. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[16] … **XII. Micro-insert Removal** … An Essure micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[17]	**VII. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional X-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[18] … **XIII. Essure Micro-insert Removal** … An Essure micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[19]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[20] … **XIII. Essure micro-insert removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[21]	**VII. Possible adverse effects** … **B. Risks associated with micro-insert placement procedure** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[22] … **XII. Essure micro-insert removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[23]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[24] … **XII. Essure Micro-Insert Removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[25]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional X-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[26] … **XII. Essure Micro-Insert Removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[27]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[28] … **XII. Essure micro-insert removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[29]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[30] … **XII. Essure micro-insert removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[31]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[32] … **XII. Essure micro-insert removal** … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[33]

[12] [BES.001.001.0029] at [0006] / page 7.
[13] [BES.001.001.0029] at [0015] / page 16.
[14] [BES.001.001.0033] at [0004] / page 5.
[15] [BES.001.001.0033] at [0016] / page 17.
[16] [BAY-EDPA-3576314] at [3576358] / page 45.
[17] [BAY-EDPA-3576314] at [3576373] / page 60.
[18] [BAY-EDPA-2425528] at [2425576] / page 49.
[19] [BAY-EDPA-2425528] at [2425592] / page 65.
[20] [GYT.001.001.3669] at [3696] / page 28.
[21] [GYT.001.001.3669] at [3699] / page 31.
[22] [GYT.001.001.4299] at [4326] / page 27.
[23] [GYT.001.001.4299] at [4329] / page 30.
[24] [BAU.001.001.4133] at [0027] / page 28.
[25] [BAU.001.001.4133] at [0030] / page 31.
[26] [BAU.001.001.0174] at [0006] / page 7.
[27] [BAU.001.001.0174] at [0024] / page 25.
[28] [BAG.001.001.2362] at [0027] / page 28.
[29] [BAG.001.001.2362] at [0030] / page 31.
[30] [BAU.001.001.5676] at [0027] / page 28.
[31] [BAU.001.001.5676] at [0030] / page 31.
[32] [AMS.001.001.0010] at [0083] / page 84.
[33] [AMS.001.001.0010] at [0086] / page 87.

TABLE 3: EXPULSION - ASOC 19(a)(ii)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	2. ~ Mar 02 - Sept 04 **BES.001.001.0033** (Entire document)	3. ~ Sept 04 - Mar 06 **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	4. ~ Mar 06 - Sept 09 **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	5. ~ Sept 09 - Oct 10 **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	6. ~ Sept 11 - Sept 12 **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	7. ~ Sept 12 - Feb 13 **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	8. ~ Feb 13 - Nov 13 **BAU.001.001.0174** (Entire document)	9. ~ Nov 13 - Dec 14 **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	10. ~ Dec 14 - 2015 **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	11. ~ 2015 - Oct 17 **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
VI. Clinical Data Summary As of December 31, 2000, 226 patients have undergone device placement in a clinical study.[34] … The following were reported as being likely related to the STOP device: … Expulsion of the STOP device- <1%[35] **VII. Possible Adverse Effects** … **C. Risks Associated with STOP Device Wearing** There is a risk that the STOP device could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the device(s), and surgery may be required to remove the device(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[36]	**VI. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-Insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events.[37]	**VI. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[38]	**VII. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional X-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[39]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[40]	**VI. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[41]	**VII. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[42]	**VII. Possible Adverse Effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[43]	**VII. Possible adverse effects** … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[44]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[45]	**VII. Possible adverse effects** … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[46]

[34] BES.001.001.0029] at [0003] / page 4.
[35] [BES.001.001.0029] at [0004] / page 5.
[36] [BES.001.001.0029] at [0006] / page 7.
[37] [BES.001.001.0033] at [0004] / page 5.
[38] [BAY-EDPA-3576314] at [3576358] / page 45.
[39] [BAY-EDPA-2425528] at [2425576] / page 49.
[40] [GYT.001.001.3669] at [3696] / page 28.
[41] [GYT.001.001.4299] at [4326] / page 27.
[42] [BAU.001.001.4133] at [0027] / page 28.
[43] [BAU.001.001.0174] at [0006] / page 7.
[44] [BAG.001.001.2362] at [0027] / page 28.
[45] [BAU.001.001.5676] at [0027] / page 28.
[46] [AMS.001.001.0010] at [0083] / page 84.

TABLE 4: BREAK OR FRAGMENT - ASOC 19(a)(iii)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
VI. Clinical Data Summary 41 patients in the study have reported adverse events. Of those, 14 adverse events are considered to be related to the STOP device. The following were reported as being likely related to the STOP device: Broken tip of device retained in tube - <1%[47] **VII. Possible Adverse Effects** … **B. Risks Associated with the Device Placement Procedure** … There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device (see section X, Device Removal). If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device *in vivo*. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.[48] … **X. Device Removal** … If the physician is not completely satisfied that the entire STOP device has been removed from the fallopian tube, another device should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a device fragment remains *in vivo*.[49]	**VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 20 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[50] … **XII. Micro-Insert Removal** … If the physician is not completely satisfied that the entire Essure micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[51]	**VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If **18** or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-Insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[52] … **XII. Micro-insert Removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should **NOT** be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains *in vivo*.*[53]*	**VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, Essure Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[54] … **XIII. Essure Micro-insert Removal** … If the physician is not completely satisfied that the entire Essure micro-insert has been removed from the fallopian tube, another micro-insert should **NOT** be placed in that tube and a post-placement X-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[55]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** ... There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[56] … **XIII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should **NOT** be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[57]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[58] … **XII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should **NOT** be placed in that tube and a post-placement X-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[59]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[60] … **XII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should **NOT** be placed in that tube and a post-placement X-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[61]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, Essure micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[62] … **XII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire Essure micro-insert has been removed from the fallopian tube, another micro-insert should **NOT** be placed in that tube and a post-placement X-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[63]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[64] … **XII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[65]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[66] … **XII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[67]	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[68] … **XII. Essure micro-insert removal** … If the physician is not completely satisfied that the entire **Essure** micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains *in vivo*.[69]

[47] [BES.001.001.0029] at [0004] / page 5.
[48] [BES.001.001.0029] at [0006] / page 7.
[49] [BES.001.001.0029] at [0014] / page 15.
[50] [BES.001.001.0033] at [0003] / page 4.
[51] [BES.001.001.0033] at [0016] / page 17.
[52] [BAY-EDPA-3576314] at [3576357] / page 44.
[53] [BAY-EDPA-3576314] at [3576373] / page 60.
[54] [BAY-EDPA-2425528] at [2425575] / page 48.
[55] [BAY-EDPA-2425528] at [2425592] / page 65.
[56] [GYT.001.001.3669] at [3696] / page 28.
[57] [GYT.001.001.3669] at [3699] / page 31.
[58] [GYT.001.001.4299] at [4326] / page 27.
[59] [GYT.001.001.4299] at [4329] / page 30.
[60] [BAU.001.001.4133] at [0027] / page 28.
[61] [BAU.001.001.4133] at [0030] / page 31.
[62] [BAU.001.001.0174] at [0005] / page 6.
[63] [BAU.001.001.0174] at [0023] / page 24.
[64] [BAG.001.001.2362] at [0027] / page 28.
[65] [BAG.001.001.2362] at [0030] / page 31.
[66] [BAU.001.001.5676] at [0027] / page 28.
[67] [BAU.001.001.5676] at [0030] / page 31.
[68] [AMS.001.001.0010] at [0083] / page 84.
[69] [AMS.001.001.0010] at [0086] / page 87.

TABLE 5: PERFORATION - ASOC 19(b)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
IV. Warnings … When introducing the STOP device into the fallopian tube, never advance the device(s) against resistance.[70] Do not continue to advance the STOP System once the positioning bump on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory device placement or tubal / uterine perforation.[71] If a tubal perforation occurs, do not continue with STOP device placement attempt.[72] … **V. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[73] … **VI. Clinical Data Summary** As of December 31, 2000, 226 patients have undergone device placement in a clinical study.[74] … 41 patients in the study have reported adverse events. Of those, 14 adverse events are considered to be related to the STOP device. … The following were reported as being likely related to the STOP device: Uterine perforation with the device- 1%[75] …	**IV. Warnings** … When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[81] Do not continue to advance the Essure System once the positioning bump on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal / uterine perforation.[82] If a tubal perforation occurs or is suspected, do not continue with Essure micro-insert placement attempt.[83] … **V. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[84] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** **…** There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[85] There is a risk of uterine perforation by the hysteroscope, Essure System or other instruments used during the procedure with possible injury to the	**IV. Warnings** … When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[90] Do not continue to advance the Essure System once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[91] If a tubal perforation occurs or is suspected, do not continue with **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[92] … **V. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[93] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or	**V. Warnings** … When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[99] Do not continue to advance the Essure system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[100] If a tubal perforation occurs or is suspected, do not continue with Essure micro-insert placement attempt. A very small percentage of women in the Essure clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[101] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[102] **VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however,	**V. Warnings** … When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[108] Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[109] If a tubal perforation occurs or is suspected, do not continue with the **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[110] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.[111] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or	**V. Warnings** … When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[117] Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[118] If a tubal perforation occurs or is suspected, do not continue with the **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[119] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.[120] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result	**V. Warnings** … When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[126] Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[127] If a tubal perforation occurs or is suspected, do not continue with the **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[128] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.[129] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or	**V. Warnings** … When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[135] Do not continue to advance the Essure system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[136] If a tubal perforation occurs or is suspected, do not continue with the Essure micro-insert placement attempt. A very small percentage of women in the Essure clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[137] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[138] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result	**V. Warnings** … When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[144] Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[145] If a tubal perforation occurs or is suspected, do not continue with the **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[146] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.[147] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or	**V. Warnings** … When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[153] Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[154] If a tubal perforation occurs or is suspected, do not continue with the **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[155] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.[156] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result	**V. Warnings** … When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.[162] Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.[163] If a tubal perforation occurs or is suspected, do not continue with the Essure micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.[164] … **VI. Precautions** … In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.[165] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding

[70] [BES.001.001.0029] at [0001] / page 2.
[71] [BES.001.001.0029] at [0002] / page 3.
[72] [BES.001.001.0029] at [0002] / page 3.
[73] [BES.001.001.0029] at [0002] / page 3.
[74] [BES.001.001.0029] at [0003] / page 4.
[75] [BES.001.001.0029] at [0004] / page 5.
[81] [BES.001.001.0033] at [0001] / page 2.
[82] [BES.001.001.0033] at [0001] / page 2.
[83] [BES.001.001.0033] at [0001] / page 2.
[84] [BES.001.001.0033] at [0001] / page 3.
[85] [BES.001.001.0033] at [0001] / page 4.
[90] [BAY-EDPA-3576314] at [3576354] / page 41.
[91] [BAY-EDPA-3576314] at [3576354] / page 41.
[92] [BAY-EDPA-3576314] at [3576354] / page 41.
[93] [BAY-EDPA-3576314] at [3576355] / page 42.
[99] [BAY-EDPA-2425528] at [2425572] / page 45.
[100] [BAY-EDPA-2425528] at [2425573] / page 46.
[101] [BAY-EDPA-2425528] at [2425573] / page 46.
[102] [BAY-EDPA-2425528] at [2425574] / page 47.
[108] [GYT.001.001.3669] at [3696] / page 28.
[109] [GYT.001.001.3669] at [3696] / page 28.
[110] [GYT.001.001.3669] at [3696] / page 28.
[111] [GYT.001.001.3669] at [3696] / page 28.
[117] [GYT.001.001.4299] at [4326] / page 27.
[118] [GYT.001.001.4299] at [4326] / page 27.
[119] [GYT.001.001.4299] at [4326] / page 27.
[120] [GYT.001.001.4299] at [4326] / page 27.
[126] [BAU.001.001.4133] at [0027] / page 28.
[127] [BAU.001.001.4133] at [0027] / page 28.
[128] [BAU.001.001.4133] at [0027] / page 28.
[129] [BAU.001.001.4133] at [0027] / page 28.
[135] [BAU.001.001.0174] at [0002] / page 3.
[136] [BAU.001.001.0174] at [0002] / page 3.
[137] [BAU.001.001.0174] at [0002] / page 3.
[138] [BAU.001.001.0174] at [0003] / page 4.
[144] [BAG.001.001.2362] at [0027] / page 28.
[145] [BAG.001.001.2362] at [0027] / page 28.
[146] [BAG.001.001.2362] at [0027] / page 28.
[147] [BAG.001.001.2362] at [0027] / page 28.
[153] [BAU.001.001.5676] at [0027] / page 28.
[154] [BAU.001.001.5676] at [0027] / page 28.
[155] [BAU.001.001.5676] at [0027] / page 28.
[156] [BAU.001.001.5676] at [0027] / page 28.
[162] [AMS.001.001.0010] at [0083] / page 84.
[163] [AMS.001.001.0010] at [0083] / page 84.
[164] [AMS.001.001.0010] at [0083] / page 84.
[165] [AMS.001.001.0010] at [0083] / page 84.

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VII. Possible Adverse Effects … **b. Risks Associated with the Device Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[76] There is a risk of uterine perforation by the hysteroscope, STOP System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[77] … There is a risk that the STOP device may perforate through the tubal wall or uterine cornua which could result in the device being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, device retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, device retrieval may not be possible if the device cannot be visualized or accessed by the physician.[78] … **VIII. Directions for Use** … Insert a sterile hysteroscope, with attached camera and operating channel (≥ 5	bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[86] … There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[87] … **VII. Directions for Use** … **B. Micro-Insert Placement Procedure** **…** Insert a sterile hysteroscope, with attached camera and operating channel (≥5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[88] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue	dissection; however, treatment is typically not required.[94] There is a risk of uterine perforation by the hysteroscope, **Essure** System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[95] … There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[96] … **VII. Directions for Use** … **B. Micro-Insert Placement Procedure** … Insert a sterile hysteroscope, with attached camera and operating channel (≥5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be terminated if excessive	treatment is typically not required.[103] There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[104] … There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[105] … **VIII. Directions for Use** … **B. Essure Micro-insert Placement Procedure** **…** Insert a sterile hysteroscope, with attached camera and operating channel (≥ 5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be terminated if excessive	dissection; however, treatment is typically not required.[112] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[113] … There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[114] … **VIII. Directions for Use** … **B. Essure micro-insert placement procedure** **…** Insert a sterile hysteroscope, with attached camera and operating channel (≥ 5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be discontinued if excessive	from such a perforation or dissection; however, treatment is typically not required.[121] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[122] … There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[123] … **VIII. Directions for use** … **B. Essure micro-insert placement procedure** … Insert a sterile hysteroscope, with attached camera and operating channel (≥ 5 French), through the cervix into the uterine cavity. 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Essure micro-insert placement procedure** **…** Insert a sterile hysteroscope, with attached camera and operating channel (≥ 5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be terminated if excessive	dissection; however, treatment is typically not required.[148] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[149] … There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[150] … **VIII. Directions for use** … **B. Essure micro-insert placement procedure** … Insert a sterile hysteroscope, with attached camera and operating channel (~ 5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be discontinued if excessive	from such a perforation or dissection; however, treatment is typically not required.[157] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[158] … There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. 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[76] [BES.001.001.0029] at [0005] / page 6.
[77] [BES.001.001.0029] at [0005] / page 6.
[78] [BES.001.001.0029] at [0006] / page 7.
[86] [BES.001.001.0033] at [0003] / page 4.
[87] [BES.001.001.0033] at [0003] / page 4.
[88] [BES.001.001.0033] at [0005] / page 6.
[94] [BAY-EDPA-3576314] at [3576356] / page 43.
[95] [BAY-EDPA-3576314] at [3576357] / page 44.
[96] [BAY-EDPA-3576314] at [3576357] / page 44.
[103] [BAY-EDPA-2425528] at [2425575] / page 48.
[104] [BAY-EDPA-2425528] at [2425575] / page 48.
[105] [BAY-EDPA-2425528] at [2425575] / page 48.
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[114] [GYT.001.001.3669] at [3696] / page 28.
[121] [GYT.001.001.4299] at [4326] / page 27.
[122] [GYT.001.001.4299] at [4326] / page 27.
[123] [GYT.001.001.4299] at [4326] / page 27.
[130] [BAU.001.001.4133] at [0027] / page 28.
[131] [BAU.001.001.4133] at [0027] / page 28.
[132] [BAU.001.001.4133] at [0027] / page 28.
[139] [BAU.001.001.0174] at [0004] page 5.
[140] [BAU.001.001.0174] at [0004] page 5.
[141] [BAU.001.001.0174] at [0005] / page 6.
[148] [BAG.001.001.2362] at [0027] / page 28.
[149] [BAG.001.001.2362] at [0027] / page 28.
[150] [BAG.001.001.2362] at [0027] / page 28.
[157] [BAU.001.001.5676] at [0027] / page 28.
[158] [BAU.001.001.5676] at [0027] / page 28.
[159] [BAU.001.001.5676] at [0027] / page 28.
[166] [AMS.001.001.0010] at [0083] / page 84.
[167] [AMS.001.001.0010] at [0083] / page 84.
[168] [AMS.001.001.0010] at [0083] / page 84.

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French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[79] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and / or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the device in order to avoid the possibility of uterine perforation or inadvertently placing the device in the uterine musculature rather than within the tubal lumen. A follow-up HSG should be undertaken to determine tubal patency.[80]	resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and / or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up HSG should be undertaken to determine tubal patency.[89]	force is required to achieve cervical dilatation.[97] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. 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A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[116]	force is required to achieve cervical dilatation.[124] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[125]	force is required to achieve cervical dilatation.[133] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[134]	force is required to achieve cervical dilatation.[142] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[143]	force is required to achieve cervical dilatation.[151] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[152]	force is required to achieve cervical dilatation.[160] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.[161]	discontinued if excessive force is required to achieve cervical dilatation.[169] … Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up Essure Confirmation Test (HSG) should be undertaken to determine tubal patency.[170]

[79] [BES.001.001.0029] at [0008] / page 9.
[80] [BES.001.001.0029] at [0009] to [0010] / pages 10 to 11.
[89] [BES.001.001.0033] at [0006] to [0007] / pages 7 to 8.
[97] [BAY-EDPA-3576314] at [3576360] / page 47.
[98] [BAY-EDPA-3576314] at [3576361] to [3576362] / pages 48 to 49.
[106] [BAY-EDPA-2425528] at [2425578] / page 51.
[107] [BAY-EDPA-2425528] at [2425579] to [2425580] / pages 52 to 53.
[115] [GYT.001.001.3669] at [3697] / page 29.
[116] [GYT.001.001.3669] at [3697] / page 29.
[124] [GYT.001.001.4299] at [4326] / page 28.
[125] [GYT.001.001.4299] at [4327] / page 28.
[133] [BAU.001.001.4133] at [0028] / page 29.
[134] [BAU.001.001.4133] at [0028] / page 29.
[142] [BAU.001.001.0174] at [0008] / page 9.
[143] [BAU.001.001.0174] at [0010] / page 11.
[151] [BAG.001.001.2362] at [0028] / page 29.
[152] [BAG.001.001.2362] at [0028] / page 29.
[160] [BAU.001.001.5676] at [0028] / page 29.
[161] [BAU.001.001.5676] at [0028] / page 29.
[169] [AMS.001.001.0010] at [0084] / page 85.
[170] [AMS.001.001.0010] at [0084] / page 85.

TABLE 6: LEACH NICKEL (or other metals) ASOC 19(c)(i)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
-	**III. Contraindications for Use** … Patient with known nickel allergy[171]	**IV. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[172]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[173]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[174]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[175]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[176]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[177]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[178]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[179]	**V. Warnings** … Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.[180]

[171] [BES.001.001.0033] at [0001] / page 2.
[172] [BAY-EDPA-3576314] at [3576354] / page 41.
[173] [BAY-EDPA-2425528] at [2425572] / page 45.
[174] [GYT.001.001.3669] at [3696] / page 28.
[175] [GYT.001.001.4299] at [4326] / page 27.
[176] [BAU.001.001.4133] at [0027] / page 28.
[177] [BAU.001.001.0174] at [0002] / page 3.
[178] [BAG.001.001.2362] at [0027] / page 28.
[179] [BAU.001.001.5676] at [0027] / page 28.
[180] [AMS.001.001.0010] at [0083] / page 84.

TABLE 7: PAIN - ASOC 19(c)(ii), 20(a) and (c)

1. ~ Mar-01 - Mar-02 BES.001.001.0029 (Entire document)	2. ~ Mar 02 - Sept 04 BES.001.001.0033 (Entire document)	3. ~ Sept 04 - Mar 06 BAY-EDPA-3576314 From [3576353] to [3576376] / Pages 40 to 63	4. ~ Mar 06 - Sept 09 BAY-EDPA-2425528 From [2425571] to [2425594] / Pages 44 to 67	5. ~ Sept 09 - Oct 10 GYT.001.001.3669 From [3696] to [3699] / Pages 28 to 31	6. ~ Sept 11 - Sept 12 GYT.001.001.4299 From [4326] to [4329] / Pages 27 to 30	7. ~ Sept 12 - Feb 13 BAU.001.001.4133 From [0027] to [0030] / Pages 28 to 31	8. ~ Feb 13 - Nov 13 BAU.001.001.0174 (Entire document)	9. ~ Nov 13 - Dec 14 BAG.001.001.2362 From [0027] to [0030] / Pages 28 to 31	10. ~ Dec 14 - 2015 BAU.001.001.5676 From [0027] to [0030] / Pages 28 to 31	11. ~ 2015 - Oct 17 AMS.001.001.0010 From [0083] to [0086] / Pages 84 to 87
V. Precautions … Do not advance the STOP System if the patient is experiencing extraordinary pain or discomfort.[181] … **VI. Clinical Data Summary** As of December 31, 2000, 226 patients have undergone device placement in a clinical study. … Patients were asked to rate their tolerance of the placement procedure. ... 153 patients reported experiencing some post-operative pain; 59% was resolved within 1 day, 88% was resolved within 3 days, 99% was resolved within 7 days and 100% was resolved within 14 days. Of those reporting pain, only 68% required medication for the pain and more than half of those women were able to use over-the-counter medications.[182] … 41 patients in the study have reported adverse events. Of those, 14 adverse events are considered to be related to the STOP device. The following were reported as being likely related to the STOP device: Severe post-op pain - <1%[183] … **VII. Possible Adverse Effects** … **B. Risks Associated with the Device Placement Procedure** … Pain, cramping and vaginal bleeding may occur during	**V. Precautions** … Do not advance the Essure System if the patient is experiencing extraordinary pain or discomfort.[190] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[191] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[192]… There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 20 or more coils of the Essure micro-insert are visible at	**V. Precautions** … Do not advance the **Essure** System if the patient is experiencing extraordinary pain or discomfort.[197] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[198] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[199] … There is a risk that the Essure micro-insert may be placed too proximally in	**VI. Precautions** … Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort.[204] … **VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[205] ... There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[206] … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[211] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[212] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[213] … There is a risk that the **Essure** micro-insert may be placed too proximally in	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[218] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[219] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. 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Typically, these incidents are tolerable, transient and successfully treated with medication.[226] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[227] … There is a risk that the **Essure** micro-insert may be placed too proximally in	**VI. Precautions** … Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. [232] … **VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[233] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. 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Typically, these incidents are tolerable, transient and successfully treated with medication.[240] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[241] … There is a risk that the **Essure** micro-insert may be placed too proximally in	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[246] … **VII. Possible Adverse Effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[247] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. 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Typically, these incidents are tolerable, transient and successfully treated with medication.[254] … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[255] … There is a risk that the **Essure** micro-insert may be placed too proximally in

[181] [BES.001.001.0029] at [0003] / page 4.
[182] [BES.001.001.0029] at [0003] / page 4.
[183] [BES.001.001.0033] at [0004] / page 5.
[190] [BES.001.001.0033] at [0002] / page 3.
[191] [BES.001.001.0033] at [0003] / page 4.
[192] [BES.001.001.0033] at [0003] / page 4.
[197] [BAY-EDPA-3576314] at [3576356] / page 43.
[198] [BAY-EDPA-3576314] at [3576356] / page 43
[199] [BAY-EDPA-3576314] at [3576357] / page 44.
[204] [BAY-EDPA-2425528] at [2425574] / page 47.
[205] [BAY-EDPA-2425528] at [2425574] / page 47.
[206] [BAY-EDPA-2425528] at [2425575] / page 48.
[211] [GYT.001.001.3669] at [3696] / page 28.
[212] [GYT.001.001.3669] at [3696] / page 28.
[213] [GYT.001.001.3669] at [3696] / page 28.
[218] [GYT.001.001.4299] at [4326] / page 27.
[219] [GYT.001.001.4299] at [4326] / page 27.
[220] [GYT.001.001.4299] at [4326] / page 27.
[225] [BAU.001.001.4133] at [0027] / page 28.
[226] [BAU.001.001.4133] at [0027] / page 28.
[227] [BAU.001.001.4133] at [0027] / page 28.
[232] [BAU.001.001.0174] at [0003] / page 4.
[233] [BAU.001.001.0174] at [0004] / page 5.
[234] [BAU.001.001.0174] at [0004] to [0005] / pages 5 to 6.
[239] [BAG.001.001.2362] at [0027] / page 28.
[240] [BAG.001.001.2362] at [0027] / page 28.
[241] [BAG.001.001.2362] at [0027] / page 28.
[246] [BAU.001.001.5676] at [0027] / page 28.
[247] [BAU.001.001.5676] at [0027] / page 28.
[248] [BAU.001.001.5676] at [0027] / page 28.
[253] [AMS.001.001.0010] at [0083] / page 84.
[254] [AMS.001.001.0010] at [0083] / page 84.
[255] [AMS.001.001.0010] at [0083] / page 84.

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	2. ~ Mar 02 - Sept 04 **BES.001.001.0033** (Entire document)	3. ~ Sept 04 - Mar 06 **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	4. ~ Mar 06 - Sept 09 **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	5. ~ Sept 09 - Oct 10 **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	6. ~ Sept 11 - Sept 12 **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	7. ~ Sept 12 - Feb 13 **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	8. ~ Feb 13 - Nov 13 **BAU.001.001.0174** (Entire document)	9. ~ Nov 13 - Dec 14 **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	10. ~ Dec 14 - 2015 **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	11. ~ 2015 - Oct 17 **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
and following the device placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[184] … There is a risk that the STOP device may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one device has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third device to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one device in the fallopian tube and/or one device in the myometrium that cannot be relied upon for contraception. Placement of the device in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the device(s) is required, salpingectomy or hysterectomy may be required.[185] … There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device (see section X, Device Removal). If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device *in vivo*. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure. [186] There is a risk that the STOP device may perforate through the tubal wall or uterine cornua which could result in the	the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[193] There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[194] … **C. Risks Associated with Essure Micro-Insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain /	the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[200] There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[201] … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in	more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, Essure Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[207] There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[208] … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. 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If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[214] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[215] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. 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If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[221] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[222] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. 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If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[228] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[229] … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. 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If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[235] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualized or accessed by the physician.[236] … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. 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If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[242] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[243] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device	the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[249] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[250] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device	the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[256] There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.[257] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device

[184] [BES.001.001.0029] at [0005] / page 6.
[185] [BES.001.001.0029] at [0005] / page 6.
[186] [BES.001.001.0029] at [0006] / page 7.
[193] [BES.001.001.0033] at [0003] / page 4.
[194] [BES.001.001.0033] at [0003] / page 4.
[200] [BAY-EDPA-3576314] at [3576357] / page 44.
[201] [BAY-EDPA-3576314] at [3576357] / page 44.
[207] [BAY-EDPA-2425528] at [2425575] / page 48.
[208] [BAY-EDPA-2425528] at [2425575] / page 48.
[214] [GYT.001.001.3669] at [3696] / page 28.
[215] [GYT.001.001.3669] at [3696] / page 28.
[221] [GYT.001.001.4299] at [4326] / page 27.
[222] [GYT.001.001.4299] at [4326] / page 27.
[228] [BAU.001.001.4133] at [0027] / page 28.
[229] [BAU.001.001.4133] at [0027] / page 28.
[235] [BAU.001.001.0174] at [0005] / page 6.
[236] [BAU.001.001.0174] at [0005] / page 6.
[242] [BAG.001.001.2362] at [0027] / page 28.
[243] [BAG.001.001.2362] at [0027] / page 28.
[249] [BAU.001.001.5676] at [0027] / page 28.
[250] [BAU.001.001.5676] at [0027] / page 28.
[256] [AMS.001.001.0010] at [0083] / page 84.
[257] [AMS.001.001.0010] at [0083] / page 84.

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
device being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilization or other surgical intervention, device retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, device retrieval may not be possible if the device cannot be visualized or accessed by the physician.[187] … **C. Risks Associated with STOP Device Wearing** There is a risk that the STOP device could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the device(s), and surgery may be required to remove the device(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events.[188] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[189]	menstrual disturbance or other adverse events.[195] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[196]	movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[202] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[203]	pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[209] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[210]	micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[216] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[217]	movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[223] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[224]	micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[230] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[231]	pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[237] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[238]	micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[244] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[245]	movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events. [251] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[252]	movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[258] … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[259]

[187] [BES.001.001.0029] at [0006] / page 7.
[188] [BES.001.001.0029] at [0006] / page 7.
[189] [BES.001.001.0029] at [0006] / page 7.
[195] [BES.001.001.0033] at [0004] / page 5.
[196] [BES.001.001.0033] at [0004] / page 5.
[202] [BAY-EDPA-3576314] at [3576358] / page 45.
[203] [BAY-EDPA-3576314] at [3576358] / page 45.
[209] [BAY-EDPA-2425528] at [2425576] / page 49.
[210] [BAY-EDPA-2425528] at [2425576] / page 49.
[216] [GYT.001.001.3669] at [3696] / page 28.
[217] [GYT.001.001.3669] at [3696] / page 28.
[223] [GYT.001.001.4299] at [4326] / page 27.
[224] [GYT.001.001.4299] at [4326] / page 27.
[230] [BAU.001.001.4133] at [0027] / page 28.
[231] [BAU.001.001.4133] at [0027] / page 28.
[237] [BAU.001.001.0174] at [0006] / page 7.
[238] [BAU.001.001.0174] at [0006] / page 7.
[244] [BAG.001.001.2362] at [0027] / page 28.
[245] [BAG.001.001.2362] at [0027] / page 28.
[251] [BAU.001.001.5676] at [0027] / page 28.
[252] [BAU.001.001.5676] at [0027] / page 28.
[258] [AMS.001.001.0010] at [0083] / page 84.
[259] [AMS.001.001.0010] at [0083] / page 84.

TABLE 8: BLEEDING - ASOC 19(c)(ii), 20(b)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
VII. Possible Adverse Effects … **B. Risks Associated with the Device Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the device placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[260] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[261] … There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device (see section X, Device Removal). If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device *in vivo*. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.[262] … … **VI. Clinical Data Summary** As of December 31, 2000, 226 patients have undergone device placement in a clinical study.[263]	**VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[268] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[269] … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 20 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[270] … **C. Risks Associated with Essure Micro-Insert Wearing** … Intermenstrual bleeding or heavier than normal	**VI. Possible Adverse Effects** .. **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[272] ... There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[273] … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[274] … **C. Risks Associated with Essure Micro-insert Wearing** … Intermenstrual bleeding or heavier than normal	**VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[276] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[277] … There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, Essure Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[278] … **C. Risks Associated with Essure Micro-insert Wearing** … Intermenstrual bleeding or heavier than normal	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[280] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[281] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[282] … **C. Risks associated with Essure micro-insert wearing** …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[284] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[285] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[286] … **C. Risks associated with Essure micro-insert wearing** … Intermenstrual bleeding or heavier than normal	**VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[288] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[289] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[290] … **C. Risks associated with Essure Micro-insert Wearing** …	**VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[292] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[293] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[294] … **C. Risks associated with Essure Micro-insert Wearing** … Intermenstrual bleeding or heavier than normal	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[296] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[297] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[298] … **C. Risks associated with Essure micro-insert wearing** …	**VII. Possible adverse effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[300] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[301] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[302] … **C. Risks associated with Essure micro-insert wearing** … Intermenstrual bleeding or heavier than normal	**VII. Possible adverse effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[304] … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[305] … There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[306] … **C. Risks associated with Essure micro-insert wearing** … Intermenstrual bleeding or heavier than normal

[260] [BES.001.001.0029] at [0005] / page 6.
[261] [BES.001.001.0029] at [0005] / page 6.
[262] [BES.001.001.0029] at [0006] / page 7.
[263] [BES.001.001.0029] at [0003] / page 4.
[268] [BES.001.001.0033] at [0003] / page 4.
[269] [BES.001.001.0033] at [0003] / page 4.
[270] [BES.001.001.0033] at [0003] / page 4.
[272] [BAY-EDPA-3576314] at [3576356] / page 43.
[273] [BAY-EDPA-3576314] at [3576356] / page 43.
[274] [BAY-EDPA-3576314] at [3576357] / page 44.
[276] [BAY-EDPA-2425528] at [2425575] / page 48.
[277] [BAY-EDPA-2425528] at [2425576] / page 49.
[278] [BAY-EDPA-2425528] at [2425575] / page 48.
[280] [GYT.001.001.3669] at [3696] / page 28.
[281] [GYT.001.001.3669] at [3696] / page 28.
[282] [GYT.001.001.3669] at [3696] / page 28.
[284] [GYT.001.001.4299] at [4326] / page 27.
[285] [GYT.001.001.4299] at [4326] / page 27.
[286] [GYT.001.001.4299] at [4326] / page 27.
[288] [BAU.001.001.4133] at [0027] / page 28.
[289] [BAU.001.001.4133] at [0027] / page 28.
[290] [BAU.001.001.4133] at [0027] / page 28.
[292] [BAU.001.001.0174] at [0004] page 5.
[293] [BAU.001.001.0174] at [0004] page 5.
[294] [BAU.001.001.0174] at [0005] / page 6.
[296] [BAG.001.001.2362] at [0027] / page 28.
[297] [BAG.001.001.2362] at [0027] / page 28.
[298] [BAG.001.001.2362] at [0027] / page 28.
[300] [BAU.001.001.5676] at [0027] / page 28.
[301] [BAU.001.001.5676] at [0027] / page 28.
[302] [BAU.001.001.5676] at [0027] / page 28.
[304] [AMS.001.001.0010] at [0083] / page 84.
[305] [AMS.001.001.0010] at [0083] / page 84.
[306] [AMS.001.001.0010] at [0083] / page 84.

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
… Of 197 patients completing follow-up questionnaires, 165 (84%) experienced bleeding after the procedure. 27% said their bleeding resolved within 1 day, 63% resolved within 3 days, 96% resolved within 7 days and 100% resolved within 15 days. Comparing the amount of bleeding to their normal menstrual bleeding, 88% characterized it as the same or less than normal menstrual bleeding, 8% characterized it as a little more, and only 4% characterized it as a lot more.[264] … 41 patients in the study have reported adverse events. Of those, 14 adverse events are considered to be related to the STOP device. Those not related to the device include: … Less than 1%: Unexplained vaginal bleeding[265] … Post-coital bleeding[266] … **C. Risks Associated with STOP Device Wearing** … Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.[267]	menstrual bleeding may be experienced.[271]	menstrual bleeding may be experienced.[275]	menstrual bleeding may be experienced.[279]	Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.[283]	menstrual bleeding may be experienced.[287]	Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.[291]	menstrual bleeding may be experienced.[295]	Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.[299]	menstrual bleeding may be experienced.[303]	menstrual bleeding may be experienced.[307]

[264] [BES.001.001.0029] at [0003] / page 4.
[265] [BES.001.001.0029] at [0003] / page 4.
[266] [BES.001.001.0033] at [0004] / page 5.
[267] [BES.001.001.0029] at [0006] / page 7.

[271] [BES.001.001.0033] at [0004] / page 5.
[275] [BAY-EDPA-3576314] at [3576358] / page 45.
[279] [BAY-EDPA-2425528] at [2425576] / page 49.
[283] [GYT.001.001.3669] at [3696] / page 28.

[287] [GYT.001.001.4299] at [4326] / page 27.
[291] [BAU.001.001.4133] at [0027] / page 28.
[295] [BAU.001.001.0174] at [0006] / page 7.
[299] [BAG.001.001.2362] at [0027] / page 28.

[303] [BAU.001.001.5676] at [0027] / page 28.
[307] [AMS.001.001.0010] at [0083] / page 84.

TABLE 9: DYSMENORRHOEA (intense uterine cramping & pain) - ASOC 20(c)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
V. Precautions … Do not advance the STOP System if the patient is experiencing extraordinary pain or discomfort.[308] … **VII. Possible Adverse Effects** … **B. Risks Associated with the Device Placement Procedure** Pain, cramping and vaginal bleeding may occur during and following the device placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[309] … **C. Risks Associated with STOP Device Wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[310]	**V. Precautions** … Do not advance the Essure System if the patient is experiencing extraordinary pain or discomfort.[311] ... **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[312] … **C. Risks Associated with Essure Micro-Insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[313]	**V. Precautions** … Do not advance the Essure System if the patient is experiencing extraordinary pain or discomfort.[314] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[315] … **C. Risks Associated with Essure Micro-insert Wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[316]	**VI. Precautions** … Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort.[317] ... **VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[318] … **C. Risks Associated with Essure Micro-insert Wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[319]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[320] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[321] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[322]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[323] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[324] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[325]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[326] … **VII. Possible Adverse Effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[327] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[328]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[329] … **VII. Possible Adverse Effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[330] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[331]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[332] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[333] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[334]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[335] … **VII. Possible Adverse Effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[336] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[337]	**VI. Precautions** … Do not advance the **Essure** system if the patient is experiencing extraordinary pain or discomfort.[338] … **VII. Possible Adverse Effects** … **B. Risks Associated with the micro-insert placement procedure** … Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[339] … **C. Risks associated with Essure micro-insert wearing** … Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.[340]

[308] [BES.001.001.0029] at [0003] / page 4.
[309] [BES.001.001.0029] at [0005] / page 6.
[310] [BES.001.001.0029] at [0006] / page 7.
[311] [BES.001.001.0033] at [0002] / page 3.
[312] [BES.001.001.0033] at [0003] / page 4.
[313] [BES.001.001.0033] at [0004] / page 5.
[314] [BAY-EDPA-3576314] at [3576356] / page 43.
[315] [BAY-EDPA-3576314] at [3576356] / page 43.
[316] [BAY-EDPA-3576314] at [3576358] / page 45.
[317] [BAY-EDPA-2425528] at [2425574] / page 47.
[318] [BAY-EDPA-2425528] at [2425574] / page 47.
[319] [BAY-EDPA-2425528] at [2425576] / page 49.
[320] [GYT.001.001.3669] at [3696] / page 28.
[321] [GYT.001.001.3669] at [3696] / page 28.
[322] [GYT.001.001.3669] at [3696] / page 28.
[323] [GYT.001.001.4299] at [4326] / page 27.
[324] [GYT.001.001.4299] at [4326] / page 27.
[325] [GYT.001.001.4299] at [4326] / page 27.
[326] [BAU.001.001.4133] at [0027] / page 28.
[327] [BAU.001.001.4133] at [0027] / page 28.
[328] [BAU.001.001.4133] at [0027] / page 28.
[329] [BAU.001.001.0174] at [0003] / page 4.
[330] [BAU.001.001.0174] at [0004] / page 5.
[331] [BAU.001.001.0174] at [0006] / page 7.
[332] [BAG.001.001.2362] at [0027] / page 28.
[333] [BAG.001.001.2362] at [0027] / page 28.
[334] [BAG.001.001.2362] at [0027] / page 28.
[335] [BAU.001.001.5676] at [0027] / page 28.
[336] [BAU.001.001.5676] at [0027] / page 28.
[337] [BAU.001.001.5676] at [0027] / page 28.
[338] [AMS.001.001.0010] at [0083] / page 84.
[339] [AMS.001.001.0010] at [0083] / page 84.
[340] [AMS.001.001.0010] at [0083] / page 84.

TABLE 10: DAMAGE TO INTERNAL ORGANS - ASOC 20(d)

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
VII. Possible Adverse Effects … **B. Risks Associated with the Device Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[341] There is a risk of uterine perforation by the hysteroscope, STOP System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[342] …	**VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[343] There is a risk of uterine perforation by the hysteroscope, Essure System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[344] ...	**VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[345] There is a risk of uterine perforation by the hysteroscope, Essure System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[346] …	**VII. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[347] There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[348] ...	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required. [349] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[350] …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[351] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[352] …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[353] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[354] …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[355] There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[356] …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[357] There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[358] …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[359] There is a risk of uterine perforation by the hysteroscope, Essure system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[360] …	**VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.[361] There is a risk of uterine perforation by the hysteroscope, **Essure** system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.[362] …

[341] [BES.001.001.0029] at [0005] / page 6.
[342] [BES.001.001.0029] at [0005] / page 6.
[343] [BES.001.001.0033] at [0003] / page 4.
[344] [BES.001.001.0033] at [0003] / page 4.
[345] [BAY-EDPA-3576314] at [3576356] / page 43.
[346] [BAY-EDPA-3576314] at [3576357] / page 44.
[347] [BAY-EDPA-2425528] at [2425575] / page 48.
[348] [BAY-EDPA-2425528] at [2425575] / page 48.
[349] [GYT.001.001.3669] at [3696] / page 28.
[350] [GYT.001.001.3669] at [3696] / page 28.
[351] [GYT.001.001.4299] at [4326] / page 27.
[352] [GYT.001.001.4299] at [4326] / page 27.
[353] [BAU.001.001.4133] at [0027] / page 28.
[354] [BAU.001.001.4133] at [0027] / page 28.
[355] [BAU.001.001.0174] at [0004] page 5.
[356] [BAU.001.001.0174] at [0004] page 5.
[357] [BAG.001.001.2362] at [0027] / page 28.
[358] [BAG.001.001.2362] at [0027] / page 28.
[359] [BAU.001.001.5676] at [0027] / page 28.
[360] [BAU.001.001.5676] at [0027] / page 28.
[361] [AMS.001.001.0010] at [0083] / page 84.
[362] [AMS.001.001.0010] at [0083] / page 84.

TABLE 11: REMOVAL LIMITATION - ASOC 21 - 22

1. ~ Mar-01 - Mar-02 BES.001.001.0029 (Entire document)	2. ~ Mar 02 - Sept 04 BES.001.001.0033 (Entire document)	3. ~ Sept 04 - Mar 06 BAY-EDPA-3576314 From [3576353] to [3576376] / Pages 40 to 63	4. ~ Mar 06 - Sept 09 BAY-EDPA-2425528 From [2425571] to [2425594] / Pages 44 to 67	5. ~ Sept 09 - Oct 10 GYT.001.001.3669 From [3696] to [3699] / Pages 28 to 31	6. ~ Sept 11 - Sept 12 GYT.001.001.4299 From [4326] to [4329] / Pages 27 to 30	7. ~ Sept 12 - Feb 13 BAU.001.001.4133 From [0027] to [0030] / Pages 28 to 31	8. ~ Feb 13 - Nov 13 BAU.001.001.0174 (Entire document)	9. ~ Nov 13 - Dec 14 BAG.001.001.2362 From [0027] to [0030] / Pages 28 to 31	10. ~ Dec 14 - 2015 BAU.001.001.5676 From [0027] to [0030] / Pages 28 to 31	11. ~ 2015 - Oct 17 AMS.001.001.0010 From [0083] to [0086] / Pages 84 to 87
I. Device Description / Mechanism of Action … The micro-coil STOP devices are permanent implants.[363] … **II. Indications for Use** The STOP System is indicated for permanent female contraception.[364] **III. Contraindications** Patient uncertainty about their desire to end fertility.[365] … **IV. Warnings** … Once the device has been placed, device removal should not be attempted hysteroscopically, unless 20 or more coils of the STOP device are trailing into the uterine cavity. Removal of such a device should be attempted immediately following the placement. However, removal may not be possible.[366] … **VII. Possible Adverse Effects** … **B. Risks Associated with the Device Placement Procedure** … There is a risk that the STOP device may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one device has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third device to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one device	**I. Micro-insert Description / Mechanism of Action** … The Essure micro-inserts are permanent implants.[378] … **II. Indications for Use** The Essure System is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[379] **III. Contraindications for Use** Patient uncertainty about her desire to end fertility.[380] … **IV. Warnings** … Once the micro-insert has been placed, micro-insert removal should not be attempted hysteroscopically, unless 20 or more coils of the Essure micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[381] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk that the Essure micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to	**I. Micro-insert Description/Mechanism of Action** … The Essure micro-inserts are permanent implants.[393] … **II. Indications for Use** The Essure System is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[394] **III. Contraindications for Use** Patient uncertainty about her desire to end fertility.[395] … **IV. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically, unless 18 or more coils of the Essure micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[396] … **VI. Possible Adverse Effects** … **B. Risks Associated with the Micro-insert Placement Procedure** … There is a risk that the Essure micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to	**II. Mechanism of Action** … The Essure micro-inserts are permanent implants.[408] … **III. Indications for Use** The Essure system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[409] **IV. Contraindications for Use** Patient uncertainty about her desire to end fertility.[410] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically, unless 18 or more coils of the Essure micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[411] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the Essure micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube	**II. Mechanism of action** ... The **Essure** micro-inserts are permanent implants.[423] … **III. Indications for use** The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[424] **IV. Contraindications for use** Patient uncertainty about her desire to end fertility.[425] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible. [426] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube	**III. Indications for use** The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[438] **IV. Contraindications for use** Patient uncertainty about her desire to end fertility.[439] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[440] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement	**III. Indications for use** The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[451] **IV. Contraindications for use** Patient uncertainty about her desire to end fertility.[452] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically, unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[453] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement	**III. Indications for use** The Essure system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[465] **IV. Contraindications for Use** Patient uncertainty about her desire to end fertility.[466] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically, unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[467] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement	**III. Indications for use** The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[479] **IV. Contraindications for use** Patient uncertainty about her desire to end fertility.[480] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[481] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement	**III. Indications for use** The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[493] **IV. Contraindications for use** Patient uncertainty about her desire to end fertility.[494] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[495] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** **…** There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement	**III. Indications for use** The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.[507] **IV. Contraindications for use** Patient uncertainty about her desire to end fertility.[508] … **V. Warnings** … Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.[509] … **VII. Possible adverse effects** … **B. Risks associated with the micro-insert placement procedure** … There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. If one micro-insert has already been properly placed in one fallopian tube, in addition to inadvertent placement into the myometrium, the physician may attempt to place a third micro-insert to complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement

[363] [BES.001.001.0029] at [0001] / page 2.
[364] [BES.001.001.0029] at [0001] / page 2.
[365] [BES.001.001.0029] at [0001] / page 2.
[366] [BES.001.001.0029] at [0002] / page 3.
[378] [BES.001.001.0033] at [0001] / page 2.
[379] [BES.001.001.0033] at [0001] / page 2.
[380] [BES.001.001.0033] at [0001] / page 2.
[381] [BES.001.001.0033] at [0002] / page 3.
[393] [BAY-EDPA-3576314] at [3576353] / page 40.
[394] [BAY-EDPA-3576314] at [3576353] / page 40.
[395] [BAY-EDPA-3576314] at [3576353] / page 40.
[396] [BAY-EDPA-3576314] at [3576354] / page 41.
[408] [BAY-EDPA-2425528] at [2425572] / page 45.
[409] [BAY-EDPA-2425528] at [2425572] / page 45.
[410] [BAY-EDPA-2425528] at [2425572] / page 45.
[411] [BAY-EDPA-2425528] at [2425573] / page 46.
[423] [GYT.001.001.3669] at [3696] / page 28.
[424] [GYT.001.001.3669] at [3696] / page 28.
[425] [GYT.001.001.3669] at [3696] / page 28.
[426] [GYT.001.001.3669] at [3696] / page 28.
[438] [GYT.001.001.4299] at [4326] / page 27.
[439] [GYT.001.001.4299] at [4326] / page 27.
[440] [GYT.001.001.4299] at [4326] / page 27.
[451] [BAU.001.001.4133] at [0027] / page 28.
[452] [BAU.001.001.4133] at [0027] / page 28.
[453] [BAU.001.001.4133] at [0027] / page 28.
[465] [BAU.001.001.0174] at [0001] / page 2.
[466] [BAU.001.001.0174] at [0001] / page 2.
[467] [BAU.001.001.0174] at [0002] / page 3.
[479] [BAG.001.001.2362] at [0027] / page 28.
[480] [BAG.001.001.2362] at [0027] / page 28.
[481] [BAG.001.001.2362] at [0027] / page 28.
[493] [BAU.001.001.5676] at [0027] / page 28.
[494] [BAU.001.001.5676] at [0027] / page 28.
[495] [BAU.001.001.5676] at [0027] / page 28.
[507] [AMS.001.001.0010] at [0083] / page 84.
[508] [BAU.001.001.5676] at [0027] / page 28.
[509] [AMS.001.001.0010] at [0083] / page 84.

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
in the fallopian tube and/or one device in the myometrium that cannot be relied upon for contraception. Placement of the device in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the device(s) is required, salpingectomy or hysterectomy may be required.[367] There is a risk that the STOP device may be placed too distally in the fallopian tube. If removal of the device is necessary, surgery (laparoscopy or laparotomy) will be required.[368] There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device (see section X, Device Removal). If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device *in vivo*. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.[369] … **C. Risks Associated with STOP Device Wearing** There is a risk that the STOP device could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the device(s), and surgery may be	complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[382] There is a risk that the Essure micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[383] There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 20 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[384] … **C. Risks Associated with Essure Micro-Insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina	complete the procedure. If bilateral fallopian tube placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[397] There is a risk that the Essure micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[398] There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XII, Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[399] … **C. Risks Associated with Essure Micro-insert Wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina	placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[412] There is a risk that the Essure micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[413] There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, Essure Micro-insert Removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the Essure micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.[414] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the Essure micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to	placement is not achieved, this may result in the patient having one micro-insert in the fallopian tube and/or one micro-insert in the myometrium that cannot be relied upon for contraception. Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[427] There is a risk that the **Essure** micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[428] There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[429] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or	of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[441] There is a risk that the **Essure** micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[442] There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert *in vivo*. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.[443] … **C. Risks associated with Essure micro-insert wearing** There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the	of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[454] There is a risk that the **Essure** micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[455] There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). 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Additional X-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the	of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.[482] There is a risk that the **Essure** micro-insert may be placed too distally in the fallopian tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.[483] There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the **Essure** micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII, **Essure** micro-insert removal). 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[367] [BES.001.001.0029] at [0005] / page 6.
[368] [BES.001.001.0029] at [0005] / page 6.
[369] [BES.001.001.0029] at [0006] / page 7.
[382] [BES.001.001.0033] at [0003] / page 4.
[383] [BES.001.001.0033] at [0003] / page 4.
[384] [BES.001.001.0033] at [0003] / page 4.
[397] [BAY-EDPA-3576314] at [3576357] / page 44.
[398] [BAY-EDPA-3576314] at [3576357] / page 44.
[399] [BAY-EDPA-3576314] at [3576357] / page 44.
[412] [BAY-EDPA-2425528] at [2425575] / page 48.
[413] [BAY-EDPA-2425528] at [2425575] / page 48.
[414] [BAY-EDPA-2425528] at [2425575] / page 48.
[427] [GYT.001.001.3669] at [3696] / page 28.
[428] [GYT.001.001.3669] at [3969] / page 28.
[429] [GYT.001.001.3669] at [3696] / page 28.
[441] [GYT.001.001.4299] at [4326] / page 27.
[442] [GYT.001.001.4299] at [4326] / page 27.
[443] [GYT.001.001.4299] at [4326] / page 27.
[454] [BAU.001.001.4133] at [0027] / page 28.
[455] [BAU.001.001.4133] at [0027] / page 28.
[456] [BAU.001.001.4133] at [0027] / page 28.
[468] [BAU.001.001.0174] at [0004] to [0005] / pages 5 to 6.
[469] [BAU.001.001.0174] at [0005] / page 6.
[470] [BAU.001.001.0174] at [0005] / page 6.
[482] [BAG.001.001.2362] at [0027] / page 28.
[483] [BAG.001.001.2362] at [0027] / page 28.
[484] [BAG.001.001.2362] at [0027] / page 28.
[496] [BAU.001.001.5676] at [0027] / page 28.
[497] [BAU.001.001.5676] at [0027] / page 28.
[498] [BAU.001.001.5676] at [0027] / page 28.
[510] [AMS.001.001.0010] at [0083] / page 84.
[511] [AMS.001.001.0010] at [0083] / page 84.
[512] [AMS.001.001.0010] at [0083] / page 84.

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
required to remove the device(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events.[370] As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the STOP device is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[371] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[372] … **VIII. Directions for Use** … **WARNING**: After the device has been placed and released into the fallopian tube, **DO NOT ATTEMPT TO REMOVE THE DEVICE HYSTEROSCOPICALLY UNLESS 20 OR MORE COILS OF THE STOP DEVICE ARE TRAILING IN THE UTERINE CAVITY**. Removal of such a device should be attempted immediately following the placement. However, removal may not be possible (see section X, Device Removal). If the device was inadvertently deployed in the uterine cavity and not into the tube, the device should be removed from the uterus and another attempt made at device placement in the tube.[373] … **X. Device Removal** **WARNING**: DEVICE REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE DEVICE HAS BEEN PLACED, UNLESS	or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and /or pain / menstrual disturbance or other adverse events.[385] As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the Essure micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[386] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[387] … **VII. Directions for Use** … **B. Micro-Insert Placement Procedure** … **WARNING**: After the micro-insert has been placed and released into the fallopian tube, **DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 20 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XII, Micro-insert Removal). If the micro-insert was inadvertently deployed in the uterine cavity and not	or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[400] As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the Essure micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[401] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[402] … **VII. Directions for Use** … **B. Micro-insert Placement Procedure** … **WARNING: AFTER THE MICRO-INSERT HAS BEEN PLACED AND RELEASED INTO THE FALLOPIAN TUBE, DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING IN THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XII, Micro-Insert Removal). If the micro-insert was	the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional X-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[415] As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the Essure micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[416] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[417] … **VIII. Directions for Use** … **B. Essure Micro-insert Placement Procedure** … **WARNING: AFTER THE MICRO-INSERT HAS BEEN PLACED AND RELEASED INTO THE FALLOPIAN TUBE, DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING IN THE UTERINE CAVITY**. Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XIII, Essure Micro-insert Removal). If the micro-insert was inadvertently deployed in the uterine	migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[430] As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the **Essure** micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[431] ... Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[432] … **VIII. Directions for use** … **B. Essure micro-insert placement procedure** … **WARNING: AFTER THE MICRO-INSERT HAS BEEN PLACED AND RELEASED INTO THE FALLOPIAN TUBE, DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING IN THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XIII, **Essure** Micro-insert Removal). If the micro-insert was inadvertently	micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events. As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the **Essure** micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[444] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[445] … **VIII. Directions for use** … **B. Essure micro-insert placement procedure** … **WARNING: AFTER THE MICRO-INSERT HAS BEEN PLACED AND RELEASED INTO THE FALLOPIAN TUBE, DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING IN THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XIII, Essure Micro-insert Removal). 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Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[500] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[501] … **VIII. Directions for use** … **B. Essure micro-insert placement procedure** … **WARNING: AFTER THE MICRO-INSERT HAS BEEN PLACED AND RELEASED INTO THE FALLOPIAN TUBE, DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING IN THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XIII, **Essure** Micro-insert Removal). If the micro-insert was inadvertently deployed in the uterine cavity and not into the tube, the micro-insert should be removed from the uterus and another attempt made at micro-insert placement in the tube.[502] …	micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.[513] As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the **Essure** micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[514] … Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.[515] … **VIII. Directions for use** … **B. 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[370] [BES.001.001.0029] at [0006] / page 7.
[371] [BES.001.001.0029] at [0006] / page 7.
[372] [BES.001.001.0029] at [0007] / page 8.
[373] [BES.001.001.0029] at [0013] / page 14.
[385] [BES.001.001.0033] at [0004] / page 5.
[386] [BES.001.001.0033] at [0004] / page 5.
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[400] [BAY-EDPA-3576314] at [3576358] / page 45.
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[417] [BAY-EDPA-2425528] at [2425576] / page 49.
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[444] [GYT.001.001.4299] at [4326] / page 27.
[445] [GYT.001.001.4299] at [4326] / page 27.
[446] [GYT.001.001.4299] at [4327] / page 28.
[457] [BAU.001.001.4133] at [0027] / page 28.
[458] [BAU.001.001.4133] at [0027] / page 28.
[459] [BAU.001.001.4133] at [0027] / page 28.
[460] [BAU.001.001.4133] at [0028] / page 29.
[471] [BAU.001.001.0174] at [0006] / page 7.
[472] [BAU.001.001.0174] at [0006] / page 7.
[473] [BAU.001.001.0174] at [0006] / page 7.
[474] [BAU.001.001.0174] at [0014] / page 15.
[485] [BAG.001.001.2362] at [0027] / page 28.
[486] [BAG.001.001.2362] at [0027] / page 28.
[487] [BAG.001.001.2362] at [0027] / page 28.
[488] [BAG.001.001.2362] at [0028] to [0029] / pages 29 to 30.
[499] [BAU.001.001.5676] at [0027] / page 28.
[500] [BAU.001.001.5676] at [0027] / page 28.
[501] [BAU.001.001.5676] at [0027] / page 28.
[502] [BAU.001.001.5676] at [0028] to [0029] / pages 29 to 30.
[513] [AMS.001.001.0010] at [0083] / page 84.
[514] [AMS.001.001.0010] at [0083] / page 84.
[515] [AMS.001.001.0010] at [0083] / page 84.
[516] [AMS.001.001.0010] at [0084] to [0085] / page 85 to 86.

1. ~ Mar-01 - Mar-02 **BES.001.001.0029** (Entire document)	**2. ~ Mar 02 - Sept 04** **BES.001.001.0033** (Entire document)	**3. ~ Sept 04 - Mar 06** **BAY-EDPA-3576314** From [3576353] to [3576376] / Pages 40 to 63	**4. ~ Mar 06 - Sept 09** **BAY-EDPA-2425528** From [2425571] to [2425594] / Pages 44 to 67	**5. ~ Sept 09 - Oct 10** **GYT.001.001.3669** From [3696] to [3699] / Pages 28 to 31	**6. ~ Sept 11 - Sept 12** **GYT.001.001.4299** From [4326] to [4329] / Pages 27 to 30	**7. ~ Sept 12 - Feb 13** **BAU.001.001.4133** From [0027] to [0030] / Pages 28 to 31	**8. ~ Feb 13 - Nov 13** **BAU.001.001.0174** (Entire document)	**9. ~ Nov 13 - Dec 14** **BAG.001.001.2362** From [0027] to [0030] / Pages 28 to 31	**10. ~ Dec 14 - 2015** **BAU.001.001.5676** From [0027] to [0030] / Pages 28 to 31	**11. ~ 2015 - Oct 17** **AMS.001.001.0010** From [0083] to [0086] / Pages 84 to 87
20 OR MORE COILS OF THE STOP DEVICE ARE TRAILING INTO THE UTERINE CAVITY. Removal of such a device should be attempted immediately following placement.[374] … Other than the above described scenario, device removal should only be attempted if a patient is experiencing an adverse event(s) with the device or if she demands device removal.[375] Should device removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[376] … A STOP device that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingostomy or salpingectomy accomplished via laparoscopy or laparotomy.[377]	into the tube, the micro-insert should be removed from the uterus and another attempt made at micro-insert placement in the tube.[388] … **XII. Micro-Insert Removal** **WARNING:** MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 20 OR MORE COILS OF THE Essure MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY. Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[389] … Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[390] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[391] … A Essure micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingostomy or salpingectomy accomplished via laparoscopy or laparotomy.[392]	inadvertently deployed in the uterine cavity and not into the tube, the micro-insert should be removed from the uterus and another attempt made at micro-insert placement in the tube.[403] … **XII. Micro-insert Removal** **WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY**. Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[404] **…** Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[405] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[406] … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[407]	cavity and not into the tube, the micro-insert should be removed from the uterus and another attempt made at micro-insert placement in the tube.[418] … **XIII. Essure Micro-insert Removal** **WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY**. Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[419] … Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[420] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[421] … An Essure micro-insert that has been improperly placed or has migrated beyond the UTJ. should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[422]	deployed in the uterine cavity and not into the tube, the micro-insert should be removed from the uterus and another attempt made at micro-insert placement in the tube.[433] … **XIII. Essure micro-insert removal** **WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[434] **…** Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[435] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[436] An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[437]	**XII. Essure micro-insert removal** **WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[447] … Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[448] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[449] … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[450]	… **XII. 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Essure micro-insert removal** **WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[503] … Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[504] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[505] … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[506]	**XII. Essure micro-insert removal** **WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY.** Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.[517] **…** Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.[518] Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.[519] … An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.[520]

[374] [BES.001.001.0029] at [0014] / page 15.
[375] [BES.001.001.0029] at [0015] / page 16.
[376] [BES.001.001.0029] at [0015] / page 16.
[377] [BES.001.001.0029] at [0015] / page 16.
[388] [BES.001.001.0033] at [0009] / page 10.
[389] [BES.001.001.0033] at [0016] / page 17.
[390] [BES.001.001.0033] at [0016] / page 17.
[391] [BES.001.001.0033] at [0016] / page 17.
[392] [BES.001.001.0033] at [0016] / page 17.
[403] [BAY-EDPA-3576314] at [3576365] / page 52.
[404] [BAY-EDPA-3576314] at [3576373] / page 60.
[405] [BAY-EDPA-3576314] at [3576373] / page 60.
[406] [BAY-EDPA-3576314] at [3576373] / page 60.
[407] [BAY-EDPA-3576314] at [3576373] / page 60.
[418] [BAY-EDPA-2425528] at [2425583] / page 56.
[419] [BAY-EDPA-2425528] at [2425591] / page 64.
[420] [BAY-EDPA-2425528] at [2425592] / page 65.
[421] [BAY-EDPA-2425528] at [2425592] / page 65.
[422] [BAY-EDPA-2425528] at [2425592] / page 65.
[433] [GYT.001.001.3669] at [3697] / page 29.
[434] [GYT.001.001.3669] at [3699] / page 31.
[435] [GYT.001.001.3669] at [3699] / page 31.
[436] [GYT.001.001.3669] at [3699] / page 31.
[437] [GYT.001.001.3669] at [3699] / page 31.
[447] [GYT.001.001.4299] at [4329] / page 30.
[448] [GYT.001.001.4299] at [4329] / page 30.
[449] [GYT.001.001.4299] at [4329] / page 30.
[450] [GYT.001.001.4299] at [4329] / page 30.
[461] [BAU.001.001.4133] at [0030] / page 31.
[462] [BAU.001.001.4133] at [0030] / page 31.
[463] [BAU.001.001.4133] at [0030] / page 31.
[464] [BAU.001.001.4133] at [0030] / page 31.
[475] [BAU.001.001.0174] at [0023] / page 24.
[476] [BAU.001.001.0174] at [0023] / page 24.
[477] [BAU.001.001.0174] at [0023] / page 24.
[478] [BAU.001.001.0174] at [0024] / page 25.
[489] [BAG.001.001.2362] at [0030] / page 31.
[490] [BAG.001.001.2362] at [0030] / page 31.
[491] [BAG.001.001.2362] at [0030] / page 31.
[492] [BAG.001.001.2362] at [0030] / page 31.
[503] [BAU.001.001.5676] at [0030] / page 31.
[504] [BAU.001.001.5676] at [0030] / page 31.
[505] [BAU.001.001.5676] at [0030] / page 31.
[506] [BAU.001.001.5676] at [0030] / page 31.
[517] [AMS.001.001.0010] at [0086] / page 87.
[518] [AMS.001.001.0010] at [0086] / page 87.
[519] [AMS.001.001.0010] at [0086] / page 87.
[520] [AMS.001.001.0010] at [0086] / page 87.

SCHEDULE 4

Aide Memoire – Physician Training Manuals

Document IDs

The documents which are summarised in this aide memoire have the following document ID numbers:

PTM	Document ID
PTM (1)	MIS.500.0001.0001 to MIS.500.0001.0014
PTM (2)	MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031
PTM (3)	GYT.002.001.0131
PTM (4)	GYT.003.001.0001
PTM (5)	AMS.001.001.5420[1]

[1] The Defendants rely on six PTMs. However, the sixth PTM (AMS.001.001.5208 and its copy AMS.001.001.0010) is a duplicate of the fifth (AMS.001.001.5420) except for minor typographical edits and the inclusion of an extra page at the end of the document setting out AMSL's brand logo and contact details. For ease of reference, excerpts in column five have been footnoted as coming from (AMS.001.001.5420).

HYPERLINKED INDEX	
TABLE 1	Who should perform the Essure procedure
TABLE 2	Scope of PTMs and training
TABLE 3	Mechanism of action ASOC 18
TABLE 4	Migration or expulsion ASOC 19(a)(i) - (ii)
TABLE 5	Break or fragment ASOC 19(a)(iii)
TABLE 6	Perforation ASOC 19(b)
TABLE 7	Leach nickel (or other metals) ASOC 19(c)(i)
TABLE 8	Pain ASOC 19(c)(ii), 20(a)
TABLE 9	Bleeding ASOC 19c(ii), 20(b)
TABLE 10	Dysmenorrhoea (intense uterine cramping and pain) ASOC 20(c)
TABLE 11	Damage to internal organs ASOC 20(d)
TABLE 12	Removal Limitation ASOC 21 - 22

1. Who should perform the Essure procedure

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
Introduction ***Course Introduction*** ***STOP Non-incisional Permanent Contraception*** ***Course Purpose*** *The purpose of this course is to provide a curriculum that is designed to train gynaecologists and obstetricians on the method of STOP Non-Incisional Permanent Contraception placement. The course will emphasize the information and training needed to provide a safe and effective procedure. Additional training from the self-instructional manual, review of case studies and post-tests for the physician is required to determine if they have acquired the knowledge about various aspects of non-incisional permanent contraception. It assumes that trainees will bring skills, knowledge and self-motivation to the training.*[2] … ***Procedure Requirements*** ***Equipment Overview*** … *The performance of safe and effective hysteroscopy requires technical skills, appropriate patient selectin, and experience in the interpretation of the visual findings.*[3] … *It is essential that all members of the team (including the physician) be trained and capable of solving all technical problems that could occur before and during the procedure.*[4]	***THE PHYSICIAN TRAINING PROGRAM*** ***Purpose*** *To provide qualified physicians with the information and skills necessary to select appropriate patients, perform competent procedures and manage possible technical issues or adverse events related to the placement of Essure TM micro-inserts for permanent birth control.* ***Training Requirements*** ***1.*** *Knowledgeable hysteroscopist (prior to Essure training).* ***2.*** *Successful completion of a Physician's Training Course at a site approved by Conceptus.* ***3.*** *Successful completion of Essure Simulator Training.* ***4.*** *Completion of the initial procedures under the observation of a Conceptus designated preceptor until competency in performing Essure is established (typically expected to be achieved in 5 cases).* *Upon successful completion of the initial training program, the Physician Training Record will be completed and signed by a Conceptus representative and the physician being trained. The training record will be filed at Conceptus and the physician's name will be added to the list of those trained to perform the procedure.*[5]	***THE PHYSICIAN TRAINING PROGRAM*** ***Purpose*** *To provide qualified physicians with the information and skills necessary to select appropriate patients, perform competent procedures and manage possible technical issues or adverse events related to the placement of Essure® micro-inserts for permanent birth control.* ***Training Requirements*** ***1.*** *Knowledgeable hysteroscopist (prior to Essure training).* ***2****. Successful completion of a Physician's Didactic Training Course*.* ***3.*** *Successful completion of Essure Simulator Training.* ***4.*** *Completion of the initial procedures under the observation of a Conceptus designated preceptor until competency in performing Essure is established (typically expected to be achieved in 5 cases).* *Upon successful completion of the initial training program, the Physician Training Record will be completed by a Conceptus representative. The training record will be filed at Conceptus and the physician's name will be added to the list of those trained to perform the procedure.*[6]	***ESSURE CLINICAL RESOURCE*** ***Physician Training Manual*** *Essure should be used only by physicians who are knowledgeable hysteroscopists; have read and understood the Instructions for Use and this Physician Training Manual; and have successfully completed the Essure training program, Including preceptoring in placement.*[7] … ***Important Safety Information*** ***Prescription Only*** ***Caution:*** *Federal law restricts this device to sale by or on the order of a physician. Device to be used only by physicians who are knowledgeable hysteroscopists; have read and understood the Instructions for Use and Physician Training manual; and have successfully completed the Essure® training program, including preceptoring in placement until competency is established, typically 5 cases.*[8]	***ESSURE CLINICAL RESOURCE*** ***Physician Training Manual*** *The Essure procedure should only be performed by skilled hysteroscopists; have read and understood the Instructions for Use and this Physician Training Manual; and have successfully completed the Essure training program.*[9] … ***Important Safety Information*** ***Caution: Prescription Only*** *The Essure procedure should only be performed by skilled hysteroscopists; have read and understood the Instructions for Use and this Physician Training Manual; and have successfully completed the Essure training program.*[10] … ***INSTRUCTIONS FOR USE*** ***Warnings*** *The Essure procedure should only be performed by skilled hysteroscopists who have completed the Bayer Healthcare LLC training programme for this procedure.*[11]

[2] MIS.500.001.0006 at [0001] / Page 2.
[3] MIS.500.001.0007 at [0001] / Page 2.
[4] MIS.500.001.0007 at [0001] / Page 2.
[5] MIS.500.001.0017 at [0001] / Page 2.
[6] GYT.002.001.0131 at [0133] / Page 3.
[7] GYT.003.001.0001 at [0001] / Page 1.
[8] GYT.003.001.0001 at [0003] / Page 3.GYT.003.001.0001 at [0003] / Page 3.
[9] AMS.001.001.5420 at Page 1.
[10] AMS.001.001.5420 at [0002] / Page 3.
[11] AMS.001.001.5420 at [0083] / Page 84.

2. Scope of PTMs & Training

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
Introduction ***Course Introduction*** ***STOP Non-incisional Permanent Contraception*** ***Course Purpose*** *The purpose of this course is to provide a curriculum that is designed to train gynecologists and obstetricians on the method of STOP Non-Incisional Permanent Contraception placement. The course will emphasize the information and training needed to provide a safe and effective procedure. Additional training from the self-instructional manual, review of case studies and post-tests for the physician is required to determine if they have acquired the knowledge about various aspects of non-incisional permanent contraception. It assumes that trainees will bring skills, knowledge and self-motivation to the training. The course will also include slide or video presentations, model training, pre and post testing and peer reviewed performance evaluations.*[12]	***1. Conceptus Incorporated*** *Welcome to the Essure Physician Training Program. We at Conceptus congratulate you on your choice to join the growing number of gynaecologists choosing to add Essure to their practice. By making Essure available to your patients, you offer one of the newest and most innovative technologies in permanent birth control.* *The Physician Training Program is a comprehensive course designed to provide you with information and skills necessary to select appropriate patients, perform competent procedures and manage possible technical issues related to the placement of Essure micro-inserts for permanent birth control.*[13] … ***THE PHYSICIAN TRAINING PROGRAM*** … ***Learning Objectives*** *At the end of the training program you will be able to:* • *explain the Essure permanent birth control procedure* • *understand the mechanism of action of Essure permanent birth control* • *effectively select and counsel your patients on the benefits and risks of Essure permanent birth control* • *understand the Basic Procedure including the Pre-placement Preparation, Placement Procedure and Post-placement Follow-up* • *understand how to manage technical issues and adverse events* • *understand the clinical safety and effectiveness data gathered in the Essure clinical trials*[14]	***1. Conceptus Incorporated*** *Welcome to the Essure Physician Training Program. We at Conceptus congratulate you on your choice to join the large number of gynecologists choosing to add Essure to their practice. By making Essure available to your patients, you offer one of the most innovative technologies in permanent birth control.* *The Physician Training Program is a comprehensive course designed to provide you with information and skills necessary to select appropriate patients, perform competent procedures and manage possible technical issues related to the placement of Essure micro-inserts for permanent birth control.*[15] … ***THE PHYSICIAN TRAINING PROGRAM*** … ***Learning Objectives*** *At the end of the training program you will be able to:* • *explain the Essure permanent birth control procedure* • *understand the mechanism of action of Essure permanent birth control* • *effectively counsel your patients on the benefits and risks of Essure permanent birth control* • *understand the Basic Procedure including the Pre-placement Preparation, Placement Procedure and Post-placement Follow-up* • *understand how to manage technical issues and adverse events* • *understand the clinical safety and effectiveness data gathered in the Essure clinical trials.*[16]	***ESSURE CLINICAL RESOURCE*** *Dear Doctor:* *Congratulations! You have joined a growing number of physicians who have chosen to provide their patients with the Essure in-office procedure for permanent birth control.* *The Essure Clinical Resource is a comprehensive resource that provides clinical instruction and information on the following:* • *Selecting appropriate Essure patients* • *Counseling patients on the benefits and risks of Essure* • *Performing the Essure permanent birth control procedure* • *Conducting and evaluating results of the Essure Confirmation Test* *If you have any questions that cannot be answered by this manual or the Instructions for Use, please do not hesitate to contact your Clinical Sales Specialist using the business card provided.*[17] … ***PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ABOUT ESSURE ON NEXT PAGE.***[18]	***ESSURE CLINICAL RESOURCE*** *Dear Doctor:* *The Essure Clinical Resource is a comprehensive resource that provides clinical instruction and information on the following:* • *Selecting appropriate Essure patients* • *Counseling patients on the benefits and risks of Essure* • *Performing the Essure permanent birth control procedure* • *Conducting and evaluating results of the Essure Confirmation Test* *If you have any questions that cannot be answered by this manual or the Instructions for Use, please do not hesitate to contact your local Essure representative.* ***PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ABOUT ESSURE IN THE ESSURE INSTRUCTIONS FOR USE (PAGE 84-87 OF THE PDF)***[19]

[12] MIS.500.001.0006 at [0001] / Page 2.
[13] MIS.500.001.0017 at Page 1.
[14] MIS.500.001.0017 at [0002] / Page 3.
[15] GYT.002.001.0131 at [0132] / Page 2.
[16] GYT.002.001.0131 at [0134] / Page 4.
[17] GYT.003.001.0001 at [0002] / Page 2.
[18] GYT.003.001.0001 at [0002] / Page 2.
[19] AMS.001.001.5420 at [0001] / Page 2.

3. Mechanism of action

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
Product Overview ***STOP Non-Incisional Permanent Contraception*** … *The mechanism of action of the STOP device is a benign tissue response, resulting in tissue in-growth into the device that anchors the device firmly into the fallopian tube This benign tissue response is local, fibrotic and occlusive in nature. Additionally, the histology evidence demonstrates that the tissue reaction is predictable and localized to the STOP device.*[20] … ***STOP System Overview: Delivery & Mechanism of Action***[21] … • *Contraception: method of action* • *Occlusion* • *Space-filling design* • *Benign localized tissue response to fibers* … ***Long-Term Device Anchoring Evidence***[22] • *Tissue ingrowth into and throughout device* • *Demonstrated by histology* • *PET: fiber well known fixation agent in medical devices* … ***Appendix C*** ***STOP Clinical Data Summary*** … ***B. Phase I-B Prehysterectomy Study*** …	***2. HISTORY OF CONCEPTUS AND ESSURE*** … ***Focus on Permanent Birth Control - Essure*** … *The Essure procedure delivers a soft and flexible micro-insert into a woman's fallopian tubes, which is designed to provide permanent birth control by causing an intended benign, occlusive tissue response, resulting in tissue in-growth that permanently anchors the micro-insert and occludes the fallopian tubes.*[26] … ***4. PRODUCT OVERVIEW*** … ***How it Works*** *Using a hysteroscopic approach, one Essure micro-insert is placed in the proximal section of each fallopian tube lumen. When the micro-insert expands upon release, it acutely anchors itself in the fallopian tube.* *Subsequently, the micro-insert elicits an intended benign occlusive tissue response. This tissue in-growth into the micro-insert permanently anchors the micro-insert and occludes the fallopian tube, resulting in permanent birth control.*[27] … ***Mechanism of Action*** … ***—The PET fibers elicit tissue in-growth.*** *The effectiveness of the Essure micro-insert in preventing pregnancy is believed to be due to a combination of the space filling design of the micro-insert and a local, occlusive, benign tissue response to the PET fibers. The tissue response is the result of a chronic inflammatory and fibrotic response to the PET*	***2. HISTORY OF CONCEPTUS AND ESSURE*** … ***Focus on Permanent Birth Control - Essure*** … *The Essure procedure delivers a soft and flexible micro- insert into a woman's fallopian tubes, which is designed to provide permanent birth control by causing an intended benign, occlusive tissue response, resulting in tissue in-growth that permanently anchors the micro-insert and occludes the fallopian tubes.*[29] … ***4. PRODUCT OVERVIEW*** … ***How it Works*** *Using a hysteroscopic approach, one Essure micro-insert is placed in the proximal section of each fallopian tube lumen. When the micro-insert expands upon release, it acutely anchors itself in the fallopian tube.* *Subsequently, the micro-insert elicits an intended benign occlusive tissue response. This tissue in-growth into the micro-insert permanently anchors the micro-insert and occludes the fallopian tube, resulting in permanent birth control.*[30] … ***Mechanism of Action*** … ***—The PET fibers elicit tissue in-growth.*** *The effectiveness of the Essure micro-insert in preventing pregnancy is believed to be due to a combination of the space filling design of the micro-insert and a local, occlusive, benign tissue response to the PET fibers. The tissue response is the result of a chronic inflammatory and fibrotic response to the PET*	***PRODUCT OVERVIEW*** … ***The Essure insert is a dynamic, spring-like device that expands once deployed to conform to varied diameters and shapes of fallopian tubes*** • *The spring-like mechanism is intended to provide the necessary anchoring forces during the acute phase of insert implantation (3 months post-insert placement), during which time the PET fibers within the device are eliciting tissue in-growth into the coils of the insert and around the PET fibers.* ***The efficacy of Essure is believed to be due to a combination of the space-filling design of the insert and a local, occlusive, benign tissue response to the PET fibers*** • *The tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibers. It is believed that the tissue in-growth into the insert caused by the PET fibers results in both insert retention and pregnancy prevention. PET fibers have had widespread use in the clinical setting.*[33]	***PRODUCT OVERVIEW*** … ***The Essure micro-insert is a dynamic, spring-like device that expands once deployed to conform to varied diameters and shapes of fallopian tubes.*** • *The spring-like mechanism is intended to provide the necessary anchoring forces during the acute phase of micro-insert implantation (3 months post-insert placement), during which time the PET fibres within the device are eliciting tissue in-growth into the coils of the micro-insert and around the PET fibres.* ***The efficacy of Essure is believed to be due to a combination of the space-filling design of the micro-insert and a local, occlusive, benign tissue response to the PET fibres.*** • *The tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibres. It is believed that the tissue in-growth into the micro-insert caused by the PET fibres results in both micro-insert retention and pregnancy prevention. PET fibres have had widespread use in the clinical setting.*[34] … ***INSTRUCTIONS FOR USE*** … ***II. Mechanism of Action*** *When the Essure micro-insert expands on release, it acutely anchors itself in the fallopian tube. Subsequently, the micro-insert elicits an intended benign tissue response, resulting in tissue in-growth into the micro-insert that anchors the micro-insert into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.*[35]

[20] MIS.500.001.0006 at [0009] / Page 10.
[21] MIS.500.001.0006 at [0017] / Page 18.
[22] MIS.500.001.0006 at [0021] / Page 22.
[26] MIS.500.001.0018 at [0001] / Page 2.
[27] MIS.500.001.0020 at Page 1.
[29] GYT.002.001.0131 at [0136] / Page 5.
[30] GYT.002.001.0131 at [0148] / Page 18.
[33] GYT.003.001.0001 at [0008] / Page 8.
[34] AMS.001.001.5420 at [0008] / Page 9.
[35] AMS.001.001.5420 at [0083] / Page 84.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
The histological response to the STOP device is characteristics of the histological response observed with the use of PET fibers in other anatomical sites. Specifically, the PET fibers appear to elicit a strong fibrous and inflammatory tissue response that extends into the space between the inner and outer coils of the STOP device. The tissue response consists predominantly of macrophages and mononuclear cells, with some foreign-body type giant cells and acute inflammatory cells. The fibrous response consists of both loose and dense fibrous tissue… In addition, the fibrous and tissue reaction were noted to be localized to the inner portions of the fallopian tube wall. There is no evidence that the fibrosis induced by the device will extend beyond the wall of the fallopian tube, or cause peritubal adhesions or serositis. Normal tubal architecture was present within 5mm distal to the end of the device. The histological analysis revealed normal tubal segments that were absent of inflammatory cells.[23] … ***5. Conclusion*** … *The histological evaluation of the specimens has been very supportive of the hypothesized mechanism of action, the long term anchoring and occlusion achieved by fibrosis into the device. The acute inflammatory response and low level chronic inflammatory response is consistent with other devices that have used PET fibres. The reaction is confined however to the area immediately adjacent to the device and does not extend into the tube wall. Also, immediately distal to the device the tube resumes its normal appearance.*[24] … ***Appendix D*** ***Instructions for Use*** ***Conceptus STOP Non-Incisional Permanent Contraception Kit*** ***I. Device Description/Mechanism of Action*** …	*fibers. It is believed that the tissue in-growth into the micro-insert caused by the PET fibers results in both micro-insert retention and pregnancy prevention.* *The PET fibers were chosen for this application due to their success in causing tissue in-growth into devices used in other medical applications, such as prosthetic arterial grafts, percutaneous catheters, aneurysm coils, and other long-term implants.* ***Permanency of Tubal Occlusion (and Sterilization)*** *The long-term nature of the tissue response to the Essure micro-insert is not known. The majority of the clinical data regarding PET in the fallopian tube is based on 12-24 months of implantation, with little data at 36 months. Therefore, beyond 24 months, the nature of the cellular/fibrotic response and the ability of the response and the micro-insert to maintain occlusion are not known. Data for up to 5 years of wear will become available as participants in the clinical trials of safety and effectiveness continue to be followed.*[28]	*fibers. It is believed that the tissue in-growth into the micro-insert caused by the PET fibers results in both micro-insert retention and pregnancy prevention.* *The PET fibers were chosen for this application due to their success in causing tissue in-growth into devices used in other medical applications, such as prosthetic arterial grafts, percutaneous catheters, aneurysm coils, and other long-term implants.*[31] … ***Permanency of Tubal Occlusion (and Sterilization)*** *The long-term nature of the tissue response to the Essure micro-insert is not known. The majority of the clinical data regarding PET in the fallopian tube is based on 12-48 months of implantation, with little data at 60 months. Therefore, beyond 48 months, the nature of the cellular/fibrotic response and the ability of the response and the micro-insert to maintain occlusion are not known. Data for up to 5 years of wear will become available as participants in the clinical trials of safety and effectiveness continue to be followed.*[32]		

[23] MIS.500.001.0014 at [0019] to [0020] / Pages 20 to 21.
[24] MIS.500.001.0014 at [0021] / Page 22.
[28] MIS.500.001.0020 at [0003] to [0004] / Pages 4 to 5.
[31] GYT.002.001.0131 at [0151] / Page 21.
[32] GYT.002.001.0131 at [0152] / Page 22.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
When the STOP micro-coil expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the device elicits an intended benign tissue response, resulting in tissue in-growth into the device that anchors the device firmly into the fallopian tube. This benign tissue response is local, fibrotic and occlusive in nature.[25]				

[25] MIS.500.001.0014 at [0040] / Page 41.

4. Migration or expulsion - ASOC 19(a)(i) - (ii)

<table>
<tr><th>(1)
STOP Training Manual dated 2000 / 2001
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GYT.003.001.0001</th><th>(5)
Physician Training Manual dated 2015 to 28 August 2017
AMS.001.001.5420 / AMS.001.001.5208</th></tr>
<tr>
<td>
Detailed STOP Procedure and Algorithm

Device Migration / Expulsion

• Device migration

- Movement towards the distal fallopian tube or into peritoneal cavity

• Device expulsion

- Movement out of the fallopian tube and into uterine cavity/cervix/vagina, or out of the body[36]

…

Unsatisfactory Device Location (UDL)

• Device located as follows:
  • Device not present or expelled into uterine cavity …
  • Device is believed to be in the peritoneal cavity
• Results from perforation or misplacement during initial placement procedure, not device movement[37]

…

Device Migration / Expulsion / UDL

• Detection of suspected device migration or expulsion or UDL
  • Pelvic x-ray post-procedure
  • Patient reports of expelled device(s)
  • 3-month HSG
  • Other diagnostic test to investigate potential adverse events[38]

…

Bilateral Device Expulsion

• Bilateral device expulsion confirmed by observation or x-ray
</td>
<td>
3. CLINICAL DATA OVERVIEW[50]

…

Adverse Events

…

Observed Adverse Events

Tables 6 and 7 below present adverse events that prevented reliance on Essure for contraception.

Table 6

Phase II

Adverse events that prevented reliance on Essure for contraception

<table>
<tr><td>Event</td><td>Number</td><td>Percent</td></tr>
<tr><td>Expulsion</td><td>1/206</td><td>0.5%</td></tr>
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Table 7

Pivotal Trial

Adverse events that prevented reliance on Essure for contraception

<table>
<tr><td>Event</td><td>Number</td><td>Percent</td></tr>
<tr><td>Expulsion</td><td>14/476</td><td>2.9%*</td></tr>
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<tr><td>Other unsatisfactory micro-insert location</td><td>3/476</td><td>0.6%</td></tr>
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*Fourteen women experienced an expulsion, however nine of these 14 women chose to
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3. CLINICAL DATA OVERVIEW[57]

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…

Observed Adverse Events

Tables 7 and 8 below present adverse events that prevented reliance on Essure for contraception.

Table 7

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</table>

* One patient relied on Essure micro-inserts for contraception for 31 months prior to laparotomy and cornual resection due to monthly pain associated with presence of the devices. The other 6 patients never relied on Essure micro-inserts for contraception.

Table 8

Pivotal Trial

Adverse events that prevented reliance on Essure for contraception

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HOW ESSURE WORKS

Using a hysteroscopic approach, one Essure insert is placed in the proximal section of each fallopian tube lumen across the uterotubal junction (UTJ).
  • Placement at the UTJ allows for the insert to be distal enough to prevent expulsion due to uterine contractions during menses, yet proximal enough to visualize trailing coils to show placement.[63]

…

CLINICAL DATA

RESULTS

…

Reliance Rate (Phase II and Pivotal Studies Combined)

95% of patients with successful bilateral placement were able to rely on Essure for permanent birth control (n=643/664)

<table>
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§9 out of 14 patients underwent a successful second placement procedure after expulsion.[64]

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CLINICAL DATA

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Reliance Rate (Phase II and Pivotal Studies Combined)

97% of patients with successful bilateral placement were able to rely on Essure for permanent birth control (n=643/664)

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…

§ Of the 14 women with expulsion, 9 had a second successful attempt.[69]

…

SPECIFIC ISSUES

…
</td>
</tr>
</table>

[36] MIS.500.001.0011 at [0007] / Page 8.
[37] MIS.500.001.0011 at [0009] / Page 10.
[38] MIS.500.001.0011 at [0010] / Page 11.
[50] MIS.500.001.0019 to [0006] / Pages 1 to 7.
[57] GYT.002.001.0131 at [0040] / Page 10.
[63] GYT.002.001.0131 at [0008] / Page 8.
[64] GYT.003.001.0001 at [0011] / Page 11.
[68] GYT.002.001.5420 at [0008] / Page 9.
[69] AMS.001.001.5420 at [0011] / Page 12.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
• *Patient instructed to use alternative contraception* • *Recommend other method of contraception*[39] … ***Unilateral Device Expulsion*** • *Unilateral device expulsion confirmed by observation or x-ray* • *Patient instructed to use alternative contraception* • *Recommend other method of contraception*[40] … ***Bilateral Device Migration / UDL*** • *Bilateral Device Migration / UDL confirmed by x-ray or HSG* • *Patient instructed to use alternative contraception* • *Patient undergoes laparoscopic sterilization?* • *Yes – Attempt device retrieval only if for AE or patient demand and can be done safely* • *No – Counsel on other methods of alternative contraception*[41] … ***Unilateral Device Migration / UDL*** • *Unilateral Device Migration / UDL confirmed by x-ray or HSG* • *Patient instructed to use alternative contraception* • *Patient undergoes laparoscopic sterilization?* • *Yes – Attempt device retrieval only if for AE or patient demand and can be done safely* • *No – Counsel on other methods of alternative contraception*[42]	*undergo a second micro-insert placement procedure, which was successful in all nine cases.*[51] … ***4. PRODUCT OVERVIEW*** … ***Mechanism of Action*** … *This specific portion of the anatomy was chosen for the site of implantation so that the micro-insert would be placed far enough into the tube to prevent expulsion due to uterine contractions during menses, yet still proximal enough to allow a portion of the micro-insert to trail into the uterus (specifically, 3-8 coils).*[52] … *In addition, placement at the UTJ is expected to aid in anchoring since it most consistently represents the narrowest portion of the fallopian tube. Unacceptable rates of expulsions and failures with transcervical sterilization devices that were placed more proximally, at the ostial section of the fallopian tube, have been noted in the literature. In addition, expulsion of the Essure micro-insert has occurred when placement was too proximal. Finally if the micro-insert is placed without any trailing portion of the micro-insert in the uterus, then direct visualization of micro-insert location is not possible.*[53] … ***8. POST-PLACEMENT FOLLOW-UP*** … ***Expulsion or Proximal Placement (micro-insert not placed far enough into tube)*** *The following scale should be used to categorize assessment of micro-insert location:* ***1.*** *The micro-insert is not present (expulsion) OR more than 50% of the length of the inner coil of the micro-insert is trailing into the uterine cavity (too proximal placement).*[54]	*y micro-insert location* | | | **Fourteen women experienced an expulsion, however nine of these 14 women chose to undergo a second micro-insert placement procedure, which was successful in all nine cases.* [58] … ***4. PRODUCT OVERVIEW*** … ***Mechanism of Action*** … *This specific portion of the anatomy was chosen for the site of implantation so that the micro-insert would be placed far enough into the tube to prevent expulsion due to uterine contractions during menses, yet still proximal enough to allow a portion of the micro-insert to trail into the uterus (specifically, 3-8 coils).*[59] … *In addition, placement at the UTJ is expected to aid in anchoring since it most consistently represents the narrowest portion of the fallopian tube. Unacceptable rates of expulsions and failures with transcervical sterilization devices that were placed more proximally, at the ostial section of the fallopian tube, have been noted in the literature. In addition, expulsion of the Essure micro-insert has occurred when placement was too proximal. Finally if the micro-insert is placed without any trailing portion of the micro-insert in the uterus, then direct visualization of micro-insert location is not possible.*[60] ***7. ESSURE PLACEMENT PROEDURE*** … ***Advance System into First Tube*** … *PRECAUTION: Do not continue to advance the Essure delivery system once the positioning marker on the catheter has*	***ESSURE EFFECTIVENESS IN THE COMMERCIAL SETTING*** *Data from the clinical trials show there have been no pregnancies among trial participants with up to 5 years of reliance. However, unintended pregnancies have been reported in women who have worn the inserts in the commercial setting. The table below summarizes the reasons for pregnancy from reports received by Conceptus (acquired by Bayer HealthCare in 2013), and additional reports from the published scientific literature.*[65] *Potential Contributing Factor* / *United States (US)* (*n*; *Percentage of US causes*) / *Outside of the United States (OUS)* (*n*; *Percent of OUS causes*) / *Total* (*n*; *Percent*) *Perforation** — 91; 14%; 4; 5%; 95; 13% *Expulsion** — 20; 3%; 4; 5%; 24; 3% … ***PATIENT SELECTION AND COUNSELING PATIENTS MAY HAVE QUESTIONS AND CONCERNS ABOUT THE ESSURE PROCEDURE. IT IS IMPORTANT TO MANAGE THEIR EXPECTATIONS WITH THE FOLLOWING INFORMATION:*** … • *However, no method of contraception is 100% effective and pregnancies have occurred in the commercial setting** … ** Reasons that prevented women from relying on Essure after the Essure Confirmation Test are: expulsions, perforations, incorrect location, and inadequate tubal blockage.*[66]	***EXPULSION OR MIGRATION OF THE ESSURE MICRO-INSERT*** *There is a risk that the Essure® micro-insert could move out of the fallopian tubes. This movement could be* *1) expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body), or* *2) migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity).* *Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events. Migration to the abdominal cavity can also occur without tubal perforation. Confirmatory radiological testing with abdominal x-ray, transvaginal ultrasound (TVU) or hysterosalpingogram (HSG), according to local protocols, is mandatory to establish satisfactory device placement and/or tubal occlusion.* ***Reports of expulsion or migration*** *In the 7-year retrospective study that evaluated complications of tubal sterilisation with Essure in 4306 women, 2 cases (0.04%) of asymptomatic migrations into the abdominal cavity where detected.16 Both women with abdominal migration of one device underwent another placement, retaining the migrated devices in the abdominal cavity.* *Malpositionings not otherwise specified were also reported in the MAUDE database* ***Management of expulsion or migration*** *Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s).* ***PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ABOUT ESSURE IN THE ESSURE INSTRUCTIONS FOR USE (PAGES 84-87 OF THE PDF).*** [70] … ***INSTRUCTIONS FOR USE*** …

[39] MIS.500.001.0011 at [0011] / Page 12.
[40] MIS.500.001.0011 at [0012] / Page 13.
[41] MIS.500.001.0011 at [0013] / Page 14.
[42] MIS.500.001.0011 at [0015] / Page 16.
[51] MIS.500.001.0019 at [0004] / Page 5.
[52] MIS.500.001.0020 at [0002] / Page 3.
[53] MIS.500.001.0020 at [0003] / Page 4.
[54] MIS.500.001.0024 at [0012] / Page 57.
[58] GYT.002.001.0131 at [0145] / Page 15.
[59] GYT.002.001.0131 at [0150] / Page 20.
[60] GYT.002.001.0131 at [0151] / Page 21.
[65] GYT.003.001.0001 at [0014] / Page 14.
[66] GYT.003.001.0001 at [0017] / Page 17.
[70] AMS.001.001.5420 at [0079] / Page 80.

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…	…	*reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement and/or tubal/uterine perforation. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and work-up the patient for a perforation.*[61]	…	***VII. Possible adverse effects***
Summary of Possible Adverse Effects:	***Management of Unsatisfactory Micro-insert Location***	…	***ESSURE CONFIRMATION TEST***	…
…	*The hysterosalpingogram may reveal that the micro-insert(s) is in an unsatisfactory location as described below:*	***8. POST-PLACEMENT FOLLOW-UP***	***UNSATISFACTORY LOCATION***	***C. Risks associated with Essure micro-insert wearing***
Risks Associated with Device Placement Procedure:	…	…	*There are 4 types of unsatisfactory location: proximal location of the insert, expulsion of the insert, distal location of the insert, and perforation or peritoneal location of the insert.*	*There is a risk that the **Essure** micro-insert could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube or out of the fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the micro-insert(s), and surgery may be required to remove the micro-insert(s). Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.*[71]
• …	*2. **Complete micro-insert(s) expulsion**; micro-insert(s) absent from the body.*	***Expulsion or Proximal Placement (micro-insert not placed far enough into tube)***	…	…
• *Inadvertent placement of device into myometrium*	…	…	***2. EXPULSION OF THE INSERT***	***C. Classification of Micro-insert Location***
• *Placement of device into distal tube*	***Management of Micro-insert Expulsion or Unsatisfactory Micro-insert Location***	*The following scale should be used to categorize assessment of micro-insert location:*	*One or both inserts are not present in the radiographic image.*[67]	…
• *Perforation through tube resulting in placement into peritoneal cavity*	*Based on the applicable micro-insert location and occlusion status in each fallopian tube, as diagnosed by HSG, below is a list of suggested patient management pathways.*	*1. The micro-insert is not present (expulsion) OR more than 50% of the length of the inner coil of the micro-insert is trailing into the uterine cavity (too proximal placement).*[62]		*d) Unsatisfactory Location*
Risks Associated with STOP Device Wearing:	***Note:** following micro-insert expulsion, a re-attempt to place a micro-insert should not be performed until an HSG demonstrates patency in the tube from which the expulsion occurred.*	…		…
• *Movement out of tubes (migration/expulsion)*[43]	*1. Bilateral micro-insert expulsion with bilateral occlusion: The patient should be counseled about the option to have incisional sterilization or to rely on her bilateral PTO for contraception, in light of the potential for a false positive diagnosis of tubal occlusion by HSG .*			*(2) Expulsion is suspected if one or both micro-inserts are not identified in the cornus in a coronal view in a single scout image.*[72]
…	*2. Bilateral micro-insert expulsion with occlusion in one tube and patency in contralateral tube: The patient may be considered for an additional micro-insert procedure to replace the micro-insert in the tube that is patent so that she may be able to rely on one Essure micro-insert and contralateral PTO for contraception. The patient should be counseled regarding this option, in light of the potential for a false positive diagnosis of tubal occlusion by HSG. She should also be counseled about the option to have incisional sterilization.*			…
Appendix C	*3. Unilateral micro-insert expulsion or unsatisfactory unilateral micro-insert location (in myometrium or intraperitoneal cavity) with contralateral micro-insert in a satisfactory location: If the HSG demonstrates tubal blockage in the tube from where the micro-*			***D. Pelvic X-ray***
STOP Clinical Data Summary				…
…				*2. Evaluate pelvic X-ray as follows:*
II. Clinical Investigations				…
…				*c) Unsatisfactory: Obvious intraperitoneal micro-insert location or expulsion.*[73]
B. Phase I-B Prehysterectomy Study				…
…				***E. Performing and Evaluating modified HSGs***
4. Results				…
…				*3. Assessing Micro-insert Location*
d. Adverse Events				…
There have been no reports of device movement in any patients.[44]				*b) Assess micro-insert location:*
…				
C. Phase II - Safety and Effectiveness Study				
…				
g. HSG results				
…				
Occlusion				
…				

[43] MIS.500.001.0012 at [0004] / Page 5.
[44] MIS.500.001.0014 at [0018] / Page 19.
[61] GYT.002.001.0131 at [0168] / Page 38.
[62] GYT.002.001.0131 at [0184] / Page 54.
[67] GYT.003.001.0001 at [0045] / Page 45.
[71] AMS.001.001.5420 at [0083] / Page 84.
[72] AMS.001.001.5420 at [0085] / Page 86.
[73] AMS.001.001.5420 at [0085] / Page 86.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
Unilateral occlusion was also demonstrated in 3 patients with a unilateral device. Each patient is described below: *…* *3. One patient whose device was not optimally placed and subsequently experience an expulsion.*[45] *…* *h. Adverse Events*[46] *Device-related or placement-related adverse events have been reported in 10/207 patients (5%). Each event is classified as either placement-related or device -related. Table 14 summarizes the adverse events and the treatment required for each.* *Table 14 Adverse events* *Adverse event type* / *Suspected cause* / *Classification* / *Follow-up required* *Procedure related* *Unsatisfactory device location* / *Unilateral expulsion due to proximal placement* / *Procedure* / *Second device attempt, tube stenotic* *…* *Procedure-Related Adverse Events* *The 3-month HSG indicated a unilateral device expulsion in one patient. The expelled device was not placed far enough into the tube initially, and at the time of device placement, the Investigator suspected that the device would be expelled.* *The 3-month HSG also indicated unsatisfactory device location in five patients, although bilateral tubal occlusion was also demonstrated in four of these patients. … In one of these patients one STOP device was found in the peritoneal cavity and the contralateral device was found in the distal fallopian tube. In three patients, one STOP device was found in the peritoneal cavity and the contra-lateral device remained well placed in the fallopian tube. … There was no local*	*insert was expelled or where the micro-insert should have been placed, the patient may rely on the satisfactorily located micro-insert and the contralateral PTO, in light of the potential for a false positive diagnosis of tubal occlusion by HSG. She should also be counselled regarding the option to undergo incisional sterilization.* *…* *6. If a patient has opted for incisional sterilization following any of the above listed scenarios, both tubes should be occluded regardless of any remaining micro-insert that is in a satisfactory location. An attempt should be made to retrieve a micro-insert if the physician believes it can be done safely, however micro-insert retrieval may not be possible. Use of intra-operative fluoroscopy is recommended to identify the location of the micro-insert(s) prior to and during surgery. Attempted retrieval should not exceed 30 minutes.*[55] *…* ***9. MANAGEMENT OF TECHNICAL ISSUES*** *…* ***Attempted Micro-insert Removal After Procedure*** *Should micro-insert removal be deemed necessary, a transabdominal approach i.e., laparotomy or laparoscopy) is required.* *…* *A micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.*[56]			*(1) Expulsion or proximal placement: Micro-insert is not present or ≥ 50% of inner coil trailing into the uterine cavity.*[74] *…* ***X. Management of Unsatisfactory Micro-insert Location (UML)*** ***A. Unsatisfactory micro-insert location diagnosed by hysterosalpingogram*** *…* *3. Complete micro-insert(s) expulsion: micro-insert(s) absent from the body.* *…* ***B. Management of micro-insert expulsion or unsatisfactory micro-insert location*** *1. <u>Bilateral micro-insert expulsion with bilateral occlusion</u>: the patient should be counselled about the option to have incisional sterilisation or to rely on her bilateral PTO for contraception, in light of the potential for a false positive diagnosis of tubal occlusion by Essure Confirmation Test (HSG).* *<u>2. Bilateral micro-insert expulsion with occlusion in one tube and patency in contralateral tube:</u> the patient may be considered for an additional micro-insert procedure to replace the micro-insert in the tube that is patent, so that she may be able to rely on one Essure micro-insert and contralateral PTO for contraception. The patient should be counselled regarding this option, in light of the potential for a false positive diagnoses of tubal occlusion by Essure Confirmation Test (HSG). She should also be counselled about the option to have incisional sterilisation.* *<u>3. Unilateral micro-insert expulsion or unsatisfactory unilateral micro-insert location (in myometrium or intraperitoneal cavity), with contralateral micro-insert in a satisfactory location:</u> if the Essure Confirmation Test (HSG) demonstrates tubal blockage in the tube from where the micro-insert was expelled or where the micro-insert should have been placed, the patient may rely on the satisfactorily located micro-insert and the contralateral PTO, in light of the potential for a*

[45] MIS.500.001.0014 at [0034] / Page 35.
[46] MIS.500.001.0014 at [0036] to [0037] / Pages 37 to 38.
[55] MIS.500.001.0024 at [0016] to [0017] / Pages 17 and 18.
[56] MIS.500.001.0025 at [0001] / Page 2.
[74] AMS.001.001.5420 at [0085] / Page 86.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
adverse reaction noted at the device retrieval site in any of these patients. *…* ***Appendix D*** ***Instructions for Use*** ***Conceptus STOP Non-Incisional Permanent Contraception Kit*** *…* ***VI. Clinical Data Summary***[47] *The following were reported as being likely related to the STOP device:* *…* *Expulsion of the STOP device- <1%* *…* ***VII. Possible Adverse Effects***[48] *…* ***c. Risks associated with STOP Device Wearing*** *1. There is a risk that the STOP Device could move out of the fallopian tubes. This movement could be expulsion (movement out of the fallopian tube and into the uterine cavity/cervix/vagina or out of the body) or migration (movement to the distal fallopian tube and into the peritoneal cavity). Additional x-rays may be required to identify the location of the device(s) and surgery may be required to remove the device. Device movement could result in pregnancy, ectopic pregnancy and/or pain / menstrual disturbance or other adverse events.*[49]				*false positive diagnosis of tubal occlusion by Essure Confirmation Test (HSG). She should also be counselled regarding the option to undergo incisional sterilisation.* *…* *5. Unilateral micro-insert expulsion; unsatisfactory unilateral micro-insert location (in myometrium or intraperitoneal cavity); unsatisfactory unilateral micro-insert location in "proximal location" (>50% of inner coil length trailing into uterus) or "distal location" (micro-insert in fallopian tube, but proximal end of inner coil is >30mm from contrast filling the uterine cornua) with contralateral micro-insert in an unsatisfactory location: the patient should be counselled regarding the option to undergo incisional sterilisation. In all cases, if the micro-insert removal is deemed necessary and hysteroscopic removal is not possible, incisional surgery may be required.*[75] *...* ***XII. Essure micro-insert removal*** *…* *An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.*[76]

[47] MIS.500.001.0014 at [0044] / Page 45.
[48] MIS.500.001.0014 at [0045] to [0047] / Pages 46 to 48.
[49] MIS.500.001.0014 at [0047] / Page 48.
[75] AMS.001.001.5420 at [0086] / Page 87.
[76] AMS.001.001.5420 at [0086] / Page 87.

5. Break or fragment - ASOC 19(a)(iii)

<table>
<tr>
<th>(1)
STOP Training Manual dated 2000 / 2001
MIS.500.0001.0001 to MIS.500.0001.0014</th>
<th>(2)
Essure Training Manual dated 1 May 2003
MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031</th>
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Physician Training Manual dated 2015 to 28 August 2017
AMS.001.001.5420 / AMS.001.001.5208</th>
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Appendix C

STOP Clinical Data Summary

…

II. Clinical Investigations

…

C. Phase II - Safety and Effectiveness Study

…

4. Results

…

h. Adverse Events

Device-related or placement-related adverse events have been reported in 10/207 patients (5%). Each event is classified as either placement-related or device -related. Table 14 summarizes the adverse events and the treatment required for each.

Table 14 Adverse events

Adverse event type	*Suspected cause*	*Classification*	*Follow-up required*
Procedure related			
Retained device fragment	*Broken distal ball tip during removal*	*Procedure*	*None*
Device Related			
Device failure	*Proximal band detached*	*Device*	*None, Non functional portion of device*
Device failure	*Proximal band detached*	*Device*	*None, Non functional portion of device*
Device failure	*Proximal band detached*	*Device*	*None, Non functional*

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3. CLINICAL DATA OVERVIEW

…

Adverse Events

…

Other adverse events or side effects reported as a result of the hysteroscopic placement procedure are shown below in tables 8 and 9.

Table 8

Phase II Study

Adverse events reported on day of placement procedure (N=233 procedures)

Event	*Number*	*Percent*
Band Detachment	*3*	*1.3%*

…

Table 9

Pivotal Trial

Adverse events reported on day of placement procedure (N=544 procedures)[80]

Event	*Number*	*Percent*
Band Detachment	*2*	*0.4%*

…

7. ESSURE PLACEMENT PROCEDURE

…

Delivery Wire Removal Troubleshooting Tips

…

Essure System Extraction

…

If removal of the expanded micro-insert results in breakage of the micro-insert, then the patient should be instructed to NOT rely on the broken micro-insert for contraception.

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3. CLINICAL DATA OVERVIEW

…

Adverse Events

…

Other adverse events or side effects reported as a result of the hysteroscopic placement procedure are shown below in tables 9 and 10.

Table 9

Phase II Study

Adverse events reported on day of placement procedure (N=233 procedures)

Event	*Number*	*Percent*
Band Detachment	*3*	*1.3%*

…

Table 10

Pivotal Trial

Adverse events reported on day of placement procedure (N=544 procedures)[84]

Event	*Number*	*Percent*
Band Detachment	*2*	*0.4%*

…

7. ESSURE PLACEMENT PROCEDURE

…

Remove Delivery System

…

Essure System Extraction

…

- *If removal of the expanded micro-insert results in breakage of the micro-insert, then the patient should be instructed to*

</td>
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Important Safety Information

…

Procedural Considerations

• *…Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.*[88]

…

CLINICAL DATA

…

ADVERSE EVENTS, DAY OF ESSURE PLACEMENT PROCEDURE[89]

Adverse Event / Side Effect	*Phase II*		*Pivotal*	
	Number (N = 233 procedures)	*Percent*	*Number (N = 44 procedures)*	*Percent*
Band Detachment	*3*	*1.3%*	*2*	*0.4%*

...

ESSURE PROCEDURE

Essure System Extraction

…

STEPS FOR EXTRACTION

…

Do not attempt insert removal hysteroscopically unless 18 or more coils of the Essure insert are trailing into the uterine cavity. Removal of insert may not be possible; attempted removal of inserts having fewer than 18 trailing coils may cause insert to fracture or patient injury.

…

If the Essure system must be extracted, each deployed insert should be pulled out of the fallopian tube by gentle, continuous

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Important Safety Information

…

Procedural Considerations

• *…Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.*[91]

…

CLINICAL DATA

…

ADVERSE EVENTS, DAY OF ESSURE PLACEMENT PROCEDURE[92]

Adverse Event / Side Effect	*Phase II*		*Pivotal*	
	Number (N = 233 procedures)	*Percent*	*Number (N = 44 procedures)*	*Percent*
Band Detachment	*3*	*1.3%*	*2*	*0.4%*

…

ESSURE PROCEDURE

Essure System Extraction

…

Do not attempt micro-insert removal hysteroscopically unless 18 or more coils of the Essure micro-insert are trailing into the uterine cavity. Removal of micro-insert may not be possible; attempted removal of micro-inserts having fewer than 18 trailing coils may cause micro-insert to fracture or patient injury.

…

If the Essure system must be extracted, each deployed insert should be pulled out of the fallopian tube by gentle, continuous backward movement of the delivery system.

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</table>

[80] MIS.500.001.0019 at [0005] / Page 6.
[84] GYT.002.001.0131 at [0146] / Page 16.
[88] GYT.003.001.0001 at [0003] / Page 3.
[89] GYT.003.001.0001 at [0012] / Page 12.
[91] AMS.001.001.5420 at [0003] / Page 4.
[92] AMS.001.001.5420 at [0012] / Page 13.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
<table><tr><td></td><td></td><td></td><td>portion of device</td></tr></table> *Procedure-Related Adverse Events* *The 3-month HSG also indicated unsatisfactory device location in five patients, although bilateral tubal occlusion was also demonstrated in four of these patients. … There was one attempt at immediate hysteroscopic device removal during the placement procedure when the Investigator was dissatisfied with device placement. Acute device retention was so great that the ball tip of the device detached during the removal attempt. The patient underwent an HSG after her subsequent menses, which revealed that the fragment remained in place in the proximal tube. There have been no reports of clinical sequelae to this event.* *…* *Device-Related Adverse Events* *In three patients, the proximal band of the device became detached during device placement and was noted in the x-ray to be located in the uterus. A thorough evaluation of this technical failure revealed that the process of attaching the proximal band to the device had variability. This manufacturing process was revised and a new inspection and release test method was established to address this issue. Since these changes were implemented, there have been no band detachment reports to date.*[77] *…* ***Appendix D*** ***Instructions for Use*** ***Conceptus STOP Non-Incisional Permanent Contraception Kit*** *…* ***VI. Clinical Data Summary***[78]	*even if tubal occlusion is demonstrated by HSG. Only if the patient is experiencing an adverse event should the broken micro-insert be removed.*[81] *…* ***Count Trailing Coils Ideal Placement 3-8 Coils*** *…* ***WARNING:*** *Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed and detached from the delivery wire. The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement… Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*[82] *…* ***9. MANAGEMENT OF TECHNICAL ISSUES*** ***Attempted Micro-insert Removal During Procedure*** *…* *If complete micro-insert removal is accomplished, an attempt should be made to place another Essure micro-insert. If micro-insert removal is not accomplished, it should be left in place and no attempt should be made to cut the micro-insert. If the physician is not completely satisfied that the entire Essure micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains in vivo.*[83]	*NOT rely on the broken micro-insert for contraception, even if tubal occlusion is demonstrated by HSG. Only if the patient is experiencing an adverse event should the broken micro-insert be removed.*[85] *…* ***8. POST-PLACEMENT FOLLOW-UP*** *…* ***Count Trailing Coils Ideal Placement 3-8 Coils*** *…* *WARNING: Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed (i.e., detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Instructions on how to attempt micro-insert removal are provided in Section 9. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*[86] *…* ***9. MANAGEMENT OF TECHNICAL ISSUES*** ***Attempted Micro-insert Removal During Procedure*** *…* *If complete micro-insert removal is accomplished, an attempt should be made to place another Essure micro-insert. If micro-insert removal is not accomplished, it should be left in place and no attempt should be made to cut the micro-insert. If the physician is not completely satisfied that the entire Essure micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains in vivo.*[87]	***backward movement of the delivery system*** *• If complete insert removal is accomplished, an attempt should be made to place another Essure insert. If insert removal is not accomplished, it should be left in place and no attempt should be made to cut the insert* *• If the physician is not completely satisfied that the entire Essure insert has been removed from the fallopian tube, another insert should not be placed in that tube and a post-procedure x-ray should be taken to determine if an insert fragment remains in vivo.*[90]	*• If complete micro-insert removal is accomplished, an attempt should be made to place another Essure micro-insert. If micro-insert removal is not accomplished, it should be left in place and not attempt should be made to cut the micro-insert.* *• If the physician is not completely satisfied that the entire Essure insert has been removed from the fallopian tube, another insert should not be placed in that tube and a post-procedure x-ray should be taken to determine if an insert fragment remains in vivo.*[93] *…* ***INSTRUCTIONS FOR USE*** *…* ***VII. Possible adverse effects*** *…* ***B. Risks associated with the micro-insert placement procedure*** *…* *There is a risk that the* ***Essure*** *micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the* ***Essure*** *micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert (see section XIII,* ***Essure*** *micro-insert removal). If micro-insert removal is attempted there is a possibility that the removal will not be successful or that the* ***Essure*** *micro-insert may break, leaving a fragment of the micro-insert in vivo. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the* ***Essure*** *micro-insert placement procedure.*[94] *…* ***XII. Essure micro-insert removal*** ***WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING***

[77] MIS.500.001.0014 at [0036] to [0037] / Pages 37 to 38.
[78] MIS.500.001.0014 at [0044] / Page 45.
[81] MIS.500.001.0023 at [0009] / Page 10.
[82] MIS.500.001.0023 at [0010] / Page 11.
[83] MIS.500.001.0025 at Page 1.
[85] GYT.002.001.0131 at [0173] / Page 43.
[86] GYT.002.001.0131 at [0174] / Page 44.
[87] GYT.002.001.0131 at [0188] / Page 58.
[90] GYT.003.001.0001 at [0033] / Page 33.
[93] AMS.001.001.5420 at [0034] / Page 35.
[94] AMS.001.001.5420 at [0083] / Page 84.

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The following were reported as being likely related to the STOP device: … *Proximal band detachment from the device - 1%* … *Broken tip of device retained in tube- <1/%* … ***VII. Possible Adverse Effects*** … *9. There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device … If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device in vivo. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.* [79]				***INTO THE UTERINE CAVITY.*** *Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible. If removal is attempted, the following steps should be employed:* … *7. If the physician is not completely satisfied that the entire* ***Essure*** *micro-insert has been removed from the fallopian tube, another micro-insert should NOT be placed in that tube and a post-placement x-ray should be taken to determine if a micro-insert fragment remains in vivo.*[95]

[79] MIS.500.001.0014 at [0046] / Page 47.

[95] AMS.001.001.5420 at [0086] / Page 87.

6. Perforation - ASOC 19(b)

<table>
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STOP Training Manual dated 2000 / 2001
MIS.500.0001.0001 to MIS.500.0001.0014</th><th>(2)
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GYT.003.001.0001</th><th>(5)
Physician Training Manual dated 2015 to 28 August 2017
AMS.001.001.5420 / AMS.001.001.5208</th></tr>
<tr>
<td>Procedure Requirements
Equipment Overview
…
Office hysteroscopy does not require much additional space and can be easily performed in the confines of a standard examination room. However, possible complications of office hysteroscopy are the same as those of hysteroscopy performed in a hospital setting. These include bleeding, infection, embolism, vasovagal reaction, perforation of the uterus, etc.[96]
…
Detailed STOP Procedure and Algorithm
Unsatisfactory Device Location (UDL)
• Device located as follows:
- Device not present or expelled into uterine cavity
…
- Device is believed to be in the peritoneal cavity
• Results from perforation or misplacement during initial placement procedure, not device movement[97]
…
Patient Selection
Benefits and Risks
Summary of Possible Adverse Effects:
…
<u>Risks Associated with Device Placement Procedure:</u>
…
• Perforation or dissection of fallopian tube or uterine cornua
• Uterine perforation by hysteroscope</td>
<td>3. CLINICAL DATA OVERVIEW
…
Adverse Events
…
Observed Adverse Events
Tables 6 and 7 below present adverse events that prevented reliance on Essure for contraception.
Table 6
Phase II
Adverse events that prevented reliance on Essure for contraception
<table>
<tr><td>Event</td><td>Number</td><td>Percent</td></tr>
<tr><td>Perforation</td><td>6/206</td><td>2.9%</td></tr>
</table>
…
Table 7
Pivotal Trial
Adverse events that prevented reliance on Essure for contraception[115]
<table>
<tr><td>Event</td><td>Number</td><td>Percent</td></tr>
<tr><td>Perforation</td><td>5/476</td><td>1.1%</td></tr>
</table>
…
Potential Adverse Events Not Observed in Clinical Studies
The following adverse events were not experienced by women who participated in clinical studies evaluation the Essure Permanent Birth Control System but are still possible:
…
• Perforation (a small hole) in internal bodily structures other than the uterus and fallopian tube.[116]</td>
<td>3. CLINICAL DATA OVERVIEW
…
Adverse Events
…
Observed Adverse Events
Tables 7 and 8 below present adverse events that prevented reliance on Essure for contraception.
Table 7
Phase II
Adverse events that prevented reliance on Essure for contraception
<table>
<tr><td>Event</td><td>Number</td><td>Percent</td></tr>
<tr><td>Perforation</td><td>7/206</td><td>3.4%*</td></tr>
</table>
…
Table 8
Pivotal Trial
Adverse events that prevented reliance on Essure for contraception[124]
<table>
<tr><td>Event</td><td>Number</td><td>Percent</td></tr>
<tr><td>Perforation</td><td>5/476</td><td>1.1%</td></tr>
</table>
…
Potential Adverse Events Not Observed in Clinical Studies
The following adverse events were not experienced by women who participated in clinical studies evaluating the Essure Permanent Birth Control System but are still possible:
…
• Perforation (a small hole) in internal bodily structures other than the uterus and fallopian tube.[125]</td>
<td>Important Safety Information
…
Procedural Considerations
…
Perform the Essure procedure during early proliferative phase of the menstrual cycle. Terminate the procedure if distension fluid deficit exceeds 1500cc or hysteroscopic time exceeds 20 minutes as it may signal uterine or tubal perforation. Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.[133]
…
CLINICAL DATA
RESULTS
…
Reliance Rate (Phase II and Pivotal Studies Combined)
95% of patients with successful bilateral placement were able to rely on Essure for permanent birth control (n=643/664)
<table>
<tr><td>Adverse Events Preventing Reliance</td><td>Phase II</td><td>Pivotal</td></tr>
<tr><td>Perforation</td><td>7/206 ‡ (3.4%)</td><td>5/476 (1.1%)</td></tr>
</table>
…
POTENTIAL ADVERSE EVENTS NOT OBSERVED IN CLINICAL STUDIES</td>
<td>Important Safety Information
…
Procedural Considerations
…
If Essure micro-insert placement attempts are not successful after 10 minutes of attempted cannulation per tube, the case should be discontinued and potentially rescheduled. Never attempt to advance Essure micro-insert(s) against excessive resistance or if the patient is experiencing extraordinary pain or discomfort. If tubal or uterine perforation occurs or is suspected, discontinue procedure. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods. Do not attempt hysteroscopic Essure micro-insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity.[146]
…
CLINICAL DATA
RESULTS
…
Reliance Rate (Phase II and Pivotal Studies Combined)
97% of patients with successful bilateral placement were able to rely on Essure for permanent birth control (n=643/664)
<table>
<tr><td>Adverse Events Preventing Reliance</td><td>Phase II</td><td>Pivotal</td></tr>
<tr><td>Perforation</td><td>6/206 ‡ (2.9%)</td><td>5/476 (1.1%)*</td></tr>
</table>
…
*Includes 1 patient with perforation + incorrect placement.[147]
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[96] MIS.500.001.0007 at [0001] / Page 2.
[97] MIS.500.001.0011 at [0009] / Page 10.
[115] MIS.500.001.0019 at [0004] / Page 5.
[116] MIS.500.001.0019 at [0006] / Page 16.
[124] GYT.002.001.0131 at [0145] / Page 15.
[125] GYT.002.001.0131 at [0147] / Page 17.
[133] GYT.003.001.0001 at [0003] / Page 3.
[146] AMS.001.001.5420 at [0003] / Page 4.
[147] AMS.001.001.5420 at [0011] / Page 12.

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<tr><th>(1)
STOP Training Manual dated 2000 / 2001
MIS.500.0001.0001 to MIS.500.0001.0014</th><th>(2)
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Essure Physician Training Manual in use from 7 January 2008 to January 2014
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- *Inadvertent placement of device into myometrium*

…

- *Perforation through tube resulting in placement into peritoneal cavity*[98]

..

Appendix C

STOP Clinical Data Summary

…

II. Clinical Investigations

A. Perihysterectomy study

…

4. Results

Three of the 112 tubes (3%) were perforated during the procedure. One of the perforations occurred with the use of a Support Catheter, which was associated with a high number of perforations and has since been discontinued. Another perforation occurred in a patient who had a prior tubal ligation, which may have been the cause of the perforation. No etiology was known for the third but it was the first case that the investigator had performed with this device.[99]

…

B. Phase 1-B Prehysterectomy Study

…

d. Adverse Events

…

There were three cases of tubal perforation, all without clinical sequelae. The Support Catheter was used during device placement in two of these patients, and is believed to be the cause of the perforations. Use of the Support Catheter has since been discontinued. The third perforation was likely caused by inexperience of the investigator while switching from an older version of the device to the new version. These patients did not report any significant pain or other

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7. ESSURE PLACEMENT PROCEDURE

…

Introduce Hysteroscope

…

WARNING*: In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation, e.g. in the case of stenotic cervix.*[117]

…

Advance System into First Tube

…

PRECAUTION: *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up the patient for possible perforation.*

Advance the catheter until the black positioning marker reaches the fallopian tube ostium. This visual marker indicates that the Essure microinsert is spanning the intramural and the proximal isthmic segments of the fallopian tube, with the outer coil spanning the uterotubal junction. This is the ideal placement for the Essure micro-insert.[118]

…

PRECAUTION:

Do not continue to advance the Essure delivery system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement and/or tubal/uterine perforation. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and work-up the patient for a perforation.

12. Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance. Resistance to advancement is usually apparent if: 1) the

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7. ESSURE PLACEMENT PROCEDURE

…

Introduce Hysteroscope

…

WARNING*: In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation, e.g. in the case of stenotic cervix.*[126]

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Advance System into First Tube

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PRECAUTION: *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up the patient for possible perforation.*

Advance the catheter until the black positioning marker reaches the fallopian tube ostium. This visual marker indicates that the Essure microinsert is spanning the intramural and the proximal isthmic segments of the fallopian tube, with the outer coil spanning the uterotubal junction. This is the ideal placement for the Essure micro-insert.[127]

…

PRECAUTION: *Do not continue to advance the Essure delivery system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement and/or tubal/uterine perforation. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and work-up the patient for a perforation.*

12. Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance. Resistance to advancement is usually apparent if: 1) the

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The following adverse events were not experienced by clinical trial participants but are still possible and/or have occurred in the commercial setting:

…

- *Perforation of internal bodily structures other than the uterus and fallopian tube*[134]

…

ESSURE EFFECTIVENESS IN THE COMMERCIAL SETTING

… The table below summarizes the reasons for pregnancy from reports received by Conceptus (acquired by Bayer HealthCare in 2013), and additional reports from the published scientific literature.[135]

Potential Contributing Factor	*United States (US)*		*Outside of the United States (OUS)*		*Total*	
	n	*Percentage of US causes*	*n*	*Percent of OUS causes*	*n*	*Percent*
*Perforation**	*91*	*14%*	*4*	*5%*	*95*	*13%*

…

PATIENT SELECTION AND COUNSELING

**Reasons that prevented women from relying on Essure after the Essure Confirmation Test are: expulsions, perforations, incorrect location, and inadequate tubal blockage.*[136]

…

- *A patient may need a surgical procedure to manage a situation where Essure has perforated the fallopian tube or uterus or there is persistent pelvic pain. One patient in clinical trials requested removal for pain. Removal will likely require surgery, and may*

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POTENTIAL ADVERSE EVENTS NOT OBSERVED IN PHASE II AND PIVOTAL CLINICAL STUDIES

The following adverse events were not experienced by clinical trial participants but are still possible and/or have occurred in the commercial setting:

…

- *Perforation of internal bodily structures other than the uterus and fallopian tube*[148]

…

ESSURE EFFECTIVENESS IN THE COMMERCIAL SETTING

… The table below summarizes the reasons for pregnancy from reports received by Conceptus (acquired by Bayer HealthCare in 2013), and additional reports from the published scientific literature. [149]

Potential Contributing Factor	*United States (US)*		*Outside of the United States (OUS)*		*Total*	
	n	*Percentage of US causes*	*n*	*Percent of OUS causes*	*n*	*Percent*
*Perforation**	*91*	*14%*	*4*	*5%*	*95*	*13%*

…

**Reasons that prevented women from relying on Essure after the Essure Confirmation Test are: expulsions, perforations, incorrect location, inadequate tubal blockage, and non-adherence to the Confirmation Test protocol (not using an alternative contraception or not attending for the confirmation test).*[150]

…

- *A patient may need a surgical procedure to manage a situation where Essure has perforated the fallopian tube or uterus or there is persistent*

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[98] MIS.500.001.0012 at [0004] / Page 5.
[99] MIS.500.001.0014 at [0013] / Page 14.
[117] MIS.500.001.0023 at Page 1.
[118] MIS.500.001.0023 at [0002] / Page 3.
[126] GYT.002.001.0131 at [0165] / Page 35.
[127] GYT.002.001.0131 at [0167] / Page 37.
[134] GYT.003.001.0001 at [0013] / Page 13.
[135] GYT.003.001.0001 at [0014] / Page 14.
[136] GYT.003.001.0001 at [0017] / Page 17.
[148] AMS.001.001.5420 at [0013] / Page 14.
[149] AMS.001.001.5420 at [0014] / Page 15.
[150] AMS.001.001.5420 at [0017] / Page 18.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
discomfort during the 12- 15 weeks that they wore the devices prior to hysterectomy.[100] … ***5. Conclusion*** ***…*** *While 3 perforations were noted at the time of hysterectomy, as noted, 2 were with a now discontinued support catheter. Despite the perforations it should be noted that these three women noted no discomfort or difference in tolerance to the devices than women without perforation.*[101] … ***C. Phase II - Safety and Effectiveness Study*** … ***4. Results*** … *b. Device Placement Procedure* *Device Placement Rates* … *In the 25 patients in whom bilateral device placement did not occur, failure to place devices bilaterally was due to … a possible perforation/ placement in endometrial tissue in 1 patient (4%).*[102] … *e. Patient Diaries* *Patients were asked to complete a diary during the first six months after device wearing, noting menstruation, coital acts, and any unusual pain, bleeding, or unusual symptoms.*[103] … *According to the diaries received, 19/120 (16 %) patients indicated that they experienced pain that was greater than normal during intercourse at some point in their diary recordings. Twelve patients (I0%) reported this pain at some point during the first month*	*black positioning marker on the outside surface of the catheter does not advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the delivery catheter. When such resistance to forward advancement of the catheter is observed or felt, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up HSG should be undertaken to determine tubal patency.* ***WARNING:*** *When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert against excessive resistance. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and work-up the patient for a perforation.*[119] … ***Delivery Wire Removal Troubleshooting Tips*** … ***Use of Hysteroscope Tip*** … ***Note: To avoid perforation, do not push the hysteroscope into the uterine wall. Maintain visibility of the micro-insert and the surrounding uterine tissue at all times.***[120] … ***Record Notes in Patient Chart*** *24. Record the number of coils of the micro-insert trailing into the uterine cavity, noting any issues with identifying or confirming either tubal ostium or any concern regarding potential perforation. These should be noted in patient records for subsequent reference when reviewing the three-month x-ray (See Section 8). Additionally, the following information should be noted in the patient records:*	*black positioning marker on the outside surface of the catheter does not advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the delivery catheter. When such resistance to forward advancement of the catheter is observed or felt, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up HSG should be undertaken to determine tubal patency.* ***WARNING:*** *When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert against excessive resistance. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and work-up the patient for a perforation.*[128] … ***Removal Delivery System*** … ***Use of Hysteroscope Tip*** … ***Note: To avoid perforation, do not push the hysteroscope into the uterine wall. Maintain visibility of the micro-insert and the surrounding uterine tissue at all times.***[129] … ***Record Notes in Patient Chart*** *24. Record the number of coils of the micro-insert trailing into the uterine cavity, noting any issues with identifying or confirming either tubal ostium or any concern regarding potential perforation. These should be noted in patient records for subsequent reference when reviewing the three-month x-ray (See Section 8). Additionally, the following information should be noted in the patient records:*	*necessitate abdominal incision, general anesthesia, or possible hysterectomy*[137] … ***ESSURE PROCEDURE*** ***Placement Steps*** *• If dilation is necessary, dilate only as much as is required to insert the hysteroscope. In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation, e.g., in the case of stenotic cervix.*[138] … *If excessive resistance occurs (ie, catheter does not advance toward tubal ostium and/or catheter bends or flexes excessively), terminate procedure to avoid uterine perforation or placement into a false passage.*[139] … *Do not continue to advance the Essure delivery system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory insert placement and/or tubal/ uterine perforation. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and examine the patient for a perforation.* *This visual marker indicates that the Essure insert is spanning the intramural and the proximal isthmic segments of the fallopian tube, with the outer coil spanning the uterotubal junction. This is the ideal placement for the Essure insert.*[140] … ***Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and examine the patient for possible perforation.*** ***When introducing the Essure insert into the fallopian tube, never advance the***	*pelvic pain. One patient in clinical trials requested removal for pain. Removal will likely require surgery, and may necessitate abdominal incision, general anaesthesia, or possible hysterectomy.*[151] … ***PATIENT INFORMATION*** ***Risks Of Essure*** ***Chronic Pain*** *There are rare reports of chronic pelvic pain in women with Essure.* • *Chronic pelvic pain may be related to malposition of the device, cornual perforation or complications with concomitant ablation* … ***Perforation*** *Perforation of the fallopian tube, uterus, or other internal bodily structures is an uncommon adverse event that has been reported with the Essure sterilization procedure.* *Management of tubal or uterine perforations caused by Essure placement may include laparoscopic retrieval of the micro-insert and laparoscopic sterilization: Additional complications resulting from perforation may require surgical intervention.*[152] … ***ESSURE PROCEDURE*** ***PLACEMENT STEPS*** … *• If dilation is necessary, dilate only as much as is required to insert the hysteroscope. In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation, e.g., in the case of stenotic cervix.*[153] …

[100] MIS.500.001.0014 at [0018] / Page 19.
[101] MIS.500.001.0014 at [0021] / Page 22.
[102] MIS.500.001.0014 at [0027] / Page 28.
[103] MIS.500.001.0014 at [0031] / Page 32.

[119] MIS.500.001.0023 at [0003] / Page 4.
[120] MIS.500.001.0023 at [0008] / Page 9.
[128] GYT.002.001.0131 at [0168] / Page 38.
[129] GYT.002.001.0131 at [0172] / Page 42.

[137] GYT.003.001.0001 at [0018] / Page 18.
[138] GYT.003.001.0001 at [0025] / Page 25.
[139] GYT.003.001.0001 at [0027] / Page 27.
[140] GYT.003.001.0001 at [0027] / Page 27.

[151] AMS.001.001.5420 at [0018] / Page 19.
[152] AMS.001.001.5420 at [0019] / Page 20.
[153] AMS.001.001.5420 at [0026] / Page 27.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
after device placement. Two of these 7 patients experienced perforations[104] … *…* *h. Adverse Events[105]* *Device-related or placement-related adverse events have been reported in 10/207 patients (5%). Each event is classified as either placement-related or device -related. Table 14 summarizes the adverse events and the treatment required for each.* *Table 14 Adverse events* *Adverse event type* / *Suspected cause* / *Classification* / *Follow-up required* *Procedure related* *Unsatisfactory device location* / *Perforation* / *Procedure* / *Laparoscopic sterilization* *Unsatisfactory device location* / *Partial perforation of myometrium* / *Procedure* / *Laparoscopic sterilization* *Unsatisfactory device location* / *Perforation* / *Procedure* / *Laparoscopic sterilization* *…* *Procedure-Related Adverse Events* *…* *The 3-month HSG also indicated unsatisfactory device location in five patients, although bilateral tubal occlusion was also demonstrated in four of these patients. … In one of these patients one STOP device was found in the peritoneal cavity and the contralateral device was found in the distal fallopian tube. In three patients, one STOP*	*• Concern, at the time of micro-insert placement, of possible perforation due to excessive force required on the delivery catheter, a sudden loss of resistance, or no visible trailing length, as seen hysteroscopically after device placement.[121]* *…* ***Management of Unsatisfactory Micro-insert Location*** *The hysterosalpingogram may reveal that the micro-insert(s) is in an unsatisfactory location as described below:* *…* *4.* ***Perforation:*** *micro-insert(s) partially or fully perforated.[122]* *…* ***9. MANAGEMENT OF TECHNICAL ISSUES*** ***Attempted Micro-insert Removal During Procedure*** ***Warning:*** *Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed and detached from the delivery wire. The only exception is during the actual placement procedure when removal may be attempted if 18 or more expanded coils of the Essure micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.[123]*	*• Concern, at the time of micro-insert placement, of possible perforation due to excessive force required on the delivery catheter, a sudden loss of resistance, or no visible trailing length, as seen hysteroscopically after device placement.[130]* *…* *Expulsion or Proximal Placement (micro-insert not placed far enough into tube)* *The following scale should be used to categorize assessment of micro-insert location:* *1. The micro-insert is not present (expulsion) OR more than 50% of the length of the inner coil of the micro-insert is trailing into the uterine cavity (too proximal placement).[131]* *…* ***9. MANAGEMENT OF TECHNICAL ISSUES*** ***Attempted Micro-insert Removal During Procedure*** ***Warning:*** *Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed (i.e., detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more expanded coils of the Essure micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.[132]*	***insert against excessive resistance. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and examine the patient for a perforation.*** ***Note:*** *Proper alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance. Resistance to advancement is usually apparent if:* *• The black positioning marker on the outside surface of the catheter does not advance forward towards the tubal ostium, and/or* *• The delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the delivery catheter. When such resistance to forward advancement of the catheter is observed or felt, no further attempts should be made to place the insert in order to avoid the possibility of uterine perforation or inadvertently placing the insert in the uterine musculature rather than within the tubal lumen. A follow-up Essure Confirmation Test should be undertaken to determine location and tubal patency.[141]* *…* *Record the number of coils of the micro-insert trailing into the uterine cavity, noting any issues with identifying or confirming either tubal ostium or any concern regarding potential perforation. These should be noted in patient records for subsequent reference when reviewing the 3-month Essure Confirmation Test. Additionally, the following information should be noted in the patient records* • *Concern, at the time of insert placement, of possible perforation due to excessive force required on the delivery catheter, a sudden loss of resistance of no visible trailing length, as seen hysteroscopically after insert placement.* *…* ***Insert removal should not be attempted hysteroscopically once the insert has been***	*If excessive resistance occurs (i.e., catheter does not advance toward tubal ostium and/or catheter bends or flexes excessively), terminate procedure to avoid uterine perforation or placement into a false passage.[154]* *…* *Do not continue to advance the Essure delivery system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement and/or tubal/ uterine perforation. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and examine the patient for a perforation.* *This visual marker indicates that the Essure micro-insert is spanning the intramural and the proximal isthmic segments of the fallopian tube, with the outer coil spanning the uterotubal junction. This is the ideal placement for the Essure micro-insert.[155]* *…* ***Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and examine the patient for possible perforation.*** ***When introducing the Essure micro-insert into the fallopian tube, never advance the micro-insert against excessive resistance. If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure and examine the patient for a perforation.*** ***Note:*** *Proper alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent if:* *• The black positioning marker on the outside surface of the catheter does not advance forward towards the tubal ostium, and/or*

[104] MIS.500.001.0014 at [0031] / Page 32.
[105] MIS.500.001.0014 at [0036] to [0037] / Pages 37 to 38.
[121] MIS.500.001.0023 at [0010] / Page 11.
[122] MIS.500.001.0024 at [0016] / Page 17.
[123] MIS.500.001.0025 at Page 1.
[130] GYT.002.001.0131 at [0174] / Page 44.
[131] GYT.002.001.0131 at [0184] / Page 54.
[132] GYT.002.001.0131 at [0188] / Page 58.
[141] GYT.003.001.0001 at [0028] / Page 28.
[154] AMS.001.001.5420 [0028] / Page 29.
[155] AMS.001.001.5420 [0028] / Page 29.

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device was found in the peritoneal cavity and the contra-lateral device remained well placed in the fallopian tube. A perforation was the suspected cause of the unsatisfactory device location in these patients, and the since discontinued Support Catheter was used with one of these patients. In two of these patients, the device was retrieved from the peritoneal cavity without incident… In the fifth patient, there was an inadvertent device placement into the myometrium (partial perforation). The Support Catheter was also used with this patient. There was no local adverse reaction noted at the device retrieval site in any of these patients. … There have been no reported serious side effects from any of these patients, and only one patient (with bilateral unsatisfactory device locations) reported intermittent pain with menses.[106] *…* *Unrelated Adverse Events* *…* *The Support Catheter was associated with a high number of perforations experienced in STOP clinical trials and has since been discontinued.*[107] *…* ***Appendix D*** ***Instructions for Use*** ***Conceptus STOP Non-Incisional Permanent Contraceptive Kit*** *…* ***IV. Warnings*** *…* *Do not continue to advance the STOP System once the positioning bump on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory device placement or tubal/uterine perforation. If a tubal perforation*			***placed (ie, detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the insert are trailing into the uterine cavity. Because of insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of an insert having fewer than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*** [142] *…* ***Post- Procedure*** *…* *The following should be recorded in the patient chart:* *…* • ***Possible perforation:*** *Concern at the time of insert placement of possible perforation due to excessive force required on the delivery catheter, a sudden loss of resistance, or no visible trailing length in the uterus as seen hysteroscopically after insert placement.*[143] *…* ***ESSURE CONFIRMATION TEST*** ***UNSATISFACTORY LOCATION*** *There are 4 types of unsatisfactory location: proximal location of the insert, expulsion of the insert, distal location of the insert, and perforation or peritoneal location of the insert.* *…* ***4. Perforation or peritoneal location of the insert*** *When perforation occurs, the insert has punctured the uterine cavity. Peritoneal location means the insert is within the peritoneal cavity through a uterine perforation.* *How to manage:* *Advise patient not to rely on Essure for contraception. If tube is patent, counsel patient on repeat placement procedure. If*	*• The delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the delivery catheter. When such resistance to forward advancement of the catheter is observed or felt, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up Essure Confirmation Test should be undertaken to determine location and tubal patency.*[156] *…* *16. Record the number of coils of the micro-insert trailing into the uterine cavity, noting any issues with identifying or confirming either tubal ostium or any concern regarding potential perforation… Additionally, x-ray and TVU should not be used as the Essure Confirmation Test under the following circumstances:* *a) difficult placement procedure including one or more of the following:* *(1) concern at the time of placement of possible perforation due to excessive force required for micro-insert delivery and/or a sudden loss of resistance* *…* ***Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed (i.e., detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of an insert having fewer than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.***[157] *…* ***POST-PROCEDURE*** *…*

[106] MIS.500.001.0014 at [0037] / Page 38.
[107] MIS.500.001.0014 at [0038] / Page 39.
[142] GYT.003.001.0001 at [0032] / Page 32.
[143] GYT.003.001.0001 at [0035] / Page 35.
[156] AMS.001.001.5420 at [0029] / Page 30.
[157] AMS.001.001.5420 at [0033] / Page 34.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
occurs or is suspected, do not continue with STOP device placement attempt. [108] … *Once the device has been placed, device removal should not be attempted hysteroscopically, unless 20 or more coils of the STOP device are trailing into the uterine cavity. Removal of such a device should be attempted immediately following the placement. However, removal may not be possible.* [109] … ***V. Precautions*** … *In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.*[110] … ***VI. Clinical Data Summary***[111] … *The following were reported as being likely related to the STOP device:* *Uterine perforation with the device- 1%* … ***VII. Possible Adverse Effects***[112] … *5. There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection, however treatment is typically not required.* *6. There is a risk of uterine perforation by the hysteroscope, STOP System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention*			*tube is occluded, advise patient on potential for false-positive diagnosis of occlusion. Also counsel patient on incisional sterilization or remaining on alternative contraception.* ***Note:*** *additional radiographs that include oblique and lateral images may be helpful to evaluate location if a perforation is suspected.*[144] … ***MANAGING TECHNICAL ISSUES*** … *USE OF HYSTEROSCOPE TIP* … *Note: To avoid perforation, do not push the hysteroscope into the uterine wall. Maintain visibility of the insert and the surrounding uterine tissue at all times.*[145]	*The following should be recorded in the patient chart:* … • ***Possible perforation:*** *Concern at the time of micro-insert placement of possible perforation due to excessive force required on the delivery catheter, a sudden loss of resistance, or no visible trailing length in the uterus as seen hysteroscopically after micro-insert placement*[158] … ***Classification of Micro Insert Location*** … *d) Unsatisfactory Location* … *(5) Perforation is suspected if the linear axis of one or both micro-inserts are parallel to the endometrial stripe in the sagittal view, or if the linear axis of a micro-insert is visualised crossing the myometrium in the midline sagittal view.*[159] … ***HYSTEROSALPINGOGRAM (HSG)*** ***Performing and Evaluating an HSG*** ***Unsatisfactory Location*** *There are 4 types of unsatisfactory location: proximal location of the micro-insert, expulsion of the micro-insert, distal location of the micro-insert, and perforation or peritoneal location of the micro-insert.* … ***4. Perforation or peritoneal location of the micro-insert*** *When perforation occurs, the micro-insert has punctured the uterine cavity. Peritoneal location means the micro-insert is within the peritoneal cavity though a uterine perforation.* … ***MANAGING TECHNICAL ISSUES*** …

[108] MIS.500.001.0014 at [0041] / Page 42.
[109] MIS.500.001.0014 at [0041] / Page 42.
[110] MIS.500.001.0014 at [0042] / Page 43.
[111] MIS.500.001.0014 at [0044] / Page 45.
[112] MIS.500.001.0014 at [0045] to [0047] / Pages 46 to 48.
[144] GYT.003.001.0001 at [0045] / Page 45.
[145] GYT.003.001.0001 at [0056] / Page 56.
[158] AMS.001.001.5420 at [0035] / Page 36.
[159] AMS.001.001.5420 at [0051] / Page 52.

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maybe required, but is unlikely, if such injury were to occur… *7. There is a risk that the STOP device may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. … Placement of the device in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the device(s) is required, salpingectomy or hysterectomy may be required.*[113] *…* ***VIII. Directions For Use*** *…* *13. … Advance the delivery system until the positioning bump on the distal catheter reaches the fallopian tube ostium. This visual marker indicates that the STOP device is spanning the distal intramural to proximal isthmic segments of the fallopian tube, with the outer coil spanning the uterotubal junction. This is the ideal placement for the STOP device.* *14. … When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the device in order to avoid the possibility of uterine perforation or inadvertently placing the device in the uterine musculature rather than the tubal lumen.* [114]				***Use of Hysteroscope Tip*** *…* ***Note**: To avoid perforation, do not push the hysteroscope into the uterine wall. Maintain visibility of the micro-insert and the surrounding uterine tissue at all times.*[160] *…* ***SPECIFIC ISSUES*** *…* ***POST-OPERATIVE OR CHRONIC PELVIC PAIN*** ***Patients who experience postoperative pain*** *…* *Chronic pelvic pain may be related to malposition of the device, cornual perforation or complications with concomitant ablation.*[161] *…* ***PERFORATION*** *Perforation of the fallopian tube, uterus or other internal bodily structures is an uncommon adverse event that has been reported with the Essure procedure.* *Procedural difficulties, such as poor visualisation and high resistance, have been identified as predisposing factors for tubal perforation using Essure micro-insert device.3 Patients with perforations from Essure placement may either be symptomatic (e.g., experience pain) or asymptomatic.* ***Incidence of perforations*** *According to the Essure Instructions for Use, 1.8% (12/673) of clinical trial patients had device-related perforations. Most perforations were diagnosed either at the time of micro-insert placement or at the 3-month HSG.* *In the Pivotal trial, tubal perforations occurred in 4 (0.9%) of 464 women who achieved bilateral placement with Essure.* *In the Phase II trial, 6 cases of perforation of the uterine wall or tubal lumen were reported (2 cases involved the micro-insert device; 4 cases involved the support catheter, which*

[113] MIS.500.001.0014 at [0046] / Page 47.

[114] MIS.500.001.0014 at [0050] to [0051] / Pages 51 to 52.

[160] AMS.001.001.5420 at [0077] / Page 78.

[161] AMS.001.001.5420 at [0078] / Page 79.

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				has subsequently been removed from the insertion protocol. *A 7-year retrospective study that evaluated complications of tubal sterilisation with Essure in 4306 women reported 1 (0.02%) woman who had tubal perforation as a longer-term complication (following the initial 3-month follow-up period).* ***Perforation management*** *Management of tubal or uterine perforations caused by Essure® placement may include laparoscopic retrieval of the micro-insert and laparoscopic sterilisation or repeat micro-insert placement.* *Additional complications resulting from perforation may require surgical intervention.* *Complications of a perforation may include bladder or bowel injury. Small bowel obstruction (SBO) secondary to perforation with the placement of Essure was discussed in 2 case reports.*[162] … ***INSTRUCTIONS FOR USE*** … ***V. Warnings*** *When introducing the **Essure** micro-insert into the fallopian tube, never advance the micro-insert(s) against excessive resistance.*[163] *Do not continue to advance the **Essure** system once the positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory micro-insert placement or tubal/uterine perforation.*[164] *If a tubal perforation occurs or is suspected, do not continue with the **Essure** micro-insert placement attempt. A very small percentage of women in the **Essure** clinical trials (1.8% or 12/682 patients) were identified as having device related tubal perforations. Retrieval of perforating micro-inserts, if necessary, will require laparoscopy or other surgical methods.*[165] … ***VI. Precautions***

[162] AMS.001.001.5420 at [0079] / Page 80.

[163] AMS.001.001.5420 at [0083] / Page 84.

[164] AMS.001.001.5420 at [0083] / Page 84.

[165] AMS.001.001.5420 at [0083] / Page 84.

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				… *In order to reduce the risk of uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.*[166] … ***VII. Possible adverse effects*** … ***B. Risks associated with the micro-insert placement procedure*** … *There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required.*[167] *There is a risk of uterine perforation by the hysteroscope,* ***Essure*** *system or other instruments used during the procedure with possible injury to the bowel, bladder and major blood vessels. Surgical intervention may be required, but is unlikely, if such injury were to occur. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.*[168] … *There is a risk that the* ***Essure*** *micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result. If the patient elects to undergo incisional sterilisation or other surgical intervention, micro-insert retrieval from the peritoneal cavity may be attempted if the physician believes it is safe to do so. However, micro-insert retrieval may not be possible if the micro-insert cannot be visualised or accessed by the physician.*[169] … ***D. Risks associated with follow-up procedures*** …

[166] AMS.001.001.5420 at [0083] / Page 84.

[167] AMS.001.001.5420 at [0083] / Page 84.

[168] AMS.001.001.5420 at [0083] / Page 84.

[169] AMS.001.001.5420 at [0083] / Page 84.

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				*The following additional risks are associated with the **Essure** Confirmation Test (HSG) procedure if needed: vasovagal response; infection, which may require antibiotic treatment and in rare cases could require hospitalisation; intravasation; perforation of the uterus; uterine cramping and/or bleeding; pain or discomfort; allergic reaction to latex. Latex exposure has been reported to be associated with anaphylactic reactions in rare cases, which may lead to death.*[170] *…* ***VIII. Directions for use*** *…* ***B. Essure micro-insert placement procedure*** *…* *4. Insert a sterile hysteroscope, with attached camera and operating channel (~ 5 French), through the cervix into the uterine cavity. If necessary, perform cervical dilation to allow insertion. In order to prevent uterine perforation, the procedure should be discontinued if excessive force is required to achieve cervical dilatation.*[171] *…* *9. Proper concentric alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualisation without undue resistance. Resistance to advancement is usually apparent in two ways: 1) the black marker on the outside surface of the catheter is seen not to advance forward towards the tubal ostium, and/or 2) the delivery catheter bends or flexes excessively, thus preventing the physician from applying forward pressure on the catheter assembly. When such resistance to forward motion of the catheter is observed, no further attempts should be made to place the micro-insert in order to avoid the possibility of uterine perforation or inadvertently placing the micro-insert in the uterine musculature rather than within the tubal lumen. A follow-up **Essure** Confirmation Test (HSG) should be undertaken to determine tubal patency.* *…*

[170] AMS.001.001.5420 at [0083] / Page 84..

[171] AMS.001.001.5420 at [0084] / Page 85

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
				19. Record the length of the micro-insert trailing into the uterine cavity, noting any issues with identifying or confirming either tubal ostium or any concerns regarding potential perforation. These should be noted in patient records for subsequent reference when review the Essure Confirmation Test.[172] … ***X. MANAGEMENT OF UNSATISFACTORY MICRO-INSERT LOCATION (UML)*** ***A. Unsatisfactory micro-insert location diagnosed by hysterosalpingogram*** … *4. Perforation: micro-insert(s) partially or fully perforated.*[173]

[172] AMS.001.001.5420 at [0085] / Page 86.

[173] AMS.001.001.5420 at [0086] / Page 87.

7. Leach nickel (or other metals) - ASOC 19(c)(i)

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
---	***5. PATIENT SELECTION, SCREENING AND COUNSELING*** … ***Contraindications*** *The Essure Permanent Birth Control System should not be used in any patient who is:* … *Or any patient with any of the following conditions:* … • *Known allergy to contrast media, or known hyper-sensitivity to nickel confirmed by skin test.* ***WARNING****: Patients with suspected hypersensitivity to nickel should undergo a skin test to assess hypersensitivity prior to an Essure placement procedure.*[174]	***5. PATIENT SELECTION, SCREENING AND COUNSELING*** … ***Contraindications*** *The Essure Permanent Birth Control System should not be used in any patient who is:* … *Or any patient with any of the following conditions:* … • *Known allergy to contrast media, or known hyper-sensitivity to nickel confirmed by skin test.* ***WARNING:*** *Patients with suspected hypersensitivity to nickel should undergo a skin test to assess hypersensitivity prior to an Essure placement procedure.*[175]	***ESSURE CLINICAL RESOURCE*** … ***Important Safety Information*** … ***Nickel Allergy*** *Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.*[176] … ***PATIENT SELECTION AND COUNSELING*** … ***Additional Considerations*** … • *The Essure insert includes nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from the device. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.*[177]	***Important Safety Information*** … ***Nickel Titanium Allergy*** *Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.*[178] … ***PATIENT SELECTION AND COUNSELING*** … ***Additional Considerations*** … • *The Essure micro-insert includes nickel-titanium alloy, which is generally considered a well-tolerated substance. However, in vitro testing has demonstrated that nickel is released from the device. Patients who are allergic to nickel-titanium may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.*[179] … ***INSTRUCTIONS FOR USE*** … ***V. Warnings*** … *Persons allergic to nickel titanium may suffer an allergic reaction to the micro-insert.*[180]

[174] MIS.500.001.0021 at Page 1.
[175] GYT.002.001.0131 at [0153] / Page 23.
[176] GYT.003.001.0001 at [0003] / Page 3.
[177] GYT.003.001.0001 at [0018] / Page 18.
[178] AMS.001.001.5420 at [0003] / Page 4.
[179] AMS.001.001.5420 at [0018] / Page 19. / Page 19.
[180] AMS.001.001.5420 at [0083] / Page 84.

8. Pain - ASOC 19(c)(ii), 20(a)

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AMS.001.001.5420 / AMS.001.001.5208</th>
</tr>
<tr>
<td>
Patient Selection
Benefits and Risks
Summary of Possible Adverse Effects:
…
<u>Risks Associated with Device Placement Procedure:</u>
…
• Pain, cramping, vaginal bleeding
<u>Risks Associated with STOP Device wearing:</u>
…
• Pelvic pain and cramping.[181]
…
Appendix C
STOP Clinical Data Summary
…
II. Clinical Investigations
…
B. Phase 1-B Prehysterectomy Study
…
4. Results
…
b. Device-Wearing, Acute
…
Post-procedure pain was reported in 65% of Patients with successful placement of at least one device. This pain was resolved within 4 days.[182]
…
c. Device-Wearing, Longer Term
…
There were no reports of pain during device wearing. No pain was reported during pelvic exams conducted just prior to the hysterectomy in any of the patients.[183]
</td>
<td>
3. CLINICAL DATA OVERVIEW[196]
…
Adverse Events
…
Table 8
Phase II Study
Adverse events reported on day of placement procedure (N=233 procedures)
<table>
<tr><th>Event</th><th>Number</th><th>Percent</th></tr>
<tr><td>Pain</td><td>2</td><td>0.9%</td></tr>
</table>
Table 9
Pivotal Trial
Adverse events reported on day of placement procedure (N=544 procedures)
<table>
<tr><th>Event</th><th>Number</th><th>Percent</th></tr>
<tr><td>Cramping</td><td>161</td><td>29.6%</td></tr>
<tr><td>Pain</td><td>70</td><td>12.9%</td></tr>
</table>
…
In addition, the majority of women experienced mild to moderate pain during and immediately following the procedure, and the majority of women experienced spotting for an average of 3 days after the procedure. Pain was managed in every case with oral non-steroidal anti-inflammatory drug (NSAIDs) or oral narcotic pain reliever.
Table 10 summarizes all adverse events rated by the Investigators to be at least "possibly" related to the Essure micro-insert or micro-insert placement procedure during the first year of reliance on Essure in the Pivotal trial (approximately 15 months post-device placement). The percentages presented reflect the number of events in the numerator and the number of women in the trial in the denominator. While women reporting numerous episodes of the same
</td>
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3. CLINICAL DATA OVERVIEW
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Adverse Events
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</td>
<td>
ESSURE CLINICAL RESOURCE
…
Important Safety Information
…
Clinical Trial Experience
…
The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain and dyspareunia.[212]
…
CLINICAL DATA
…
Adverse Events. Day of Essure Placement Procedure
<table>
<tr><th rowspan="2">Adverse Event / Side Effect</th><th colspan="2">Phase II</th><th colspan="2">Pivotal</th></tr>
<tr><th>Number (N=233 procedures)</th><th>Percent</th><th>Number (N=544 procedures)</th><th>Percent</th></tr>
<tr><td>Cramping</td><td>*</td><td>*</td><td>161</td><td>29.6</td></tr>
<tr><td>Pain</td><td>2</td><td>0.9%</td><td>70</td><td>12.9</td></tr>
</table>
Most women experienced mild to moderate pain during and immediately following the procedure. Pain was managed with oral nonsteroidal anti-inflammatory drugs (NSAIDs) or oral narcotic pain reliever.
Adverse Events, First Year of Reliance (Pivotal Trial)*
The following adverse events were rated as "possibly" related to the insert or procedure during the first year of reliance in the Pivotal trial… Percentages reflect the number of events divided by the number of participants in the trial. When numerous episodes of the same event were reported by one participant,
</td>
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Important Safety Information
…
Clinical Trial Experience
…
The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain and dyspareunia.[220]
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CLINICAL DATA
…
Adverse Events, Day of Essure Placement Procedure
<table>
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<tr><th>Number (N=233 procedures)</th><th>Percent</th><th>Number (N=544 procedures)</th><th>Percent</th></tr>
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Most women experienced mild to moderate pain during and immediately following the procedure. Pain was managed with oral nonsteroidal anti-inflammatory drugs (NSAIDs) or oral narcotic pain reliever.
The majority of women experienced spotting for an average of 3 days after the procedure.
…
Adverse Events, First Year of Reliance (Pivotal Trial)
The following adverse events* were related to the micro-insert or procedure during the first year of reliance in the Pivotal trial (approximately 15 months post-device placement.) Percentages reflect the number of events divided by the number of
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[181] MIS.500.001.0012 at [0004] / Page 5.
[182] MIS.500.001.0014 at [0017] / Page 18.
[183] MIS.500.001.0014 at [0018] / Page 19.
[196] MIS.500.001.0019 to [0006] / Pages 1 to 7.
[212] GYT.003.001.0001 at [0003] / Page 3.
[220] AMS.001.001.5420 at [0003] / Page 4.

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<td>…
C. Phase II - Safety and Effectiveness Study
…
4. Results
…
b. Device Placement Procedure
…
Pain during device placement was noted in 140 (65%) patients. Pain during device placement was rated as less than or equal to that expected in 130 (6 1 %) patients and greater than expected in 60 (28%) patients. The remaining 24 (11 %) patients answered "n/a" to this question because placement was not achieved; the patient was under general anesthesia for the placement procedure; or for unknown reasons. The most painful part of the procedure appears to be the time of tubal canulation (pain reported in 48% of cases) with device anchoring and removal of the guidewire as the least painful part of the procedure (reported in 15 % of placements).[184]
…
Post-Procedure Pain
Post-procedure pain was reported in 135 patients (79%). Post- procedure pain was resolved within 1 day in 59% of these patients, within 3 days in 87% of these patients, and within 1 week in 98% of patients reporting pain. Pain was resolved within 2 weeks for the remaining 2% of cases (based on information from the 3- month follow-up visit).
Of those experiencing pain, only 66% had pain significant enough to take medications for the pain. Drugs taken to alleviate pain included non-steroidal medications 48% (ibuprofen, paracetamol); narcotics 35% (paracetamol with codeine, Tylenol with codeine) and other 2%.
Patients who stated that they experienced pain following the procedure, were asked to compare that pain with the pain they experienced during a normal menses. Pain</td>
<td>event is represented in the numerator as multiple reports of that event, she is only represented in the denominator once. Consequently, in some cases these percentages over-represent the percentage of women who have experienced that event.
Table 10
Pivotal Trial
Clinical Data Overview
Adverse Events by Body Systems, First Year of Reliance* (N=476 patients implanted with at least one device)
<table>
<tr><th>Adverse Events by Body System</th><th>Number</th><th>Percentage</th></tr>
<tr><td colspan="3">Abdominal:</td></tr>
<tr><td>Abdominal pain/abdominal cramps</td><td>18</td><td>3.8</td></tr>
<tr><td colspan="3">Musculo-skeletal:</td></tr>
<tr><td>Back Pain/low Back Pain</td><td>43</td><td>9.0</td></tr>
<tr><td>Pelvic/lower abdominal pain (severe)</td><td>12</td><td>2.5</td></tr>
<tr><td>Dyspareunia</td><td>17</td><td>3.6</td></tr>
<tr><td>Pain / discomfort - uncharacterized:</td><td>14</td><td>2.9</td></tr>
</table>
…
In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[197]
…
5. PATIENT SELECTION, SCREENING AND COUNSELING
…
Patient Counseling, Informed Consent Process and Risks</td>
<td>trial in the denominator. While women reporting numerous episodes of the same event is represented in the numerator as multiple reports of that event, she is only represented in the denominator once. Consequently, in some cases these percentages over-represent the percentage of women who have experienced that event.
Table 11
Pivotal Trial
Clinical Data Overview
Adverse Events by Body Systems, First Year of Reliance* (N=476 patients implanted with at least one device)
<table>
<tr><th>Adverse Events by Body System</th><th>Number</th><th>Percentage</th></tr>
<tr><td colspan="3">Abdominal:</td></tr>
<tr><td>Abdominal pain/abdominal cramps</td><td>18</td><td>3.8</td></tr>
<tr><td colspan="3">Musculo-skeletal:</td></tr>
<tr><td>Back Pain/low Back Pain</td><td>43</td><td>9.0</td></tr>
<tr><td colspan="3">Genitourinary:</td></tr>
<tr><td>Pelvic/lower abdominal pain (severe)</td><td>12</td><td>2.5</td></tr>
<tr><td>Dyspareunia</td><td>17</td><td>3.6</td></tr>
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</table>
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In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[205]
…
5. PATIENT SELECTION, SCREENING AND COUNSELING</td>
<td>each report was counted as a separate event. Therefore, percentages may over-represent the percentage of women who have experienced that event.
…
<table>
<tr><th></th><th>Adverse Events by Body System</th><th>Number (N=476)</th><th>Percent</th></tr>
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<tr><td colspan="2">Pain / discomfort - uncharacterized</td><td>14</td><td>2.9</td></tr>
</table>
* Only events occurring in ≥0.5% are reported
† Eight women reported persistent decrease in menstrual flow
In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[213]
…
PATIENT SELECTION AND COUNSELING
…
• A patient may need a surgical procedure to manage a situation where Essure has perforated the fallopian tube or uterus or there is persistent pelvic pain. One patient in clinical trials requested removal for pain. Removal will likely require surgery, and may necessitate abdominal incision, general anesthesia, or possible hysterectomy[214]
…
ESSURE PROCEDURE</td>
<td>participants in the trial. When numerous episodes of the same event were reported by one participant, each report was counted as a separate event. Therefore, percentages may over-represent the percentage of women who have experienced that event.
…
<table>
<tr><th></th><th>Adverse Events by Body System</th><th>Number (N=476)</th><th>Percent</th></tr>
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* Only events occurring in ≥0.5% are reported
† 8 women reported persistent decrease in menstrual flow
In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[221]
…
PATIENT SELECTION AND COUNSELING
• A patient may need a surgical procedure to manage a situation where Essure has perforated the fallopian tube or uterus or there is persistent pelvic pain. One patient in clinical trials requested removal for pain. Removal will likely require surgery, and may necessitate abdominal incision, general anesthesia, or possible hysterectomy[222]
…</td>
</tr>
</table>

[184] MIS.500.001.0014 at [0028] / Page 29.
[197] MIS.500.001.0019 at [0005] to [0006] / Pages 6 to 7.
[205] GYT.002.001.0131 at [0146] to [0147] / Pages 16 to 17.
[213] GYT.003.001.0001 at [0012] to [0013] / Pages 12 to 13.
[214] GYT.003.001.0001 at [0018] / Page 18.
[221] AMS.001.001.5420 at [0012] to [0013] / Pages 13 to 14.
[222] AMS.001.001.5420 at [0018] / Page 19.

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was reported as the same or less than previous menstrual cycles by 24%, a little more by 40%, and a lot more by 36% of respondents. *Patients were asked about activities that elicited pain during the one -week post-placement timeframe. Of the patients reporting post-procedure pain, 5% reported pain during sexual activity, 6% reported pain during urination, 20% reported pain during menstruation, 22% reported pain during exercise, and 56% reported pain during "other" times (standing, sitting, resting, lying on side, during all activities, when tired, when pressure placed on pelvic area, during bowel movements, walking, doing housework, just immediately after placement, etc.)*[185] *…* *"Other" Symptoms* *…* *In summary, patient tolerance of the device placement procedure was good to excellent in 89% of cases with local anesthesia block or less used in 43% of cases. The post-procedure pain, bleeding, and other symptoms were transient, well tolerated, and typical of operative hysteroscopy procedures.*[186] *…* *e. Patient Diaries* *Patients were asked to complete a diary during the first six months after device wearing, noting menstruation, coital acts, and any unusual pain, bleeding, or unusual symptoms.*[187] *…* *According to the diaries received, 19/120 (16 %) patients indicated that they experienced pain that was greater than normal during intercourse at some point in their diary recordings. Twelve patients (I0%) reported this pain at some point during the first month after device placement. Two of these 7 patients experienced perforations and a separate patient was diagnosed with anxiety.*	*…* ***Removal of the Essure micro-inserts requires surgery*** *A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested micro-insert removal due to pain;*[198] *…* ***As with all procedures, there are risks associated with Essure*** *The patient should be aware of these risks and discuss them in detail with the physician doctor before making her decision.* ***Some of the risks associated with Essure have been discussed above, but additional risks, such as pain and bleeding following the Essure placement procedure as well as risks associated with future medical procedures the patient may undergo after Essure placement, are listed in the risk section of the Patient Information Booklet****. Some of these risks were reported during the clinical trials of Essure (see section 3) and some were not reported during the clinical trials but should still be considered as a potential risk of Essure. The patient should talk to the physician about the likelihood of these risks, particularly in relation to her own situation.*[199] *…* ***6. PRE-PROCEDURE***[200] *…* ***Placement Failure Rate*** *The patient should also be reminded that there is a 14% chance that micro-insert placement in both fallopian tubes may not be achieved during the first attempted procedure due to … procedure related difficulties such as poor visualization or tubal spasm.* *…* ***Pain/Discomfort Expectations*** *The patient should be reminded that she may experience pain/discomfort during the*	*...* ***Patient Counseling, Informed Consent Process and Risks*** *…* *Removal of the Essure micro-inserts requires surgery A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested micro-insert removal due to pain; however, if micro-insert removal is required for any reason it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.*[206] ***As with all procedures, there are risks associated with Essure*** *The patient should be aware of these risks and discuss them in detail with the physician doctor before making her decision.* ***Some of the risks associated with Essure have been discussed above, but additional risks, such as pain and bleeding following the Essure placement procedure as well as risks associated with future medical procedures the patient may undergo after Essure placement, are listed in the risk section of the Patient Information Booklet.*** *Some of these risks were reported during the clinical trials of Essure (see section 3) and some were not reported during the clinical trials but should still be considered as a potential risk of Essure. The patient should talk to the physician about the likelihood of these risks, particularly in relation to her own situation.*[207] *…* ***6. PRE-PROCEDURE*** *…* ***Placement Failure Rate*** *The patient should also be remined that there is a 5.4% chance that micro-insert placement in both fallopian tubes may not be achieved during the first attempted procedure due to… procedure related difficulties such as poor visualization or tubal spasm.*[208]	*…* ***Pre-Procedure*** *…* *Distension media* *Use a bag of 0.9% sterile saline that has been pre-warmed to body temperature, preferably 3 liters, to distend the uterine cavity enough for evaluation. It is strongly recommended that the saline solution by pre-warmed to body temperature (but no higher than body temperature) and introduced under gravity feed to minimize spasm of fallopian tubes.*[215] *…* ***Placement Steps*** *…* *Consider using gravity feed instead of a pressure cuff to minimize the risk of overdistension and tubal spasm.*[216] *…* *8. Using the thumb and forefinger, gently grasp the Essure delivery catheter and advance the Essure delivery catheter into the fallopian tube with gentle, constant forward movement (to prevent tubal spasm).*[217] *…* ***Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and examine the patient for possible perforation.***[218] *…* ***INSERT(S) REMOVAL*** *A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain; one woman requested device removal due to pain; however, if device removal is required for any reason, it will likely require surgery. Linear salpingotomy via laparoscopy or laparotomy can be used to remove the insert. Do not remove the insert(s) unless patient is experiencing an adverse event(s) associated with its presence, or if*	***PATIENT INFORMATION*** ***Risks of Essure*** *…* ***Risks of the Essure procedure*** *Risks during or immediately after the procedure may include mild to moderate cramping, nausea/vomiting, dizziness/light-headedness and bleeding/spotting.* *In clinical trials, the most common (≥10%) side effects resulting from the placement procedure were cramping, pain and nausea/vomiting.* ***Side effects in the first year of reliance*** *The most common side effects (≥3%) in the first year of reliance were back pain, abdominal pain and dyspareunia.* ***Chronic pain*** *There are rare reports of chronic pelvic pain in women with Essure.* • *Chronic pelvic pain may be related to malposition of device, cornual perforation or complications with concomitant ablation.* • *Patients with preexisting chronic pain diagnoses may be at increased risk of developing pelvic pain.* • *Other causes might explain chronic pelvic pain with Essure but remain unknown/* • *Micro-insert removal via laparoscopy is recommended in such cases.* [223] *…* ***ESSURE PROCEDURE*** *…* ***Pre-Procedure*** *…* *Distension media* *Use a bag of 0.9% sterile saline that has been pre-warmed to body temperature, preferably 3 liters, to distend the uterine cavity enough for evaluation. It is strongly recommended that the saline solution be pre-warmed to body*

[185] MIS.500.001.0014 at [0029] / Page 30.
[186] MIS.500.001.0014 at [0030] / Page 31.
[187] MIS.500.001.0014 at [0031] / Page 32.
[198] MIS.500.001.0021 at [0004] / Page 5.
[199] MIS.500.001.0021 at [0005] / Page 6.
[200] MIS.500.001.0022 to [0004] / Pages 1 to 5.
[206] GYT.002.001.0131 at [0157] / Pages 27.
[207] GYT.002.001.0131 at [0157] / Page 27.
[208] GYT.002.001.0131 at [0160] / Page 30.
[215] GYT.003.001.0001 at [0020] / Page 20.
[216] GYT.003.001.0001 at [0026] / Page 26.
[217] GYT.003.001.0001 at [0027] / Page 27.
[218] GYT.003.001.0001 at [0028] / Page 28.
[223] AMS.001.001.5420 at [0019] / Page 20.

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Two patients (2%) reported this pain during the second month after device placement. Three patients (2%) reported this pain during the third month after device placement. In the fourth month, 2/67 patients reported pain during intercourse. One of the patients who reported greater than normal pain during intercourse during the fourth month after device placement underwent a second device placement during that month. No other reports of such pain were noted for the fifth or sixth month after device placement. Of the 19 patients reporting greater than normal pain on intercourse; 15 took medication for the pain. The majority took over the counter medications. *Nineteen of the 120 patients (16%) indicated that they experienced pain that was greater than normal during menstruation at some point in their diary. 10/19 patients (53%) were al so those who reported pain greater than normal during intercourse at some time during the six months. Seventeen patients (14%) reported this pain during the first month after device placement. One of these 13 patients was a patient who had a device in her peritoneal cavity; one reported hot flashes; one reported an infected toe (obviously unrelated); and one was diagnosed with anxiety. Eight patients (7%) reported pain during the second month after device placement, and 4 patients (3%) during the third month after device placement. Three patients reported pain greater than normal with menses at least 2 of the three diary months, including the patient reported above that had a device in her peritoneal cavity. One patient reported greater than normal pain in each diary month.* *Diary information is available on 67 patients for 4 months of follow-up; 5 of these 67 patients (8%) reported greater than normal pain during menstruation during the fourth month after device placement. Again, one of these 3 patients is the patient with the device in her peritoneal cavity. Diary information is available on 63 patients for 5 months of follow-up; 2 of these patients (3%) reported greater than normal pain during menstruation*	*procedure. In the Pivotal Trial, 4% of the patients experienced severe pain and 77% experienced mild to moderate pain. Also, 17% of patients experienced no pain. A well-informed patient may promote improved relaxation, cooperation and a higher pain threshold resulting in a positive experience.*[201] … ***7. ESSURE PLACEMENT PROCEDURE*** … ***Distend Uterus*** ***5.*** *… It is strongly recommended that the saline solution be pre-warmed to body temperature (but no greater than body temperature) and introduced under gravity feed to minimize spasm of fallopian tubes.*[202] … ***Advance System into First Tube*** … ***11.*** *Advance the Essure delivery catheter into the proximal fallopian tube with gentle, constant forward movement to prevent tubal spasm.* ***PRECAUTION:*** *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up the patient for possible perforation.*[203] … ***8. POST-PLACEMENT FOLLOW-UP*** … ***Post-Placement Warnings and Precautions*** ***Micro-insert(s) Removal*** *A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain and only one woman requested device removal due to persistent pain; however, if device removal is required for any reason, it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.*[204]	***Pain/Discomfort Expectations*** *The patient should be reminded that she may experience pain/discomfort during the procedure. In the Pivotal Trial, 4% of the patients experienced severe pain and 78% experienced mild to moderate pain. Also, 17% of patients experienced no pain. A well-informed patient may promote improved relaxation, cooperation and a higher pain threshold resulting in a positive experience.*[209] … ***7. 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A cornual resection of the proximal fallopian tube may be required for removal.*[219]	*temperature (but no higher than body temperature) and introduced under gravity feed, or by pump or pressure cuff, to minimise risk of spasm of the fallopian tubes.*[224] … ***… It is strongly recommended that the saline solution be prewarmed to body temperature and introduced under gravity feed to minimise spasm of the fallopian tubes. Excellent uterine distension must be achieved and maintained throughout the procedure.***[225] … *8. Using the thumb and forefinger, gently grasp the Essure delivery catheter and advance the Essure delivery catheter into the fallopian tube with gentle, constant forward movement (to prevent tubal spasm).*[226] … ***Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and examine the patient for possible perforation.***[227] … ***Placement Steps*** *… Additionally, X-ray and TVU should not be used as the Essure Confirmation Test under the following circumstances:* … *d) Unusual post-operative pain, transient or persistent, or onset at some later time post-procedure, without any other identifiable cause.*[228] … ***Micro-Insert(s) Removal*** *A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain; one woman requested device removal due to pain; however, if device removal is required for any reason, it will likely require surgery.*[229]

[201] MIS.500.001.0022 at [0002] / Page 3.
[202] MIS.500.001.0023 at Page 1.
[203] MIS.500.001.0023 at [0002] / Page 3.
[204] MIS.500.001.0024 at [0001] / Page 2.
[209] GYT.002.001.0131 at [0161] / Page 31.
[210] GYT.002.001.0131 at [0167] / Page 37.
[211] GYT.002.001.0131 at [0177] / Page 47.
[219] GYT.003.001.0001 at [0037] / Page 37.
[224] AMS.001.001.5420 at [0021] / Page 22.
[225] AMS.001.001.5420 at [0027] / Page 28.
[226] AMS.001.001.5420 at [0028] / Page 29.
[227] AMS.001.001.5420 at [0029] / Page 30.
[228] AMS.001.001.5420 at [0033] / Page 34.
[229] AMS.001.001.5420 at [0039] / Page 40.

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during the fifth month after device placement. Diary information is available on 57 patients for 6 months of follow-up; 2/ 57 patients (4%) reported pain. One was the patient who reported pain each diary month and one was the patient with the device in her peritoneal cavity. The patient with the peritoneal device also reported pain in the seventh month (she kept diaries longer because of her repeat device placement). However, this patient underwent a laparoscopic sterilization at 5 months post second device placement. While only 19 women reported pain that was greater than normal during menstruation during the 6 months of diary keeping, 33/ 120 women (28%) took some kind of medication for menstrual pain during this time. The majority took over the counter medications. *f. Follow-up Visits* *In addition to the diaries, patients are asked about adverse events at each of the follow-up visits. At the three-month follow -up visit, 10/150 (7%) reported pain that was not reported on their diaries. Types of pain described are: a minor pinching sensation for 3 days pre-menstrual, decreasing with each period and not requiring medication; a 4-hour self-limited episode of pain in the lower abdomen when placing pressure/weight on her leg; intermittent right sided dull ache; pain during exercise; menstrual cramps; and dysmenorrhea. One patient was observed to have pain or tenderness during the pelvic exam performed at this visit.* *At the six-month follow-up visit, 5/117 (4%) of participants reported unusual pain since the last follow-up visit, which consisted of dysmenorrhea, urinary tract infection, ovarian cyst, and single episode of cramps. Five patients (4%) reported unusual bleeding since the last follow-up visit. Complaints included: irregular menses (2); changes in menstrual flow (2) and one had a change in menstrual cycle related to discontinuing oral contraceptives. All complaints of pain and bleeding resolved.*[188] *…* ***III. Clinical Appraisal*** *In summary, the following has been demonstrated in the patients enrolled to date*				*…* ***ESSURE CONFIRMATION TEST PROTOCOL*** *…* ***Essure Confirmation Test Options*** *…* *For the first-line confirmation test, either a pelvic x-ray or a TVU may be performed 3 months after an uncomplicated bilaterial micro-insert placement procedure.* *1. X-ray and TVU should not be used as the Essure Confirmation Test under the following circumstances:* *…* *d) Unusual post-operative pain, transient or persistent, or onset at some later time post procedure, without any other identifiable cause*[230] *…* ***PELVIC X-RAY*** ***When Pelvic X-ray Should be Carried Out*** *…* • *X-ray should not be used as the Essure Confirmation Test under the following circumstances:* *…* *- Unusual postoperative pain, transient or persistent, or onset at some later time post-procedure, without any other identifiable cause.*[231] *…* ***MANAGING TECHNICAL ISSUES*** ***Advancing the Micro-insert into the Tube*** *…* *Problem: Spasms* *Cause:* • *Cannot be predicted and may arise under general anaesthesia* • *Stress is an undeniable factor*

[188] MIS.500.001.0014 at [0031] to [0033] / Pages 32 to 34.

[230] AMS.001.001.5420 at [0041] / Page 42.

[231] AMS.001.001.5420 at [0053] / Page 54.

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in the perihysterectomy, prehysterectomy and Phase II studies: … *3. In all studies, post-procedure pain and bleeding was transient, well tolerated, and typical of operative hysteroscopy procedures.*[189] … ***Appendix D*** ***Instructions for Use*** ***Conceptus STOP Non-Incisional Permanent Contraception Kit*** … ***VI. Clinical Data Summary***[190] *As of December 31, 2000, 226 patients have undergone device placement in a clinical study … Of 197 patients completing follow-up questionnaires … 153 patients reported experiencing some post-operative pain; 59% was resolved within 1 day, 88% was resolved within 3 days, 99% was resolved within 7 days and 100% was resolved within 14 days.* … *The following were reported as being likely related to the STOP device:* … • *Severe post-op pain <1%* … ***VII. Possible Adverse Effects***[191] … *b. Risks associated with the Device Placement Procedure* … *2. Pain, cramping and vaginal bleeding may occur during and following the device placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.* … *7. There is a risk that the STOP device may be inadvertently placed into the myometrium*				• *It is difficult to differentiate between a spasm caused by an obstacle or be stenosis* *Potential solution:* … • *It is not possible to alleviate the spasm in some cases*[232] … ***Deploying the Micro-insert*** … *Problem: Too many coils are visible in the uterine cavity* *Cause:* • *Micro-insert not inserted far enough into the tube* *Potential Solutions* ***…*** • *If 18 or more coils extend into the uterine cavity, the micro-insert needs to be withdrawn with forceps that work with the 5Fr working channel and another one needs to be inserted. In these circumstances, the risk of spasm is considerable.*[233] … ***SPECIFIC ISSUES*** … ***POST-OPERATIVE OR CHRONIC PELVIC PAIN*** ***Patients who experience postoperative pain*** *All patients should be informed that they may experience postoperative pain after Essure micro-insert placement.* *Pain caused by postoperative contractions can be managed with an NSAID. Persistent pain must be investigated; a transvaginal ultrasound, pelvic x-ray or HSG is indicated.* *Chronic pelvic pain may be related to malposition of device, cornual perforation or complications with concomitant ablation.*

[189] MIS.500.001.0014 at [0038] to [0039] / Pages 39 to 40.
[190] MIS.500.001.0014 at [0043] / Page 44.
[191] MIS.500.001.0014 at [0045] / Page 46.
[232] AMS.001.001.5420 at [0073] / Page 74.
[233] AMS.001.001.5420 at [0076] / Page 77.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
of the uterus and not into the fallopian tube lumen. … Placement of the device in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the device(s) is required, salpingectomy or hysterectomy may be required.[192] *…* *9. There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device … If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device in vivo. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.*[193] *…* ***c. Risks associated with STOP Device Wearing*** *1. There is a risk that the STOP Device could move out of the fallopian tubes... Device movement could result in pregnancy, ectopic pregnancy and/or pain / menstrual disturbance or other adverse events.* *…* *3. Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.*[194] *…* ***VII. Directions for Use*** *…* *9. …It is strongly recommended that the saline solution be pre-warmed to body temperature and introduced under gravity feed to minimize spasm of the fallopian tubes.* *…*				*Rarely, the patient may experience unexplained chronic pain even though the micro-inserts are placed correctly. Micro-insert removal via laparoscopy might be recommended in such cases.* *Patients with preexisting chronic pain diagnoses may be at increased risk of developing pelvic pain. Other causes might explain chronic pelvic pain with Essure but remain unknown.* *Any pain that lasts for more than 3 days is suspicious. An investigation is necessary.*[234] *…* ***EXPULSION OR MIGRATION OF THE ESSURE MICRO-INSERT*** *There is a risk that the Essure micro-insert could move out of the fallopian tubes.* *…* *Device movement could result in pregnancy, ectopic pregnancy, and/or pain/menstrual disturbance or other adverse events.*[235] *…* ***INSTRUCTIONS FOR USE*** *…* ***VII. Possible Adverse Effects*** *…* ***B. Risks Associated with the micro-insert placement procedure*** *…* *Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.*[236] *…* *There is a risk that the* ***Essure*** *micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen... Placement of the micro-insert in the myometrium may result in post-operative pain or other adverse event. If surgical removal of the micro-insert(s) is*

[192] MIS.500.001.0014 at [0046] / Page 47.
[193] MIS.500.001.0014 at [0046] / Page 47.
[194] MIS.500.001.0014 at [0047] / Page 48.
[234] AMS.001.001.5420 at [0078] / Page 79.
[235] AMS.001.001.5420 at [0079] / Page 80.
[236] AMS.001.001.5420 at [0083] / Page 84.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
13. Advance the STOP delivery system into the proximal fallopian tube with slow, steady movement to prevent tubal spasm. *…* *Advance STOP Device slowly to prevent tubal spasm. Advance until positioning bump at tubal ostium. This is visual indicator for proper position for deployment.*[195]				*required, salpingectomy or hysterectomy may be required.*[237] *… If micro-insert removal is attempted, there is a possibility that the removal will not be successful or that the **Essure** micro-insert may break, leaving a fragment of the micro-insert in vivo. If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.*[238] *There is a risk that the **Essure** micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result.*[239] ***C. Risks associated with Essure micro-insert wearing*** *There is a risk that the **Essure** micro-insert could move out of the fallopian tubes...Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.* [240] *Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.*[241] *…* ***VIII. DIRECTIONS FOR USE*** *…* ***B. Essure micro-insert placement procedure*** *…* *5. … It is strongly recommended that the saline solution be pre-warmed to body temperature and introduced under gravity feeed to minimise spasm of the fallopian tubes.* *…*

[195] MIS.500.001.0014 at [0049] to [0050] / Pages 50 to 51.
[237] AMS.001.001.5420 at [0083] / Page 84.
[239] AMS.001.001.5420 at [0083] / Page 84.
[241] AMS.001.001.5420 at [0083] / Page 84.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
				8. Advance the Essure delivery system into the proximal fallopian tube with slow, steady movement to prevent tubal spasm.[242] … ***IX. ESSURE CONFIRMATION TEST*** ***A.*** *An Essure Confirmation Test should be performed three months after micro-insert placement to evaluate micro-inesrt retention and location.* … *1. X-ray and TVU should not be used as the Essure Confirmation Test under the following circumstances:* … *d) Unusual post-operative pain, transient or persistent, or onset at some later time post procedure, without any other identifiable cause.*[243]

[242] AMS.001.001.5420 at [0084] / Page 85.

[243] AMS.001.001.5420 at [0085] / Page 86.

9. Bleeding - ASOC 19c(ii), 20(b)

<table>
<tr>
<th>(1)
STOP Training Manual dated 2000 / 2001
MIS.500.0001.0001 to MIS.500.0001.0014</th>
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AMS.001.001.5420 / AMS.001.001.5208</th>
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History of Sterilization

Sterilization overview

…

Complications can occur with any kind of surgery. Some of the major complications that can occur during or after sterilisation are:

- *Bleeding*[244]

…

Procedure Requirements

Equipment Overview

…

Office hysteroscopy does not require much additional space and can be easily performed in the confines of a standard examination room. However, possible complications of office hysteroscopy are the same as those of hysteroscopy performed in a hospital setting. These include bleeding, infection, embolism, vasovagal reaction, perforation of the uterus, etc.[245]

…

Benefits and Risks

Summary of Possible Adverse Effects:

…

<u>Risks Associated with Device Placement Procedure:</u>

..

- *Pain, cramping, vaginal bleeding*

<u>Risks Associated with STOP Device wearing:</u>

…

- *Intermenstrual bleeding or heavy bleeding*[246]

…

Appendix C

STOP Clinical Data Summary

…

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3. CLINICAL DATA OVERVIEW[259]

…

Adverse Events

…

Table 9

Pivotal Trial

Adverse events reported on day of placement procedure (N=544 procedures)

Event	*Number*	*Percent*
Bleeding / spotting	*37*	*6.8%*

…

Table 10

Pivotal Trial

Clinical Data Overview

Adverse Events by Body Systems, First Year of Reliance* (N=476 patients implanted with at least one device)

Adverse Events by Body System	*Number*	*Percentage*
Genitourinary:		
Persistent increase in menstrual flow	*9***	*1.9*
Abnormal bleeding -timing not specified (severe)	*9*	*1.9*
Menorrhagia/prolonged menses (severe)	*5*	*1.1*

*** Eight women reported persistent decrease in menstrual flow*

In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[260]

…

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3. CLINICAL DATA OVERVIEW

…

Adverse Events

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In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[264]

…

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CLINICAL DATA

…

Adverse Events. Day of Essure Placement Procedure

Adverse Event / Side Effect	*Phase II*		*Pivotal*	
	Number (N=233 procedures)	*Percent*	*Number (N=544 procedures)*	*Percent*
Bleeding / spotting	*	*	*37*	*6.8%*

…

The majority of women experienced spotting for an average of 3 days after the procedure.

Adverse Events, First Year of Reliance (Pivotal Trial)*

The following adverse events were rated as "possibly" related to the insert or procedure during the first year of reliance in the Pivotal trial… Percentages reflect the number of events divided by the number of participants in the trial. When numerous episodes of the same event were reported by one participant, each report was counted as a separate event. Therefore, percentages may over-represent the percentage of women who have experienced that event.

	Adverse Events by Body System	Number (N=476)	Percent
Genitourinary	*Persistent increase in menstrual flow*	*9†*	*1.9*
	Abnormal bleeding -timing not specified (severe)	*9*	*1.9*
	Menorrhagia/prolonged	*5*	*1.1*

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CLINICAL DATA

…

Adverse Events. Day of Essure Placement Procedure

Adverse Event / Side Effect	*Phase II*		*Pivotal*	
	Number (N=233 procedures)	*Percent*	*Number (N=544 procedures)*	*Percent*
Bleeding / spotting	*	*	*37*	*6.8%*

…

The majority of women experienced spotting for an average of 3 days after the procedure.

Adverse Events, First Year of Reliance (Pivotal Trial)

…

	Adverse Events by Body System	Number (N=476)	Percent
Genitourinary	*Persistent increase in menstrual flow*	*9†*	*1.9*
	Abnormal bleeding -timing not specified (severe)	*9*	*1.9*
	Menorrhagia/prolonged menses (severe)	*5*	*1.1*

** Only events occurring in ≥0.5% are reported*

† 8 women reported persistent decrease in menstrual flow

In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.[267]

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[244] MIS.500.001.0006 at [0003] / Page 4.
[245] MIS.500.001.0007 at [0001] / Page 2.
[246] MIS.500.001.0012 at [0004] / Page 5.
[259] MIS.500.001.0019 to [0006] / Pages 1 to 7.
[260] MIS.500.001.0019 at [0005] to [0006] / Pages 6 to 7.
[264] GYT.002.001.0131 at [0146] to [0147] / Pages 16 to 17.
[267] AMS.001.001.5420 at [0012] to [0013] / Pages 13 to 14.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
II. Clinical Investigations … ***B. Phase 1-B Prehysterectomy Study*** … ***4. Results*** … *b. Device-Wearing, Acute* *Post- procedure bleeding was reported in 34% of patients and was resolved within 7 days.*[247] *…* … *c. Device-Wearing, Longer Term* … *There was no evidence of inflammation, ulceration or hemorrhage on gross examination of the uterus, except one patient with adenomyosis who was noted to have ulceration and hemorrhage in the uterine cavity, both fallopian tubes in this patient were unremarkable.*[248] … ***C. Phase II - Safety and Effectiveness Study*** … ***4. Results*** … *c. Patient Questionnaire* … *Post-Procedure Bleeding* *Post- procedure bleeding was reported in 144 (84%) of respondents. …* *Those respondents reporting bleeding after the procedure, were asked to compare the post-procedure bleeding experienced with the bleeding experienced during a normal menses. Post-procedure bleeding was reported as the same or less than previous periods in 88% of patients reporting bleeding, a little more by 8%, and a lot more by 4%. Although this part of the patient questionnaire	***5. PATIENT SELECTION, SCREENING AND COUNSELING*** … ***Patient Counseling, Informed Consent Process and Risks*** … ***As with all procedures, there are risks associated with Essure*** *The patient should be aware of these risks and discuss them in detail with the physician doctor before making her decision.* ***Some of the risks associated with Essure have been discussed above, but additional risks, such as pain and bleeding following the Essure placement procedure as well as risks associated with future medical procedures the patient may undergo after Essure placement, are listed in the risk section of the Patient Information Booklet****. Some of these risks were reported during the clinical trials of Essure (see section 3) and some were not reported during the clinical trials but should still be considered as a potential risk of Essure. The patient should talk to the physician about the likelihood of these risks, particularly in relation to her own situation.*[261] … ***8. POST-PLACEMENT FOLLOW-UP*** ***Three Month Pelvic X-ray*** *The pelvic x- ray should be evaluated, in light of the following information (which should be included in the procedure notes or patient chart):* … • *The patient has been complaining of persistent uterine cramping and/or bleeding/spotting since the procedure.*[262] … ***Pelvic X-ray Algorithm*** *Review patient chart / procedure notes. Pelvic x-ray should be evaluated in light of the*	***5. PATIENT SELECTION, SCREENING AND COUNSELING*** … ***Patient Counseling, Informed Consent Process and Risks*** … ***As with all procedures, there are risks associated with Essure*** *The patient should be aware of these risks and discuss them in detail with the physician doctor before making her decision.* ***Some of the risks associated with Essure have been discussed above, but additional risks, such as pain and bleeding following the Essure placement procedure as well as risks associated with future medical procedures the patient may undergo after Essure placement, are listed in the risk section of the Patient Information Booklet.*** *Some of these risks were reported during the clinical trials of Essure (see section 3) and some were not reported during the clinical trials but should still be considered as a potential risk of Essure. The patient should talk to the physician about the likelihood of these risks, particularly in relation to her own situation.*[265] …	<table><tr><td></td><td>menses (severe)</td><td></td><td></td></tr></table> … *† Eight women reported persistent decrease in menstrual flow* *In the Phase II trial, 12/206 (5.8%) women reported episodes of period pain, ovulatory pain, or changes in menstrual function.*[266]	***…*** ***PATIENT INFORMTION*** ***RISKS OF ESSURE*** ***…*** ***Risks of the Essure procedure*** *Risks during or immediately after the procedure may include, mild to moderate cramping, nausea/vomiting, dizziness/light-headedness and bleeding/spotting.*[268] … ***SPECIFIC ISSUES*** … ***Expulsion or migration of the micro-insert*** *There is a risk that the Essure micro-insert could move out of the fallopian tubes… Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.*[269] … ***INSTRUCTIONS FOR USE*** … ***VII. Possible Adverse Effects*** … ***B. Risks associated with the micro-insert placement procedure*** … • *Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.* … • *There is a risk that the Essure micro-insert may be placed too proximally in the fallopian tube. If 18 or more coils of the Essure micro-insert are visible at the time of placement, an immediate attempt should be made to remove the micro-insert… If micro-insert removal is attempted and/or achieved, there is*

[247] MIS.500.001.0014 at [0017] / Page 18.
[248] MIS.500.001.0014 at [0018] / Page 19.
[261] MIS.500.001.0021 at [0005] / Page 6.
[262] MIS.500.001.0024 at [0004] / Page 5.
[265] GYT.002.001.0131 at [0157] / Page 27.
[266] GYT.003.001.0001 at [0012] to [0013] / Pages 12 to 13.
[268] AMS.001.001.5420 at [0019] / Page 20.
[269] AMS.001.001.5420 at [0079] / Page 80.

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was intended to capture only bleeding associated with the procedure, due to variations in time in menstrual cycle that the device placement procedure occurred, some patients may have experienced their normal menses during the one week post-placement. Therefore, it is presumed that this category captures bleeding associated with device placement and with normal menses.[249] *…* *The post-procedure pain, bleeding, and other symptoms were transient, well tolerated, and typical of operative hysteroscopy procedures.*[250] *…* *f. Follow-up Visits* *…* *At the six-month follow-up visit, 5/117 (4%) of participants reported unusual pain since the last follow-up visit, which consisted of dysmenorrhea, urinary tract infection, ovarian cyst, and single episode of cramps. Five patients (4%) reported unusual bleeding since the last follow-up visit. Complaints included: irregular menses (2); changes in menstrual flow (2) and one had a change in menstrual cycle related to discontinuing oral contraceptives. All complaints of pain and bleeding resolved.* *At the 12-month visit, 3/48 (6%) patients reported unusual bleeding since the last visit. These complaints were characterized by spotting in two patients and an irregular menses by one patient.*[251] *…* ***III. Clinical Appraisal*** *In summary, the following has been demonstrated in the patients enrolled to date in the perihysterectomy, prehysterectomy and Phase II studies:* *…* *3. In all studies, post-procedure pain and bleeding was transient, well tolerated, and typical of operative hysteroscopy procedures.*[252]	*following information documented at the time of placement:* *…* • *Since placement, the patient has been complaining of persistent uterine cramping and/or bleeding/spotting.*[263]			*also a possibility that the patient may experience increased pain, cramping and bleeding during and following the Essure micro-insert placement procedure.* • *There is a risk that the Essure micro-insert may perforate through the tubal wall or uterine cornua, which could result in the micro-insert being released into the peritoneal cavity. Post-operative pain and/or menstrual disturbance or other adverse event may occur as a result.* [270] *…* ***C. Risks associated with Essure micro-insert wearing*** *…* • *There is a risk that the Essure micro-insert could move out of the fallopian tubes… Device movement could result in pregnancy, ectopic pregnancy and/or pain/menstrual disturbance or other adverse events.* *…* • *Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.* [271]

[249] MIS.500.001.0014 at [0029] to [0030] / Pages 30 to 31.
[250] MIS.500.001.0014 at [0030] / Page 31.
[251] MIS.500.001.0014 at [0033] / Page 34.
[252] MIS.500.001.0014 at [0038] to [0039] / Pages 39 to 40.
[263] MIS.500.001.0024 at [0007] / Page 8.
[270] AMS.001.001.5420 at [0083] / Page 84.
[271] AMS.001.001.5420 at [0083] / Page 84.

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…				
Appendix D				
Instructions for Use				
Conceptus STOP Non-Incisional Permanent Contraception Kit				
…				
VI. Clinical Data Summary[253]				
As of December 31, 2000, 226 patients have undergone device placement in a clinical study … Of 197 patients completing follow-up questionnaires, 165 (84%) experienced bleeding after the procedure. 27% said their bleeding resolved within 1 day, 63% resolved within 3 days, 96% resolved within 7 days and 100% resolved within 15 days. Comparing the amount of bleeding to their normal menstrual bleeding, 88% characterised it as the same or less than normal menstrual bleeding, 8% characterised it as a little more, and only 4% characterised it as a lot more.				
…				
VII. Possible Adverse Effects				
…				
b. Risks Associated with the Device Placement Procedure				
…				
2. Pain, cramping and vaginal bleeding may occur during and following the device placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.[254]				
…				
5. There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection, however treatment is typically not required.[255]				
…				
9. …If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.[256]				
…				

[253] MIS.500.001.0014 at [0043] / Page 44.

[254] MIS.500.001.0014 at [0045] / Page 46.

[255] MIS.500.001.0014 at [0046] / Page 47.

[256] MIS.500.001.0014 at [0046] / Page 47.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
c. Risks associated with STOP Device Wearing *1. There is a risk that the STOP Device could move out of the fallopian tubes… Device movement could result in pregnancy, ectopic pregnancy and/or pain / menstrual disturbance or other adverse events.*[257] *…* *4. Intermenstrual bleeding or heavier than normal menstrual bleeding may be experienced.*[258]				

[257] MIS.500.001.0014 at [0047] / Page 48.

[258] MIS.500.001.0014 at [0047] / Page 48.

10. Dysmenorrhoea (intense uterine cramping and pain) - ASOC 20(c)

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<tr>
<td>
Patient Selection
Benefits and Risks
Summary of Possible Adverse Effects:
…
<u>Risks Associated with Device Placement Procedure:</u>
…
• Pain, cramping, vaginal bleeding
<u>Risks Associated with STOP Device Wearing:</u>
…
• Pelvic pain and cramping.[272]
…
Appendix C
II. Clinical Investigations
…
C. Phase II - Safety and Effectiveness Study
…
4. Results
…
f. Follow-up Visits
In addition to the diaries, patients are asked about adverse events at each of the follow-up visits. At the three-month follow -up visit, 10/150 (7%) reported pain that was not reported on their diaries. Types of pain described are: a minor pinching sensation for 3 days pre-menstrual, decreasing with each period and not requiring medication; a 4-hour self-limited episode of pain in the lower abdomen when placing pressure/weight on her leg; intermittent right sided dull ache; pain during exercise; menstrual cramps; and dysmenorrhea. One patient was observed to have pain or tenderness during the pelvic exam performed at this visit.
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3. CLINICAL DATA OVERVIEW
…
Adverse Events
…
Table 9
Pivotal Trial
Adverse events reported on day of placement procedure (N=544 procedures)[276]
<table>
<tr><th>Event</th><th>Number</th><th>Percent</th></tr>
<tr><td>Cramping</td><td>161</td><td>29.6%</td></tr>
</table>
…
Table 10
Pivotal Trial
Clinical Data Overview
Adverse Events by Body Systems, First Year of Reliance* (N=476 patients implanted with at least one device) [277]
<table>
<tr><th>Adverse Events by Body System</th><th>Number</th><th>Percentage</th></tr>
<tr><td colspan="3">Genitourinary:</td></tr>
<tr><td>Dysmenorrhea/menstrual cramps (severe)</td><td>14</td><td>2.9</td></tr>
</table>
…
8. POST-PLACEMENT FOLLOW-UP
Three Month Pelvic X-ray
The pelvic x- ray should be evaluated, in light of the following information (which should be included in the procedure notes or patient chart):
…
</td>
<td>
3. CLINICAL DATA OVERVIEW
…
Adverse Events
…
Table 10
Pivotal Trial
Adverse events reported on day of placement procedure (N=544 procedures)[280]
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Adverse Events by Body Systems, First Year of Reliance* (N=476 patients implanted with at least one device) [281]
<table>
<tr><th>Adverse Events by Body System</th><th>Number</th><th>Percentage</th></tr>
<tr><td colspan="3">Genitourinary:</td></tr>
<tr><td>Dysmenorrhea/menstrual cramps (severe)</td><td>14</td><td>2.9</td></tr>
</table>
</td>
<td>
Important Safety Information
Clinical Trial Experience
…
• The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain and dyspareunia.[282]
…
CLINICAL DATA
…
Adverse Events. Day of Essure Placement Procedure
<table>
<tr><th rowspan="2">Adverse Event / Side Effect</th><th colspan="2">Phase II</th><th colspan="2">Pivotal</th></tr>
<tr><th>Number (N=233 procedures)</th><th>Percent</th><th>Number (N=544 procedures)</th><th>Percent</th></tr>
<tr><td>Cramping</td><td>*</td><td>*</td><td>161</td><td>29.6</td></tr>
</table>
…
Adverse Events, First Year of Reliance (Pivotal Trial)* [283]
…
<table>
<tr><th></th><th>Adverse Events by Body System</th><th>Number (N=476)</th><th>Percent</th></tr>
<tr><td>Abdominal</td><td>Abdominal pain / abdominal cramps</td><td>18</td><td>3.8%</td></tr>
<tr><td>Genitourinary</td><td>Dysmenorrhea/menstrual cramps (severe)</td><td>14</td><td>2.9</td></tr>
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[272] MIS.500.001.0012 at [0004] / Page 5.
[276] MIS.500.001.0019 to [0005] / Page 6.
[277] MIS.500.001.0019 at [0006] / Page 7.
[280] GYT.002.001.0131 at [0146] / Page 16.
[281] GYT.002.001.0131 at [0146] to [0147] / Pages 16 to 17.
[282] GYT.003.001.0001 at [0003] / Page 3.
[283] GYT.003.001.0001 at [0012] to [0013] / Pages 12 to 13.
[284] AMS.001.001.5420 at [0003] / Page 4.
[285] AMS.001.001.5420 at [0012] to [0013] / Pages 13 to 14.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
At the six-month follow-up visit, 5/117 (4%) of participants reported unusual pain since the last follow-up visit, which consisted of dysmenorrhea, urinary tract infection, ovarian cyst, and single episode of cramps.[273] … ***Appendix D*** ***Instructions for Use*** ***Conceptus STOP Non-Incisional Permanent Contraception Kit*** … ***VII. Possible Adverse Effects*** … ***b. Risks Associated with the Device Placement Procedure*** … *If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device in vivo. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.*[274] … ***c. Risks associated with STOP Device Wearing*** … *3. Abdominal/pelvic pain and cramping may occur. Pain and cramping may be a more likely occurrence during the menstrual period, during and after sexual intercourse or with other physical activity.*[275]	• *The patient has been complaining of persistent uterine cramping and/or bleeding/spotting since the procedure.*[278] … ***Pelvic X-ray Algorithm*** *Review patient chart / procedure notes. Pelvic x-ray should be evaluated in light of the following information documented at the time of placement:* … *Since placement, the patient has been complaining of persistent uterine cramping and/or bleeding/spotting.*[279]		…	… ***PATIENT INFORMATION*** ***Risks of Essure*** … ***Risks of the Essure Procedure*** *Risks during or immediately after the procedure may include mild to moderate cramping, nausea/vomiting, dizziness/light-headedness and bleeding/spotting.* *In clinical trials, the most common (≥10%) side effects resulting from the placement procedure were cramping, pain and nausea/vomiting.*[286] … ***INSTRUCTIONS FOR USE*** … ***VII. Possible Adverse Effects*** … ***B. Risks associated with the micro-insert placement procedure*** … • *Pain, cramping and vaginal bleeding may occur during and following the micro-insert placement procedure. Typically, these incidents are tolerable, transient and successfully treated with medication.*[287] … • *…If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the* ***Essure*** *micro-insert placement procedure.*[288] … ***C. Risks associated with Essure micro-insert wearing*** … • *Abdominal/pelvic pain and cramping may occur. Pain and cramping may*

[273] MIS.500.001.0014 at [0032] to [0033] / Pages 33 to 34.
[274] MIS.500.001.0014 at [0046] / Page 47.
[275] MIS.500.001.0014 at [0047] / Page 48.
[278] MIS.500.001.0024 at [0004] / Page 5.
[279] MIS.500.001.0024 at [0007] / Page 8.
[286] AMS.001.001.5420 at [0019] / Page 20.
[287] AMS.001.001.5420 at [0083] / Page 84.
[288] AMS.001.001.5420 at [0083] / Page 84.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
				be a more likely occurrence during the menstrual period, during and after sexual intercourse or with physical activity. [289]

[289] AMS.001.001.5420 at [0083] / Page 84.

11. Damage to internal organs - ASOC 20(d)

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
Patient Selection ***Benefits and Risks*** ***Summary of Possible Adverse Effects:*** … <u>*Risks Associated with Device Placement Procedure:*</u> • *Perforation or dissection of fallopian tube or uterine cornua* • *Uterine perforation by hysteroscope* • *Inadvertent placement of device into myometrium* • *Placement of device into distal tube* • *Perforation through tube resulting in placement into peritoneal cavity* … <u>*Risks Associated with STOP Device Wearing:*</u> • *Surgery if device removal required due to adverse event*[290] … ***VII. Possible Adverse Effects*** … ***b. Risks Associated with the Device Placement Procedure*** … *6. There is a risk of uterine perforation by the hysteroscope, STOP System or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Surgical intervention maybe required, but is unlikely, if such injury were to occur…* *7. There is a risk that the STOP device may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen. … Placement of the device in the myometrium may result in post-operative pain or other adverse event. If surgical removal of*	***3. CLINICAL DATA OVERVIEW***[292] … ***Adverse Events*** … ***Potential Adverse Events Not Observed in Clinical Studies*** *The following adverse events were not experienced by women who participated in clinical studies evaluating the Essure Permanent Birth Control System but are still possible:* … *• Perforation (a small hole) in internal bodily structures other than the uterus and fallopian tube.*[293]	***3. CLINICAL DATA OVERVIEW*** … ***Adverse Events*** … ***Potential Adverse Events Not Observed in Clinical Studies*** *The following adverse events were not experienced by women who participated in clinical studies evaluating the Essure Permanent Birth Control System but are still possible:* … *• Perforation (a small hole) in internal bodily structures other than the uterus and fallopian tube.*[294]	***CLINICAL DATA*** … ***Potential Adverse Events Not Observed in Clinical Studies*** *The following adverse events were not experienced by clinical trial participants but are still possible and/or have occurred in the commercial setting:* … • *Perforation of internal bodily structures other than the uterus and fallopian tube.*[295] … ***PATIENT SELECTION AND COUNSELING*** … *A patient may need a surgical procedure to manage a situation where Essure has perforated the fallopian tube or uterus or there is persistent pelvic pain. One patient in clinical trials requested removal for pain. Removal will likely require surgery, and may necessitate abdominal incision, general anesthesia, or possible hysterectomy*[296]	***Potential Adverse Events Not Observed in Clinical Studies*** *The following adverse events were not experienced by clinical trial participants but are still possible and/or have occurred in the commercial setting:* … • *Perforation of internal bodily structures other than the uterus and fallopian tube.*[297] … ***PATIENT SELECTION AND COUNSELING*** … *A patient may need a surgical procedure to manage a situation where Essure has perforated the fallopian tube or uterus or there is persistent pelvic pain. One patient in clinical trials requested removal for pain. Removal will likely require surgery, and may necessitate abdominal incision, general anesthesia, or possible hysterectomy*[298] … ***PATIENT INFORMATION*** ***Risks of Essure*** … ***Perforation*** *Perforation of the fallopian tube, uterus, or other internal bodily structures is an uncommon adverse event that has been reported with the Essure sterilization procedure.* *Management of tubal or uterine perforations caused by Essure placement may include laparoscopic retrieval of the micro-insert and laparoscopic sterilization: Additional complications resulting from perforation may require surgical intervention.*[299] … ***ESSURE PROCEDURE***

[290] MIS.500.001.0012 at [0004] / Page 5.
[292] MIS.500.001.0019 to [0006] / Pages 1 to 7.
[293] MIS.500.001.0019 at [0006] / Page 7.
[294] GYT.002.001.0131 at [0147] / Page 17.
[295] GYT.003.001.0001 at [0013] / Page 13.
[296] GYT.003.001.0001 at [0018] / Page 18.
[297] AMS.001.001.5420 at [0013] / Page 14.
[298] AMS.001.001.5420 at [0018] / Page 19.
[299] AMS.001.001.5420 at [0019] / Page 20.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
the device(s) is required, salpingectomy or hysterectomy may be required. *8. There is a risk that the STOP device may be placed too distally in the fallopian tube. If removal of the device is necessary, surgery (laparoscopy or laparotomy) will be required.*[291] *…* ***c. Risks associated with STOP Device Wearing*** *1. There is a risk that the STOP Device could move out of the fallopian tubes … surgery may be required to remove the device. Device movement could result in pregnancy, ectopic pregnancy and/or pain / menstrual disturbance or other adverse events.*				*…* ***SPECIFIC ISSUES*** *…* ***CHRONIC PAIN*** *There are rare reports of chronic pelvic pain in women with Essure:* • *Chronic pelvic pain may be related to malposition of device, cornual perforation or complications with concomitant ablation.* [300] ***…*** ***PERFORATION*** *Perforation of the fallopian tube, uterus or other internal bodily structures is an uncommon adverse event that has been reported with the Essure procedure.* *Procedural difficulties, such as poor visualisation and high resistance, have been identified as predisposing factors for tubal perforation using Essure micro-insert device. 3 Patients with perforations from Essure placement may either be symptomatic (e.g.., experience pain) or asymptomatic.* ***Incidence of perforations*** *According to the Essure Instructions for Use, 1.8% (12/673) of clinical trial patients had device-related perforations. Most perforations were diagnosed either at the time of micro-insert placement or at the 3-month HSG.* *In the Pivotal trial, tubal perforations occurred in 4 (0.9%) of 464 women who achieved bilateral placement with Essure.* *In the Phase II trial, 6 cases of perforation of the uterine wall or tubal lumen were reported (2 cases involved the micro-insert device; 4 cases involved the support catheter, which has subsequently been removed from the insertion protocol.* *A 7-year retrospective study that evaluated complications of tubal sterilisation with Essure in 4306 women reported 1 (0.02%) woman who had tubal perforation as a longer-term complication (following the initial 3-month follow-up period).* ***Perforation management***

[291] MIS.500.001.0014 at [0046] / Page 47.

[300] AMS.001.001.5420 at [0078] / Page 79.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
				Management of tubal or uterine perforations caused by Essure® placement may include laparoscopic retrieval of the micro-insert and laparoscopic sterilisation or repeat micro-insert placement. *Additional complications resulting from perforation may require surgical intervention.* *Complications of a perforation may include bladder or bowel injury. Small bowel obstruction (SBO) secondary to perforation with the placement of Essure was discussed in 2 case reports.*[301]

[301] AMS.001.001.5420 at [0079] / Page 80.

12. Removal Limitation - ASOC 21 - 22

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
Detailed STOP Procedure and Algorithm ***Device Removal*** ***WARNING****: Device removal should not be attempted hysteroscopically once the device has been placed, unless 20 or more coils of the STOP device are trailing into the uterine cavity. Removal of such a device should be attempted immediately following placement However, removal may not be possible.* *…* *g. If complete device removal is accomplished, an attempt should be made to place another STOP device.* *• Other than the above described scenario, device removal should only be attempted if patient is experiencing an adverse event(s) or demands removal* *• If required, use:* *- Laparoscopy or laparotomy* *• For properly positioned device* *- Perform cornual resection* *• For improperly placed device (or one that has migrated beyond the utero-tubal junction [UTJ])* *- Perform linear salpingostomy or salpingectomy.*[302] *…* ***Patient Selection*** ***Who is STOP for?*** *The STOP system is indicated for permanent female contraception. Patient selection is critical.*[303] *…* *<u>Some indications for considering a patient for the STOP procedure may be:</u>* • *The patient is seeking permanent contraception.*	***5. PATIENT SELECTION, SCREENING AND COUNSELING***[318] ***Contraindications*** *The Essure Permanent Birth Control System should not be used in any patient who is:* • *Uncertain about her desire to end fertility.*[319] *…* ***Patient Counseling, Informed Consent Process and Risks*** *…* ***The procedure should be considered irreversible*** *There are no data on the safety or effectiveness of surgery to reverse the Essure procedure. Any attempt at surgical reversal will likely require utero-tubal reimplantation. Pregnancy following such a procedure carries with it the risk of uterine rupture and serious maternal and fetal morbidity and mortality.* *Essure is only meant to be used by women who are certain they no longer want to have children.* *Women who undergo sterilization at a relatively young age are at greater risk of regretting their decision to undergo sterilization. The Essure procedure should not be considered reversible at any age.*[320] *…* ***Removal of the Essure micro-inserts requires surgery*** *A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested micro-insert removal due to pain; however, if micro-insert removal is required for any reason it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.*[321]	***5. PATIENT SELECTION, SCREENING AND COUNSELING*** ***Contraindications*** *The Essure Permanent Birth Control System should not be used in any patient who is:* • *Uncertain about her desire to end fertility.*[334] *…* ***Patient Counseling, Informed Consent Process and Risks*** *…* ***The procedure should be considered irreversible*** *There are no data on the safety or effectiveness of surgery to reverse the Essure procedure. Any attempt at surgical reversal will likely require utero-tubal reimplantation. Pregnancy following such a procedure carries with it the risk of uterine rupture and serious maternal and fetal morbidity and mortality.* *Essure is only meant to be used by women who are certain they no longer want to have children.* *Women who undergo sterilization at a relatively young age are at greater risk of regretting their decision to undergo sterilization. The Essure procedure should not be considered reversible at any age.*[335] *…* ***Removal of the Essure micro-inserts requires surgery*** *A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested micro-insert removal due to pain; however, if micro-insert removal is required for any reason it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.*[336]	***ESSURE CLINICAL RESOURCE*** *…* ***Important Safety Information*** *…* ***Who should not use Essure*** • *Essure is contraindicated in patients who are uncertain about ending fertility.*[344] *…* ***Pregnancy Considerations*** • *The Essure procedure should be considered irreversible. Patients should not rely on Essure inserts for contraception until an Essure Confirmation Test (modified hysterosalpingogram [HSG]) demonstrates bilateral tubal occlusion and satisfactory location of inserts.* *…* ***Procedural Considerations*** *…* • *… Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.*[345] *…* ***PATIENT SELECTION AND COUNSELING*** ***ESSURE IS AN APPROPRIATE OPTION FOR WOMEN WHO DESIRE PERMANENT BIRTH CONTROL:*** • *The patient must be certain that her family is complete, and understand that the procedure should be considered irreversible.*[346] *…*	***ESSURE CLINICAL RESOURCE*** *…* ***Indication*** *The Essure system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.*[353] *…* ***Important Safety Information*** *…* ***Who should not use Essure*** *Essure is contraindicated in patients who are uncertain about ending fertility*[354] *…* ***Pregnancy Considerations*** • *The Essure procedure should be considered irreversible. Patients should not rely on Essure inserts for contraception until an Essure Confirmation Test (modified hysterosalpingogram [HSG]) demonstrates bilateral tubal occlusion and satisfactory location of inserts.*[355] *…* ***PRODUCT OVERVIEW*** ***What is Essure?*** *The Essure system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception. Essure was designed as an alternative to incisional methods of tubal ligation that require general anaesthesia.* *Essure is contraindicated in patients who:* • *Are uncertain about ending their fertility*[356] *…* ***PATIENT SELECTION AND COUNSELING***

[302] MIS.500.001.0011 at [0005] / Page 6.
[303] MIS.500.001.0012 at [0001] / Page 2.
[318] MIS.500.001.0021 to [0005] / Pages 1 to 6.
[319] MIS.500.001.0021 at Page 1.
[320] MIS.500.001.0021 at [0003] / Page 4.
[321] MIS.500.001.0021 at [0004] / Page 5.
[334] GYT.002.001.0131 at [0153] / Page 23.
[335] GYT.002.001.0131 at [0156] / Page 26.
[336] GYT.002.001.0131 at [0157] / Page 27.
[344] GYT.003.001.0001 at [0002] / Page 2.
[345] GYT.003.001.0001 at [0003] / Page 3.
[346] GYT.003.001.0001 at [0016] / Page 16.
[353] AMS.001.001.5420 at [0002] / Page 3.
[354] AMS.001.001.5420 at [0002] / Page 3.
[355] AMS.001.001.5420 at [0002] / Page 3.
[356] AMS.001.001.5420 at [0006] / Page 7.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
• *The patient does not want any more children.* … • *The patient and her partner agree that their family is complete, and no more children are wanted.*[304] … *Do not consider a patient for permanent contraception if:* • *The patient may want to have a child in the future.* • *The patient is being pressured by her partner, friends, or family. She must want the procedure.* • *The patient has problems that may be temporary (marriage or sexual problems, short-term mental or physical illnesses, financial worries, or being out of work). Permanent contraception is not a good solution for problems such as these.* • *The patient has not considered possible changes in her life, such as divorce, remarriage, or death of children.* • *The patient has not discussed it fully with her partner.* ***Contraindications*** • *Patient uncertainty about their desire to end fertility*[305] … ***Patient Selection*** ***Benefits and Risks*** ***Summary of Possible Adverse Effects:*** … *Risks Associated with STOP Device Wearing:* • *Surgery if device removal required due to adverse event*[306]	… ***Is Essure right for the patient?*** *The Essure procedure is only appropriate if the patient is sure that she does not want any more children, would like to have permanent birth control and believes that she will not change her mind. If there is any chance that the patient may want to have children in the future, she should choose another form of birth control. Patients should avoid making this choice during times of stress, such as divorce or after a miscarriage, and NEVER under pressure from a partner or others.*[322] … ***Disclosure to the patient*** *Conceptus recommends that the physician disclose to the patient (in written form) all risks associated with the Essure Permanent Birth Control System, and that the Essure procedure is permanent and irreversible.*[323] … ***6. PRE-PROCEDURE***[324] … ***Pre-op Counseling and Patient Prep*** ***Essure is Permanent*** *Before the Essure procedure commences, the physician or nurse should reconfirm the patient's decision for permanent birth control. The patient should be reminded that the Essure procedure is irreversible. She should be absolutely certain about her decision to end her fertility.*[325] … ***7. ESSURE PLACEMENT PROCEDURE***[326] … **Count Trailing Coils Ideal Placement 3-8 Coils** … ***WARNING:*** *Micro-insert removal should not be attempted hysteroscopically once the*	… ***Is Essure right for the patient?*** *The Essure procedure is only appropriate if the patient is sure that she does not want any more children, would like to have permanent birth control and believes that she will not change her mind. If there is any chance that the patient may want to have children in the future, she should choose another form of birth control. Patients should avoid making this choice during times of stress, such as divorce or after a miscarriage, and NEVER under pressure from a partner or others.*[337] … ***Disclosure to the patient*** *Conceptus recommends that the physician disclose to the patient (in written form) all risks associated with the Essure Permanent Birth Control System, and that the Essure procedure is permanent and irreversible.*[338] … ***6. PRE-PROCEDURE***[339] … ***Pre-op Counseling and Patient Prep*** ***Essure is Permanent*** *Before the Essure procedure commences, the physician or nurse should reconfirm the patient's decision for permanent birth control. The patient should be reminded that the Essure procedure is irreversible. She should be absolutely certain about her decision to end her fertility.*[340] … ***7. ESSURE PLACEMENT PROCEDURE*** … ***Count Trailing Coils Ideal Placement 3-8 Coils*** … ***WARNING:*** *Micro-insert removal should not be attempted hysteroscopically once the*	***ESSURE IS CONTRAINDICATED FOR PATIENTS WHO:*** • *Are uncertain about ending their fertility* … *Women who undergo sterilization at a relatively young age are at greater risk of regretting their decision to undergo sterilization. If there is any chance that the patient may want to have children in the future, she should choose a reversible method of birth control.*[347] ***PATIENTS MAY HAVE QUESTIONS AND CONCERNS ABOUT THE ESSURE PROCEDURE. IT IS IMPORTANT TO MANAGE THEIR EXPECTATIONS WITH THE FOLLOWING INFORMATION:*** … • *Essure is a permanent birth control procedure that works with the body to create a natural barrier against pregnancy* • *The Essure procedure should be considered irreversible*[348] … ***ESSURE PROCEDURE*** *PLACEMENT STEPS* *Insert removal should not be attempted hysteroscopically once the insert has been placed (ie, detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the insert are trailing into the uterine cavity. Because of insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of an insert having fewer than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*[349] … ***Essure System Extraction***	***ESSURE IS AN APPROPRIATE OPTION FOR WOMEN WHO DESIRE PERMANENT BIRTH CONTROL:*** • *The patient must be certain that her family is complete. and understand that the procedure should be considered irreversible.*[357] … ***PATIENTS MAY HAVE QUESTIONS AND CONCERNS ABOUT THE ESSURE PROCEDURE. IT IS IMPORTANT TO MANAGE THEIR EXPECTATIONS WITH THE FOLLOWING INFORMATION:*** … • *The Essure systems is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.* • *The Essure procedure should be considered irreversible*[358] … • *A patient may need a surgical procedure to manage a situation where Essure perforated the fallopian tube or uterus or there is persistent pelvic pain… Removal will likely require surgery, and may necessitate abdominal incision, general anaesthesia, or possible hysterectomy.*[359] … ***PATIENT INFORMATION*** ***Risks of Essure*** … *Patients must be fully informed regarding the potential risks associated with Essure and the permanent and irreversible nature of the procedure. Written information must be provided.*[360] … ***ESSURE PROCEDURE***

[304] MIS.500.001.0012 at [0001] / Page 2.
[305] MIS.500.001.0012 at [0001] to [0002] / Pages 2 to 3.
[306] MIS.500.001.0012 at [0004] / Page 5.
[322] MIS.500.001.0021 at [0005] / Page 6.
[323] GYT.002.001.0131 at [0158] / Page 28.
[324] MIS.500.001.0022 to [0004] / Pages 1 to 5.
[325] MIS.500.001.0022 at Page 1.
[326] MIS.500.001.0023 to [0011] / Pages 1 to 12.
[337] GYT.002.001.0131 at [0158] / Page 28.
[338] GYT.002.001.0131 at [0158] / Page 28.
[339] MIS.500.001.0022 to [0004] / Pages 1 to 5.
[340] GYT.002.001.0131 at [0159] / Page 29.
[347] GYT.003.001.0001 at [0016] / Page 16.
[348] GYT.003.001.0001 at [0017] / Page 17.
[349] GYT.003.001.0001 at [0032] / Page 32.
[357] AMS.001.001.5420 at [0016] / Page 17.
[358] AMS.001.001.5420 at [0017] / Page 18.
[359] AMS.001.001.5420 at [0018] / Page 19.
[360] AMS.001.001.5420 at [0019] / Page 20.

(1) **STOP Training Manual dated 2000 / 2001** MIS.500.0001.0001 to MIS.500.0001.0014	(2) **Essure Training Manual dated 1 May 2003** MIS.500.001.0016 to MIS.500.001.0027 and MIS.500.001.0031	(3) **Essure Physician Training Manual in use from 7 January 2008 to January 2014** GYT.002.001.0131	(4) **Essure Physician Training Manual in use from February 2014 to 2015** GYT.003.001.0001	(5) **Physician Training Manual dated 2015 to 28 August 2017** AMS.001.001.5420 / AMS.001.001.5208
…	*micro-insert has been placed and detached from the delivery wire. The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Instructions on how to attempt micro-insert removal are provided in Section 9. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*[327]	*micro-insert has been placed (i.e., detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Instructions on how to attempt micro-insert removal are provided in Section 9. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*[341]	*If there are 18 or more expanded outer coils trailing into the uterus, then the insert should be immediately removed from the uterus (as described in steps 1-5 below) and another attempt made at insert placement in the tube. Insert removal may not always be possible.*[350]	***Placement Steps***
Patient Counseling	…	…	…	…
…	***8. POST-PLACEMENT FOLLOW-UP***[328]	***8. POST-PLACEMENT FOLLOW-UP***	***Steps for Extraction:***	*Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed (i.e., detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more coils of the micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of an insert having fewer than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*[361]
Counseling and Informed-Decision Making	…	…	…	…
…	***Post-Placement Warnings and Precautions***	***Post-Placement Warnings and Precautions***	*Do not attempt insert removal hysteroscopically unless 18 or more coils of the Essure insert are trailing into the uterine cavity. Removal of insert may not be possible; attempted removal of inserts having fewer than 18 trailing coils may cause insert to fracture or patient injury.*[351]	***Essure System Extraction***
<u>*The intended permanence of STOP must be stressed*</u>*. A physician should inform the patient that this is a permanent procedure and cannot be reversed.*[307]	***Micro-insert(s) Removal***	***Micro-insert(s) Removal***	…	*If there are 18 or more expanded outer coils trailing into the uterus, then the micro-insert should be immediately removed from the uterus (as described in steps 1-5 below) and another attempt made at micro-insert placement in the tube. Micro-insert removal may not always be possible.*[362]
…	*A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested device removal due to pain; however, if device removal is required for any reason, it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.*[329]	*A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain, and only one woman requested device removal due to pain; however, if device removal is required for any reason, it will likely require surgery, including an abdominal incision and general anesthesia, and possible hysterectomy.*[342]	***Insert(s) removal***	…
Any patient who is indecisive about undergoing hysteroscopy or concerned about reversal of the STOP procedure should be advised to consider their decision further.[308]	…	…	*A very small percentage of women in the Essure clinical trials reported recurrent or persistent pelvic pain; one woman requested device removal due to pain; however, if device removal is required for any reason, it will likely require surgery. Linear salpingotomy or salpingectomy via laparoscopy or laparotomy can be used to remove the insert. Do not remove insert(s) unless patient is experiencing an adverse event(s) associated with its presence, or if removal is demanded. A cornual resection of the proximal fallopian tube may be required for removal.*	***Steps for Extraction:***
…	***9. MANAGEMENT OF TECHNICAL ISSUES***[330]	***9. MANAGEMENT OF TECHNICAL ISSUES***	*1. To perform a linear salpingotomy, make a small incision (approximately 2 cm in length) along the antimesenteric border of the fallopian tube directly overlying the insert.*	…
Screening for Regret	***Attempted Micro-insert Removal During Procedure***	***Attempted Micro-insert Removal During Procedure***	*2. To perform total or partial salpingectomy, use a transabdominal approach (ie, laparotomy or laparoscopy). Removal may be along with, or independent of, an incisional sterilization procedure.*[352]	*Do not attempt micro-insert removal hysteroscopically unless 18 or more coils of the Essure micro-insert are trailing into the uterine cavity. Removal of micro-insert may not be possible; attempted removal of micro-inserts having fewer than 18 trailing coils may cause micro-insert to fracture or patient injury.*[363]
STEP I. Assessing the Patient's Decision to Have STOP Non-Incisional Permanent Contraception	***WARNING:*** *Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed and detached from the delivery wire. The only exception is during the actual placement procedure when removal may be attempted if 18 or more expanded coils of the Essure micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*	*WARNING: Micro-insert removal should not be attempted hysteroscopically once the micro-insert has been placed (i.e., detached from the delivery wire). The only exception is during the actual placement procedure when removal may be attempted if 18 or more expanded coils of the Essure micro-insert are trailing into the uterine cavity. Because of micro-insert anchoring, however, removal may not be possible even immediately after placement. Attempted removal of a micro-insert having less than 18 coils trailing into the uterine cavity may result in fallopian tube perforation or other patient injury.*	…	…
Because STOP is a permanent method of contraception, it is critical to determine whether a patient's decision to have permanent contraception is a sound one.[309]				***Steps for Extraction:***
…				…
Patient Comprehension and Consent				*Do not attempt micro-insert removal hysteroscopically unless 18 or more coils of the Essure micro-insert are trailing into the uterine cavity. Removal of micro-insert may not be possible; attempted removal of micro-inserts having fewer than 18 trailing coils may cause micro-insert to fracture or patient injury.*[363]
…				…
7. … Be sure the patient understands the six points of informed consent listed below … The six points of informed consent are:				***Micro-insert(s) removal***
…				*… if device removal is required for any reason, it will likely require surgery. Linear salpingotomy or salpingectomy via laparoscopy or laparotomy can be used to remove the micro-insert. Do not remove micro-insert(s) unless the patient is*
• *The understanding that it is intended to be permanent and cannot be reversed*				
• *The understanding that, if STOP is successful, the patient will have no more children*[310]				
…				
Appendix D				
Instructions for Use				

[307] MIS.500.001.0013 at [0002] / Page 3.
[308] MIS.500.001.0013 at [0002] / Page 3.
[309] MIS.500.001.0013 at [0006] / Page 7.
[310] MIS.500.001.0013 at [0008] / Page 9.
[327] MIS.500.001.0023 at [0010] / Page 11.
[328] MIS.500.001.0024 to [0017] / Pages 1 to 18.
[329] MIS.500.001.0024 at [0001] / Page 2.
[330] MIS.500.001.0025 to [0012] / Page 12.
[341] GYT.002.001.0131 at [0174] / Page 44.
[342] GYT.002.001.0131 at [0177] / Page 47.
[350] GYT.003.001.0001 at [0033] / Page 33.
[351] GYT.003.001.0001 at [0033] / Page 33.
[352] GYT.003.001.0001 at [0037] / Page 37.
[361] AMS.001.001.5420 at [0033] / Page 34.
[362] AMS.001.001.5420 at [0034] / Page 35.
[363] AMS.001.001.5420 at [0034] / Page 35.

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Conceptus STOP Non-Incisional Permanent Contraception Kit … ***II. Indications for Use***[311] *The STOP System is indicated for permanent female contraception.* ***III. Contraindications***[312] *Patient uncertainty about their desire to end fertility* … ***VII. Possible Adverse Effects*** … ***b. Risks Associated with the Device Placement Procedure*** .. *5. Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.*[313] … *9. There is a risk that the STOP device may be placed too proximally in the fallopian tube. If 20 or more coils of the STOP device are visible at the time of placement, an immediate attempt should be made to remove the device … If device removal is attempted, there is a possibility that the removal will not be successful or that the STOP device may break, leaving a fragment of the device in vivo. If device removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the STOP device placement procedure.*[314] … ***c. Risks associated with STOP Device Wearing*** … *2. As with currently available methods of mechanical permanent contraception (i.e. clips, rings), if the STOP device is to be*	*… Micro-insert removal may not always be possible. Removal of a microinsert should only be attempted during the same procedure in which the microinsert was placed.*[331] … *Other than the above-described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro- insert removal.*[332] ***Attempted Micro-insert Removal After Procedure*** *Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required.*[333]	*… Micro-insert removal may not always be possible. Removal of a microinsert should only be attempted during the same procedure in which the microinsert was placed.*[343]		*experiencing an adverse event(s) associated with its presence, or if removal is demanded. A cornual resection of the proximal fallopian tube may be required for removal.*[364] … ***INSTRUCTIONS FOR USE*** … ***III. Indications for use*** *The **Essure** system is intended for use as a tubal occlusion micro-insert for purposes of permanent contraception.*[365] ***IV. Contraindications for use*** • *Patient uncertainty about her desire to end fertility.*[366] … ***V. Warnings*** … • *Once the micro-insert has been placed (i.e., detached from the delivery wire), micro-insert removal should not be attempted hysteroscopically unless 18 or more coils of the **Essure** micro-insert are trailing into the uterine cavity. Removal of such a micro-insert should be attempted immediately following the placement. However, removal may not be possible.*[367] … ***VII. Possible adverse effects*** … ***B. Risks associated with the micro-insert placement procedure*** … *There is a risk that the **Essure** micro-insert may be inadvertently placed into the myometrium of the uterus and not into the fallopian tube lumen… If surgical removal of the micro-insert(s) is required, salpingectomy or hysterectomy may be required.*[368] *There is a risk that the **Essure** micro-insert may be placed too distally in the fallopian*

[311] MIS.500.001.0014 at [0040] / Page 41.
[312] MIS.500.001.0014 at [0041] / Page 42.
[313] MIS.500.001.0014 at [0046] / Page 47.
[314] MIS.500.001.0014 at [0046] / Page 47.
[331] MIS.500.001.0025 at Page 1.
[332] MIS.500.001.0025 at Page 1.
[333] MIS.500.001.0025 at [0001] / Page 2.
[343] GYT.002.001.0131 at [0188] / Page 58.
[364] AMS.001.001.5420 at [0039] / Page 40.
[365] AMS.001.001.5420 at [0083] / Page 84.
[366] AMS.001.001.5420 at [0083] / Page 84.
[367] AMS.001.001.5420 at [0083] / Page 84.
[368] AMS.001.001.5420 at [0083] / Page 84.

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removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.[315] *…* ***VIII. Directions For Use*** *…* *21. … WARNING: After the device has been placed and released into the fallopian tube, DO NOT ATETMPT TO REMOVE THE DEVICE HYSTEROSCOPICALLY UNLESS 20 OR MORE COILS OF THE STOP DEVICE ARE TRAILING IN THE UTERINE CAVITY. Removal of such a device should be attempted immediately following the placement. However, removal may not be possible …*[316] *…* ***X. Device Removal*** *1. WARNING: DEVICE REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE DEVICE HAS BEEN PLACED UNLESS 20 OR MORE COILS OF THE STOP DEVICE ARE TRAILING INTO THE UTERINE CAVITY. Removal of such a device should be attempted immediately following placement. However, removal may not be possible …* *2. Other than the above described scenario, device removal should only be attempted if a patient is experiencing an adverse event(s) with the device or if she demands device removal.* *3. Should device removal be deemed necessary, a transabdominal approach (i.e. laparotomy or laparoscopy) is required.* *4. A cornual resection of the proximal fallopian tube will be required if the device is properly located across the utero-tubal junction (UTJ).* *5. A STOP device that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingostomy or salpingectomy*				*tube. If removal of the micro-insert is necessary, surgery (laparoscopy or laparotomy) will be required.*[369] *There is a risk that the **Essure** micro-insert may be placed too proximally in the fallopian tube… If micro-insert removal is attempted and/or achieved, there is also a possibility that the patient may experience increased pain, cramping and bleeding during and following the **Essure** micro-insert placement procedure.*[370] *…* ***C. Risks associated with Essure micro-insert wearing*** *…* *As with currently available methods of mechanical permanent contraception (i.e., clips, rings), if the **Essure** micro-insert is to be removed, surgery will be required. Further, it is possible that surgical removal of the fallopian tubes (salpingectomy) and uterus (hysterectomy) may be required.*[371] *…* *Occasionally, a woman may regret her decision to undergo permanent contraception and experience mild depression or other emotional disturbances as a result.*[372] ***VIII. Directions for use*** *…* ***B. Essure micro-insert placement procedure*** *…* ***17. WARNING: AFTER THE MICRO-INSERT HAS BEEN PLACED AND RELEASED INTO THE FALLOPIAN TUBE, DO NOT ATTEMPT TO REMOVE THE MICRO-INSERT HYSTEROSCOPICALLY UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING IN THE UTERINE CAVITY**. Removal of such a micro-insert should be attempted immediately during the placement attempt. However, removal may not be possible (see section XIII, **Essure** Micro-insert Removal). If the micro-insert was inadvertently deployed in the uterine cavity and not into the tube, the micro-insert should*

[315] MIS.500.001.0014 at [0047] / Page 48.
[316] MIS.500.001.0014 at [0053] / Page 54.
[369] AMS.001.001.5420 at [0083] / Page 84.
[370] AMS.001.001.5420 at [0083] / Page 84.
[371] AMS.001.001.5420 at [0083] / Page 84.
[372] AMS.001.001.5420 at [0083] / Page 84.

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accomplished via laparoscopy or laparotomy.[317]				*be removed from the uterus and another attempt made at micro-insert placement in the tube.*[373] … ***X. Management of Unsatisfactory Micro-insert Location (UML)*** … ***B. Management of micro-insert expulsion or unsatisfactory micro-insert location*** … *5. Unilateral micro-insert expulsion; unsatisfactory unilateral micro-insert location in "proximal location" (>50% of inner coil length trailing into uterus) or "distal location" (micro-insert in fallopian tube, but proximal end of inner coil is >30mm from contrast filling the uterine cornua) with contralateral micro-insert in an unsatisfactory location: … In all cases, if the micro-insert removal is deemed necessary and hysteroscopic removal is not possible, incisional surgery may be required.* *6. … An attempt should be made to retrieve a micro-insert if the physician believes it can be done safely, however micro-insert retrieval may not be possible.*[374] … ***XII. Essure micro-insert removal*** ***WARNING: MICRO-INSERT REMOVAL SHOULD NOT BE ATTEMPTED HYSTEROSCOPICALLY ONCE THE MICRO-INSERT HAS BEEN PLACED, UNLESS 18 OR MORE COILS OF THE ESSURE MICRO-INSERT ARE TRAILING INTO THE UTERINE CAVITY.*** *Removal of such a micro-insert should be attempted immediately following placement. However, removal may not be possible.*[375] … *Other than the above described scenario, micro-insert removal should only be attempted if a patient is experiencing an adverse event(s) with the micro-insert or if she demands micro-insert removal.*[376]

[317] MIS.500.001.0014 at [0055] / Page 56.
[373] AMS.001.001.5420 at [0084] / Page 85.
[374] AMS.001.001.5420 at [0086] / Page 87.
[375] AMS.001.001.5420 at [0086] / Page 87.
[376] AMS.001.001.5420 at [0086] / Page 87.

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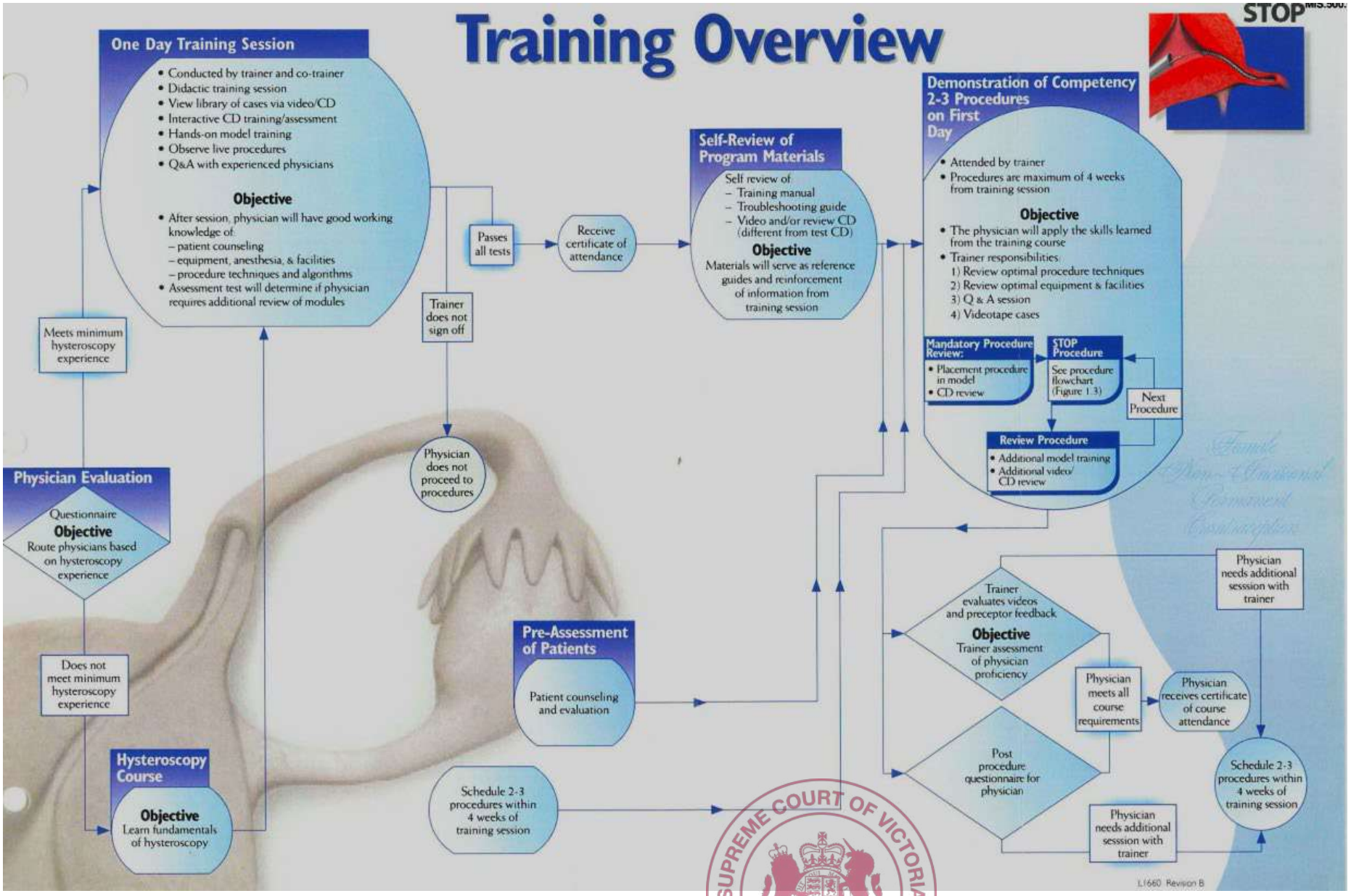
				Should micro-insert removal be deemed necessary, a transabdominal approach (i.e., laparotomy or laparoscopy) is required. *A cornual resection of the proximal fallopian tube will be required if the micro-insert is properly located across the utero-tubal junction (UTJ).* *An **Essure** micro-insert that has been improperly placed or has migrated beyond the UTJ should be removed with traditional linear salpingotomy or salpingectomy accomplished via laparoscopy or laparotomy.*[377]

[377] AMS.001.001.5420 at [0086] / Page 87.

SCHEDULE 5 [1]



[1] MIS.500.001.0005