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Official Title:	An open-label, non-randomized, prospective observational cohort study to assess post-procedural outcomes in two cohorts of women who chose to undergo either hysteroscopic sterilization (Essure) or laparoscopic tubal sterilization
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An open-label, non-randomized, prospective observational cohort study to assess post-procedural outcomes in two cohorts of women who chose to undergo either hysteroscopic sterilization (Essure®) or laparoscopic tubal sterilization

This protocol version is an integration of the following documents / sections:

- **Original protocol**, Version 1.0, dated 24 JAN 2017
- **Amendment 1** (described in Section 16.1)
  forming Integrated Protocol Version 2.0, dated 12 OCT 2017
- **Amendment 2** (described in Section 16.2)
  forming Integrated Protocol Version 3.0, dated 25 OCT 2018
- **Amendment 3** (described in Section 16.3)
  forming Integrated Protocol Version 4.0, dated 31 JUL 2020
- **Amendment 4** (described in Section 16.4)
  forming Integrated Protocol Version 5.0, dated 28 JUN 2022

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.

1. Title page

An open-label, non-randomized, prospective observational cohort study to assess post-procedural outcomes in two cohorts of women who chose to undergo either hysteroscopic sterilization (Essure®) or laparoscopic tubal sterilization

Test device:	BAY 1454032 / Essure ® (ESS305)		
Study purpose:	Postmarket Surveillance		
Clinical study phase:	IV	Date:	28 JUN 2022
Registration:	NCT03127722	Version no.:	5.0
Sponsor's study no.:	18894		
Sponsor:	Bayer HealthCare, LLC., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981, USA		

Sponsor's medical expert: PPD,
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PPD

The study will be conducted in compliance with the protocol, International Council for Harmonisation – Good Clinical Practice and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, ™) may not be displayed.
Hence, the appearance of product names without these symbols does not imply that these names are not protected.

Signature of the sponsor's medically responsible person

Section modified by Amendment 2 (Modification 1).

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: PPD

Date: 7/13/2022 Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis - amended

Title	An open-label, non-randomized, prospective observational cohort study to assess post-procedural outcomes in two cohorts of women who chose to undergo either hysteroscopic sterilization (Essure®) or laparoscopic tubal sterilization
Clinical study phase	IV
Study objective(s)	This study has the following objectives: • To evaluate the proportion of subjects who experience new onset or worsening chronic lower abdominal and / or pelvic pain who have undergone Essure placement (anyone who has had an attempt at placement defined as an insert that was placed in the operating channel of the hysteroscope will be included in the analysis, regardless of whether or not they are relying on Essure for contraception) compared to the proportion of subjects who had an attempt at laparoscopic tubal sterilization (defined as anyone who has had an incision or puncture of the skin, regardless of whether or not sterilization was successfully completed), and to better characterize these reported outcomes and identify pre-procedural and procedure-related characteristics that may be related to their occurrence. • To evaluate the proportion of subjects who experience new onset or worsening abnormal uterine bleeding who have undergone Essure placement (as defined above) compared to the proportion of subjects who have undergone laparoscopic tubal sterilization (as defined above) and to better characterize these reported outcomes and identify pre-procedural and procedure-related characteristics that may be related to their occurrence. • To evaluate the proportion of subjects who undergo gynecologic or related surgical intervention (including “insert removal” and hysterectomy) after undergoing hysteroscopic sterilization with Essure versus laparoscopic tubal sterilization. • To identify the proportion of subjects who experience new onset or worsening allergic, hypersensitivity, or autoimmune-like reactions after Essure placement or laparoscopic tubal sterilization and to better characterize these reported outcomes and any characteristics that may be related to their occurrence. • To collect data on patient reported outcomes in subjects who have undergone hysteroscopic or laparoscopic tubal sterilization procedures. • To collect rates of adverse events (AEs) in subjects undergoing Essure placement or laparoscopic tubal sterilization.
Test device **Name of device** **Device type** **Duration of treatment**	*Section modified by Amendment 2 (Modification 17).* Essure System (ESS305) Permanent birth control system (Class III) Through 60 months after sterilization procedure
Indication	Permanent birth control

Diagnosis and criteria for inclusion	*Section modified by Amendment 2 (Modification 8, Modification 9).* 1. Signed and dated informed consent; 2. Subjects who are at least 21 years of age; 3. Subjects of all weights will be included; 4. Subjects who are scheduled to undergo an Essure insert placement procedure for permanent birth control or laparoscopic tubal sterilization. Decision for either treatment based upon clinical practice and physician / patient counseling; 5. For the Essure group only: • Subjects selecting hysteroscopic sterilization who are not contraindicated for the Essure procedure according to the most current approved version of the Essure Instructions for Use; • Subjects must have received the most current approved version of the Patient Information Booklet and completed the Essure patient checklist; • Subjects selecting Essure who are willing to use alternative contraception for at least 3 months post-Essure placement procedure, until a satisfactory Essure Confirmation Test is documented; • Subjects who are believed to have two viable fallopian tubes. 6. For the laparoscopic tubal sterilization group only: • Subjects selecting laparoscopic sterilization who are not contraindicated for laparoscopic tubal sterilization according to common clinical practice standard of care; • After signed informed consent, subjects must have received the American College of Obstetricians and Gynecologist's Patient Information Brochure on Sterilization by Laparoscopy and completed the laparoscopic tubal sterilization patient checklist. 7. Subjects who are willing to accept the risk of pregnancy occurring while relying on the Essure device or laparoscopic tubal sterilization for prevention of pregnancy; 8. Subjects who have the capacity to understand the informed consent, comply with the protocol requirements, and provide reliable feedback during the follow-up period; 9. Subjects who agree to participate in the scheduled study visits; 10. Subjects who are willing to allow data to be shared with the sponsor and with regulatory bodies.
Diagnosis and criteria for exclusion	*Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 10, Modification 11).* 1. Subjects who are post-menopausal; 2. Subjects suspected of being or who are confirmed to be pregnant; 3. Subjects post-partum or having undergone pregnancy termination ≤ 6 weeks prior to scheduled procedure (Note: subjects may be screened

	and consented for the study prior to 6 weeks post-partum / post pregnancy termination; however, patient reported outcome tools must be administered > 6 weeks post-partum/pregnancy termination and the sterilization procedure must occur > 6 weeks post-partum/pregnancy termination); 4. Subjects uncertain about ending fertility; 5. Subjects with an active upper or lower genital tract infection; 6. Subjects with gynecologic malignancy (suspected or known); 7. Subjects who have had an attempted prior sterilization procedure (either laparoscopic or hysteroscopic); 8. Subjects scheduled to undergo concomitant intrauterine or laparoscopic procedures at the time of insert placement (intrauterine device removal/placement is not considered a concomitant procedure) or tubal sterilization; 9. Subjects with unexplained vaginal bleeding; 10. Any diseases or conditions that might interfere with the conduct of the study or the interpretation of the results (subjects with pre-existing conditions such as pelvic pain, autoimmune disease, or menorrhagia may be included at the discretion of the principal investigator); 11. Subjects who are direct employees or immediate family members of the Sponsor company or site investigators; For the Essure group only: 1. Subjects who can have only one insert placed (including contralateral proximal tubal occlusion or suspected unicornuate uterus); 2. Subjects who have a known abnormal uterine cavity that makes visualization of the tubal ostia impossible and / or abnormal tubal anatomy or previous tubal ligation (including failed ligation); 3. Subjects who have had total or partial salpingectomies; 4. Subjects who are currently taking corticosteroids or immunosuppressive therapy; 5. Subjects with a known allergy to all contrast media available for use in hysterosalpingogram.
Study design	Open-label, non-randomized, prospective observational postmarket surveillance study of two cohorts of subjects who chose to undergo either hysteroscopic sterilization (Essure®) or laparoscopic tubal sterilization.
Methodology	*Section modified by Amendment 2 (Modification 2, Modification 3, Modification 17) and Amendment 3 (Modification 2).* Study subjects will be women who are seeking permanent contraception and who have elected to undergo either hysteroscopic sterilization (Essure System ESS305) or laparoscopic tubal sterilization. Candidates who meet the inclusion and exclusion criteria, are willing to participate in the study, and are able to provide informed consent will be eligible for the study. The sterilization procedure will proceed as it would if the subject were not in the trial. For subjects who elect to have hysteroscopic sterilization, 3 months

	following the placement procedure, the subject will be scheduled to return to the physician's office or radiology facility for a confirmation test to evaluate Essure insert location and retention. Upon a satisfactory confirmation test, subject will be instructed to rely on Essure for contraception. Follow-up contact will take place at 3 months (± 2weeks), 12 months (± 4 weeks), 24 months (± 4 weeks), 36 months (±4 weeks), 48 months (± 4 weeks), and 60 months (-4 weeks, +1 week) post procedure. These visits will collect information that includes (but is not limited to) pelvic / lower abdominal pain, bleeding, gynecological procedures, AEs, and concomitant medication use. Patient reported outcomes for pain (Patient Reported Outcomes Measurement Information System Scale V1.0, Pain Intensity 3a and Pain Interference 8a Participant Format) will be assessed at Baseline, Week 1, Week 2, Week 3, Week 4, Month 2, Month 3, and then every 3 months starting Month 6 until 36, if the response is "Yes" to the question "Did you experience pain in your pelvic area or in your lower abdomen during the past week?" Patient reported outcomes for bleeding (Aberdeen Menorrhagia Severity Scale) will be assessed at baseline and then every 3 months starting Month 3 until Month 36. Patient reported outcomes for health status (Medical Outcomes Study Short Form-36) will be assessed at Baseline, Month 6, Month 12, Month 24, Month 36, and Month 60. Subjects will also complete a baseline questionnaire (Fibromyalgia Survey Questionnaire) that may help to identify women who are more likely to report pain events. Subjects will complete Supplemental PRO Questionnaires at 12, 24, 36, 48, and 60 months, and a Social Media Questionnaire at 60 months (or Premature Discontinuation [dropout] visit if applicable). The final study visit is in the physician's office 60 months (-4 weeks, +1 week) after the procedure. Due to local regulations impacting the study center due to COVID-19, it is possible that not all planned assessments could be performed or if they had been included in the eCRF, they could not all be verified. The protocol deviations related to COVID-19 will be identified in the by-subject listings.
Type of control	Not applicable.
Data Monitoring and Adjudication Committees - amended	*Section modified by Amendment 4 (Modification 1)* The role of the Data Monitoring Committee (DMC) has concluded. An adjudication committee will be assembled at the beginning of the study. The adjudication committee will consist of a group of experts in allergy / immunology who are also experienced in evaluating immunological symptoms in subjects with medical devices. A gynecologist will be included. The committee will operate based on the allergy / immunology adjudication committee charter.
Number of subjects	*Section modified by Amendment 2 (Modification 6).* Overall enrollment will be dependent on availability of Essure.

	Recruitment in the Essure arm is planned to continue as long as Essure is being implanted. Enrollment in the laparoscopic tubal sterilization arm will be ceased once its enrollment reaches approximately 2:1 ratio laparoscopic tubal sterilization : Essure (anticipated).
Main variable(s)	*Section modified by Amendment 2 (Modification 7).* **Pain**: The proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after insertion of Essure System (ESS305) compared to the proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after laparoscopic tubal sterilization. Total incidence of pain events will be based on AE reporting. **Bleeding**: The proportion of subjects reporting AEs of abnormal uterine bleeding after insertion of Essure System compared to the proportion of subjects reporting AEs of abnormal uterine bleeding after laparoscopic tubal sterilization. Total incidence of new onset or worsening abnormal bleeding events will be based on AE reporting. **Hypersensitivity / allergy**: The proportion of subjects with adjudicated new onset or worsening allergic / hypersensitivity reactions (e.g., urticaria, rash, itching, as well as other symptoms that may be related to inflammation) in subjects wearing Essure inserts and in subjects undergoing laparoscopic tubal sterilization. **Autoimmune disorder**: The proportion of subjects with adjudicated newly diagnosed or worsening autoimmune disorders in subjects wearing Essure inserts and in subjects undergoing laparoscopic tubal sterilization. **Proportion of subjects undergoing invasive gynecologic surgery after Essure placement (excluding second placement attempts)**; including Essure insert removal compared to the proportion of subjects undergoing invasive gynecologic surgery after laparoscopic tubal sterilization.
Time point / frame of measurement for primary variable(s)	*Section modified by Amendment 2 (Modification 17).* The main endpoints will be evaluated through 60 months of follow up after the procedure.
Plan for statistical analysis - amended	*Section modified by Amendment 2 (Modification 26), Amendment 3 (Modification 1), and Amendment 4 (Modification 2).* Three interim analyses will be performed in addition to the main analysis. The first will be initiated at the end of enrollment, the second will be initiated after all subjects complete 1 year of follow-up, and the third will be initiated at the point all subjects complete three years of follow-up. The purpose of these analyses is to formally review study data, at the request of FDA. Statistical analyses will be explorative and descriptive in nature and no confirmatory hypothesis tests will be performed. P-values will be interpreted as a metric for uncertainty. Therefore, no adjustment for multiplicity will be necessary. All endpoints and variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, lower and upper quartiles, median, and maximum will be calculated for continuous data. Frequency tables will be generated for categorical data,

	including the number of missing values as an additional category. Relative frequencies will be shown as percentages which will be calculated as a proportion including the category of missing values. Incidence rates and proportions will be used to summarize main endpoints and other variables. For time-to-event endpoints, hazard ratios derived from a Cox regression model, and Kaplan-Meier estimates will be provided. Additional details regarding endpoints, variables, and tables will be described in the Statistical Analysis Plan. If not specified otherwise, the analyses will be presented in a way that events will be assigned to the treatment which was attempted initially at the index event. The main analyses will be performed on a propensity score (PS) matched population in order to adjust for measured confounding as well as on the total population. In other words, the main analysis sets are the Adjusted Full Analysis Set (PS matched population among subjects where a sterilization procedure of choice was attempted) and the Full Analysis Set (sterilization procedure of choice was attempted). A Reliance Set will consider women relying on the sterilization method selected at the index event. The propensity score model will be developed, after all subjects have been enrolled, by an outcome-blinded independent party which will only have access to baseline characteristics. Balance of the PS baseline characteristics will be assessed at the 3-year interim analysis and end of study; if necessary, the PS process will be reevaluated to ensure balance of baseline characteristics throughout the study. All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities.

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List of abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADE	Adverse device effect
AE	Adverse event
AMSS	Aberdeen Menorrhagia Severity Scale
AUB	Abnormal uterine bleeding
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CREST	Collaborative Review of Sterilization
CRF	Case report form
CRO	Contract research organization
DMC	Data monitoring committee
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
FSQ	Fibromyalgia Survey Questionnaire
GCP	Good clinical practice
HLA	Human leukocyte antigen
HLA-DR	Human Leukocyte Antigen-antigen D Related
HR	Heart rate
HSG	Hysterosalpingogram
ICF	Informed Consent Form
ICPMS	Inductively coupled plasma mass spectrometry
IEC	Independent ethics committee
IFU	Instruction for Use
IME	Important medical event
IRB	Institutional review board
ISF	Investigator Site File
LPT	Lymphocyte Proliferation Test
LTS	Laparoscopic Tubal Sterilization
MDR	Medical device reporting
MedDRA	Medical Dictionary for Regulatory Activities
MOS	Medical Outcomes Study
NiLPT	Nickel lymphocyte proliferation test
PIB	Patient information booklet
PRO	Patient reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PS	Propensity score
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-36	Short Form - 36

SI	Stimulation Index
TVU	Transvaginal ultrasound
UADE	Unanticipated adverse device effect
US	United States

3. Introduction

3.1 Background

The Essure System (ESS305; “system”) for Permanent Birth Control is designed for permanent contraception by physical occlusion of the fallopian tubes. Using a transvaginal approach, one flexible Essure insert (“insert”) is placed in the proximal portion of each fallopian tube lumen. The insert expands upon release to conform to and acutely anchor in the lumen of the fallopian tube. Subsequently, the insert elicits a benign tissue in-growth that permanently occludes the fallopian tube, resulting in contraception.

3.2 Device description

The ESS305 System is comprised of a disposable delivery system and a wound-down insert. A disposable introducer is also provided to facilitate delivery system entry into the hysteroscope operating channel. Each insert consists of a Nitinol (nickel-titanium alloy) outer coil, a 316L stainless steel inner coil wrapped in polyethylene terephthalate fibers, platinum marker bands (2), and a silver-tin solder. The wound-down insert is approximately 4 cm in length and 0.8 mm in diameter. The insert is designed with a 15-degree angle at the tip to facilitate entry into the fallopian tube. When released, the outer coil expands up to 2.0 mm in diameter, conforming itself to the varied diameters and shapes of the fallopian tube. The disposable delivery system and the DryFlow® introducer (“introducer”) help facilitate entry and advancement of the insert during insertion into the hysteroscope, also minimizing fluid back splash.

3.3 Essure procedure

The ESS305 System received Food and Drug Administration (FDA) Premarket Authorization approval in 2002 (P020014) and is commercially available in the United States (US), Canada, the European Union (CE Mark approval received 07 FEB 2001), Australia, New Zealand, and several Latin and South American countries. Data from the original Essure clinical studies show there were no pregnancies reported in women relying on Essure for contraception within the study cohorts up to five years of reliance on the inserts for contraception. The subjects in the original clinical trials underwent a hysterosalpingogram (HSG) 3 months post-Essure placement to evaluate insert location and fallopian tube occlusion.

3.4 Essure confirmation test

Until June 2015, the US Instruction for Use (IFU) required an HSG be performed 3 months post-Essure placement as the Essure Confirmation Test. Subjects would then be counseled to rely on Essure for contraception only after a satisfactory confirmation test was obtained and the results communicated to the woman.

In June 2015, transvaginal ultrasound (TVU) was approved by the FDA for use as a 3-month confirmation test to evaluate insert retention and location. An HSG is required for only those subjects who do not meet the criteria set forth in the “TVU / HSG algorithm” included in the approved US IFU. In the TVU clinical trial, 3 pregnancies were reported after one year of follow up, giving a one-year cumulative failure rate of 0.67%.

The HSG evaluates both insert location and tubal occlusion while TVU solely evaluates location. However, tubal patency does not unequivocally equate with pregnancy or fertility. In a review of the literature, Grunert (1) reported the tubal patency rate following incisional tubal ligation to be 3.2% and yet the failure rate was only 0.8%. Grunert concluded that "although there may be a failure of absolute physical occlusion of the tubes, this cannot be directly equated with failure of the sterilization." The Essure clinical trials demonstrated a 3-month patency rate of 3.5% following HSG with 100% of subjects showing tubal occlusion by 6 to 7 months following Essure placement.

Notably, the 3.5% patency rate observed in the clinical trials of the Essure System (ESS305) at the 3-month HSG performed mirrors the 3.2% patency rate noted by Grunert on over 1000 subjects who underwent incisional tubal ligation. Thus, the likelihood of pregnancy following a confirmation test evaluating insert location only is expected to be similar to that found in the Grunert study.

3.5 Laparoscopic tubal sterilization

Laparoscopy can be used to perform interval tubal sterilization procedures and is often performed as an outpatient procedure. Typically, the procedure is performed under general anesthesia in an operating room setting. Several specific procedures are available (electrocoagulation, mechanical devices, or tubal excision), though all require the placement of the laparoscope into the peritoneal cavity. Additional laparoscopic ports may also be required. The procedure is immediately effective and does not require a confirmation test.

The first major study to evaluate the efficacy and risks associated with bilateral tubal ligation was the US Collaborative Review of Sterilization (CREST), a large, prospective, multicenter observational study of 10 685 women conducted by the Center for Disease Control and Prevention that reported results on long-term failure rates for several types of sterilization procedures (2). Overall, CREST found that the failure rate for bilateral tubal ligation varied by type of sterilization procedure performed and by age at time of procedure, with an overall failure rate of 1.3%. Of the 9475 women in the study who underwent interval laparoscopic tubal ligation, the overall standard complication rate was 1.6% (3). This included an unintended major surgery rate of 0.9%.

3.6 Rationale of the study

Under Section 522 of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 3601, the FDA required Bayer (the manufacturer of Essure) to conduct a postmarket surveillance study. The Essure System (ESS305) is a Class III device intended to be implanted in the body for more than one year (and meets the criteria under the Act).

3.7 Benefit-risk assessment

3.7.1 Potential benefits and risks

The benefits to subjects of undergoing Essure placement and insert wearing are not different from those subjects who undergo the Essure procedure and do not participate in this study. The benefits to subjects undergoing laparoscopic tubal sterilization are not different from

those subjects who undergo laparoscopic tubal sterilization outside of the context of this study.

Both the Essure System and laparoscopic tubal sterilization have known risks. The risks to women undergoing their chosen permanent birth control procedure (Essure System or laparoscopic tubal sterilization) are not different from those women who undergo the procedure and do not participate in this study.

4. Study objectives

This study has the following objectives:

- To evaluate the proportion of subjects who experience new onset or worsening chronic lower abdominal and / or pelvic pain who have undergone Essure placement (anyone who has had an attempt at placement defined as an insert that was placed in the operating channel of the hysteroscope will be included in the analysis, regardless of whether or not they are relying on Essure for contraception) compared to the proportion of subjects who have had an attempt at laparoscopic tubal sterilization (defined as anyone who has had an incision or puncture of the skin, regardless of whether or not sterilization was successfully completed), and to better characterize these reported outcomes and identify pre-procedural and procedure-related characteristics that may be related to their occurrence.
- To evaluate the proportion of subjects who experience new onset or worsening abnormal uterine bleeding who have undergone Essure placement (as defined above) compared to the proportion of subjects who have undergone laparoscopic tubal sterilization (as defined above), and to better characterize these reported outcomes and identify pre-procedural and procedure-related characteristics that may be related to their occurrence.
- To evaluate the proportion of subjects who undergo gynecologic or related surgical intervention (including “insert removal” and hysterectomy) after undergoing hysteroscopic sterilization with Essure versus laparoscopic tubal sterilization.
- To identify the proportion of subjects who experience new onset or worsening allergic, hypersensitivity, or autoimmune-like reactions after Essure placement or laparoscopic tubal sterilization, and to better characterize these reported outcomes and any characteristics that may be related to their occurrence.
- To collect data on patient reported outcomes in subjects who have undergone hysteroscopic or laparoscopic tubal sterilization procedures.
- To collect rates of adverse events (AEs) in subjects undergoing Essure placement or laparoscopic tubal sterilization.

5. Study design

5.1 Design overview

Section modified by Amendment 2 (Modification 2)

This will be an open-label, non-randomized, continuous enrollment, prospective observational postmarket surveillance study of two cohorts of subjects who chose to undergo:

- hysteroscopic sterilization (Essure System), or
- laparoscopic tubal sterilization.

The targeted number of sites for participation in the study is up to 90.

5.2 Endpoints and variables

5.2.1 Main endpoints

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 3, Modification 4, Modification 5, Modification 7).

- **Pain:** The proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after insertion of Essure System compared to the proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after laparoscopic tubal sterilization. Total incidence of pain events will be based on AE reporting. If a potential pain event is spontaneously reported outside of a scheduled visit or scheduled patient-reported outcome (PRO) tool administration, the pain PRO tools (Patient-Reported Outcomes Measurement Information System [PROMIS] Scale V1.0 – Pain Intensity 3a and PROMIS Scale V1.0 – Pain Interference 8a Participant Format; see Section 9.2.3) will be administered off-schedule in order to characterize pain intensity and interference. If during the course of a scheduled PRO administration (see Table 9–2 and Section 9.2.3) the subject reaches a preset threshold for pain on a PRO tool, even if she has not spontaneously reported a pain event to the investigator, the investigator will be alerted and instructed to investigate this finding in order to determine whether or not an AE has occurred. Standard criteria for AE assessment (e.g., new or worsening symptom) will be used and all investigators will be trained on standard AE assessment.

  The preset thresholds that will trigger investigation of pain as an AE are as follows: on the PROMIS Pain Intensity Scale, a score of 3 (moderate intensity) for the 'pain at its worst' question will trigger investigation regardless of the other scores or results of the PROMIS Pain Interference Scale. For PROMIS Pain Interference Scale, a t-score of ≥ 60 (which corresponds to a raw score of ≥ 22) or any single item raw score of ≥ 4 will trigger investigation regardless of the results of the PROMIS Pain Intensity Scale. Section 9.2.3 includes justification for these thresholds. Not all reports of pain that are reported on the PRO tool will be considered AEs. This is particularly notable in the case of a subject who has pre-existing pain that continues to be unchanged post-sterilization procedure.

- In addition, any subject who experiences an AE of pelvic / lower abdominal pain in this study will be evaluated for possible hypersensitivity / allergic reaction including central laboratory evaluation and case adjudication (see below for further details on hypersensitivity / allergy).

  Per the definition by the American College of Obstetricians and Gynecologists, chronic pelvic pain is pain in the pelvic area that lasts for 6 months or longer. In those subjects reporting lower abdominal / pelvic pain at any time during the study, either spontaneously or in response to the regularly scheduled PRO tool and who have been judged to have experienced an AE, it will be determined if duration of the pain meets this definition. The percentage of subjects in each group (laparoscopic and hysteroscopic) who are determined to have new onset or worsening chronic pelvic / lower abdominal pain will be reported. Additional analyses will be carried out looking at total number of pain reports (regardless of chronicity), intensity, and pain interference.

- **Bleeding:** The proportion of subjects reporting AEs of abnormal uterine bleeding (AUB) after insertion of Essure System compared to the proportion of subjects reporting AEs of AUB after laparoscopic tubal sterilization. Total incidence of new onset or worsening abnormal bleeding events will be based on AE reporting. If a potential bleeding AE is reported at a scheduled visit or if the subject spontaneously reports such an event to the site at some other time, the event will be evaluated per standard AE assessment. In the event of a report outside of a scheduled visit or scheduled PRO administration, the Aberdeen Menorrhagia Severity Scale (AMSS) and two intermenstrual bleeding questions will not be re-administered as the recall period for these PRO tools is 3 months and these data are captured during the scheduled PRO tool administration which occurs every 3 months.

  If during the course of a scheduled PRO administration (see Table 9–2 and Section 9.2.3.1) the subject indicates that she has experienced abnormal bleeding that reaches a preset threshold on the AMSS, even if the subject has not spontaneously reported this event, the investigator will be alerted and instructed to investigate this finding in order to determine whether or not an AE has occurred. Standard criteria for AE assessment (e.g., new or worsening symptom) will be used and all investigators will be trained on standard AE assessment. The threshold for investigation of bleeding as an AE will be a total Aberdeen Scale score of ≥ 40. Investigation will also be triggered by responses that meet a preset threshold on specified single questions, including those on the two intermenstrual bleeding questions. These are summarized in Section 9.2.3.1. The percentage of subjects in each group (laparoscopic and hysteroscopic) who are determined to have an AE related to AUB will be reported. Not all reports of AUB reported on the PRO will be considered AEs. This is particularly notable in the case of a subject who has pre-existing AUB that continues to be unchanged post-sterilization procedure. Additional analyses will be carried out looking at duration and severity of abnormal bleeding, type of abnormality (e.g., menorrhagia, metrorrhagia), and subject impact based on the PRO tools.

- **Hypersensitivity / allergy:** The proportion of subjects with adjudicated new onset or worsening allergic / hypersensitivity reactions (e.g., urticaria, rash, itching, as well as other symptoms that may be related to inflammation). For potential allergic / hypersensitivity reactions, investigators will be instructed that an evaluation per standard medical practice must be performed in any subject presenting with urticaria, angioedema, unexplained rash, or unexplained itching. Evaluation will also be performed in subjects who present with other symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain). Supplemental PRO Questionnaires will be used in both groups to actively solicit for such events. In addition, this evaluation will include collection and submission of blood and serum or plasma samples to a central laboratory for a nickel lymphocyte proliferation test (NiLPT), which is a measure of sensitization to nickel, a chromium lymphocyte proliferation test (LPT), which is a measure of sensitization to chromium, serum or plasma nickel level, serum or plasma titanium level, and inflammatory cytokines panel.

  In addition, any subject presenting with an AE of pelvic / lower abdominal pain and any subject presenting with symptoms she believes are due to hypersensitivity or allergic reaction will be evaluated per standard medical practice. In addition, this evaluation will include collection and submission of blood and serum samples to a central laboratory for a NiLPT, which is a measure of sensitization to nickel; a chromium LPT, which is a measure of sensitization to chromium; serum or plasma nickel level; and serum or plasma titanium level. If removal of a device or any other surgery is performed, pathological evaluation and metallurgic studies (if applicable) will be included. After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not a hypersensitivity / allergic reaction has occurred, all information will be forwarded to the adjudication committee (see Section 14.3) in a blinded fashion. If pathology / metallurgic studies are provided to the adjudication committee, it may not be possible to blind the members as to which group the subject belongs. Information forwarded to the adjudication committee will include all laboratory work for the subject, including baseline, 12 month (if applicable), and unscheduled draws. The final determination of whether or not a hypersensitivity / allergic event has occurred will be made by this committee.
- **Autoimmune disorders:** The proportion of subjects with adjudicated newly diagnosed or worsening autoimmune disorders in subjects wearing Essure inserts and in subjects undergoing laparoscopic tubal sterilization. Any subject presenting with symptoms indicating a potential autoimmune disorder will be evaluated per standard medical practice. All efforts will be made to obtain records of any diagnostic workup conducted by outside physicians. Blood samples for NiLPT, chromium LPT, serum or plasma nickel level, and serum or plasma titanium level will also be collected by the study site. An appropriate human leukocyte antigen (HLA) panel will be run on previously obtained baseline samples, if not already obtained at baseline. (The specific HLA type to be run will be dependent on the specific autoimmune disease the subject developed). If insufficient baseline sample exists, an additional sample may need to be drawn. After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not an autoimmune disorder exists, all

information will be forwarded to the adjudication committee in a blinded fashion. If pathology / metallurgic studies are provided to the adjudication committee, it may not be possible to blind the members as to which group the subject belongs. Information forwarded to the adjudication committee will include all laboratory work for the subject, including baseline, 12 month (if applicable), and unscheduled draws. The final determination of whether or not an autoimmune disorder has occurred will be made by this committee.

- **Proportion of subjects undergoing invasive gynecologic surgery after Essure placement:** (excluding second placement attempts); including Essure insert removal compared to the proportion of subjects undergoing invasive gynecologic surgery after laparoscopic tubal sterilization.
- **Patient reported outcome measures** (details for PROs can be found in Section 9.2.3):
    - Medical Outcomes Study (MOS) Short Form-36 (SF-36; Version 2) (a global measure of quality of life);
    - Screening question for lower abdominal / pelvic pain;
    - PROMIS Scale V1.0 – Pain Intensity 3a - to be completed if screening question is positive (a measure of pain intensity);
    - PROMIS Scale V1.0 – Pain Interference 8a Participant Format - to be completed if screening question is positive (a measure of how pain interferes with daily life);
    - AMSS (includes items querying menstrual volume, regularity, and interference across the previous 3 menstrual periods);
    - Two intermenstrual bleeding questions (probe for instances of vaginal bleeding between periods);
    - Fibromyalgia Survey Questionnaire (FSQ) – for baseline only (a measure of a centralized pain state, shown to be useful in prediction of chronic pain);
    - Supplemental PRO Questionnaires – for use at 12, 24, 36, 48, and 60 months only: a series of PRO tools used to actively solicit information on AEs commonly found in medical device reporting (MDR) reports with Essure;
    - Social Media Questionnaire – for use at 60 months (or Premature Discontinuation visit if applicable) only: to elicit information about sources of influence on medical decisions, in particular, use of social media.
- **Rates of AEs in subjects undergoing Essure placement and laparoscopic tubal sterilization.** It is recognized that some AEs may be more likely to be reported in one group over the other during the course of the study, potentially due to outside influences (such as social media). To help control for this potential bias, the Supplemental PRO Questionnaires will actively solicit information on possible AEs related to depression, anxiety, pruritus, rash, pain in extremities, hair loss, nausea/vomiting, dysgeusia, fatigue, dental issues, and weight change in subjects in both groups. Active solicitation of AEs is likely to lead to higher rates of AEs than normally encountered; however, the influence should be the same on both groups.

Results of these tools will also be used to identify subjects with positive versus negative responses in order to create comparative groups for baseline and subsequent lab work.

5.2.2 Physician and subject characterizations

- Characteristics of physicians performing the procedures;
- Characteristics of subjects undergoing Essure Confirmation Test compared to subjects who do not comply with the requirement for Essure confirmation testing.

5.3 Managing differences in recruitment rates

Section modified by Amendment 2 (Modification 6).

Overall enrollment will be dependent on availability of Essure.

Recruitment in the Essure arm is planned to continue as long as Essure is available at the study sites and being implanted.

Enrollment in the laparoscopic tubal sterilization arm will be ceased once its enrollment reaches approximately 2:1 ratio laparoscopic tubal sterilization: Essure (anticipated).

5.4 End of study

Section modified by Amendment 2 (Modification 17).

The end of the study as a whole will be reached as soon as the last visit (60-month visit) of the last subject has been reached in all centers.

6. Study population

Section modified by Amendment 2 (Modification 8).

The study population will include subjects of reproductive age, at least 21 years of age, who have not been pregnant within the past 6 weeks.

The Essure study population group will include subjects who chose to undergo hysteroscopic sterilization and who meet the criteria as outlined in the most updated approved Essure IFU.

Subjects seeking laparoscopic tubal sterilization must be considered appropriate surgical candidates by the investigator.

6.1 Inclusion criteria

Section modified by Amendment 2 (Modification 8, Modification 9).

1. Signed and dated informed consent;
2. Subjects who are at least 21 years of age;
3. Subjects of all weights will be included;
4. Subjects who are scheduled to undergo an Essure insert placement procedure for permanent birth control or laparoscopic tubal sterilization. Decision for either treatment based upon clinical practice and physician / patient counseling;

5. For the Essure group only:

- Subjects selecting hysteroscopic sterilization who are not contraindicated for the Essure procedure according to the most current approved version of the Essure IFU;
- Subjects must have received the most current approved version of the Patient Information Booklet (PIB) and completed the Essure patient checklist;
- Subjects selecting Essure who are willing to use alternative contraception for at least 3 months post-Essure placement procedure, until a satisfactory Essure Confirmation Test is documented;
- Subjects who are believed to have two viable fallopian tubes.

6. For the laparoscopic tubal sterilization group only:

- Subjects selecting laparoscopic sterilization who are not contraindicated for laparoscopic tubal sterilization according to common clinical practice standard of care;
- After signed informed consent, subjects must have received the American College of Obstetricians and Gynecologists (ACOG) Patient Information Brochure on Sterilization by Laparoscopy and completed the laparoscopic tubal sterilization patient checklist.

7. Subjects who are willing to accept the risk of pregnancy occurring while relying on the Essure device or laparoscopic tubal sterilization for prevention of pregnancy;
8. Subjects who have the capacity to understand the informed consent, comply with the protocol requirements, and provide reliable feedback during the follow-up period;
9. Subjects who agree to participate in the scheduled study visits;
10. Subjects who are willing to allow data to be shared with the sponsor and with regulatory bodies.

6.2 Exclusion criteria

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 10, Modification 11).

1. Subjects who are post-menopausal;
2. Subjects suspected of being or who are confirmed to be pregnant;
3. Subjects post-partum or having undergone pregnancy termination ≤ 6 weeks prior to scheduled procedure (Note: subjects may be screened and consented for the study prior to 6 weeks post-partum / post pregnancy termination; however, PRO tools must be administered > 6 weeks post-partum / pregnancy termination and the sterilization procedure must occur > 6 weeks post-partum / pregnancy termination);
4. Subjects uncertain about ending fertility;
5. Subjects with an active upper or lower genital tract infection;
6. Subjects with gynecologic malignancy (suspected or known);

7. Subjects who have had an attempted prior sterilization procedure (either laparoscopic or hysteroscopic);
8. Subjects scheduled to undergo concomitant intrauterine or laparoscopic procedures at the time of insert placement (intrauterine device removal/placement is not considered a concomitant procedure) or laparoscopic sterilization;
9. Subjects with unexplained vaginal bleeding;
10. Any diseases or conditions that might interfere with the conduct of the study or the interpretation of the results (subjects with pre-existing conditions such as pelvic pain, autoimmune disease, or menorrhagia may be included at the discretion of the principal investigator);
11. Subjects who are direct employees or immediate family members of the Sponsor company or site investigators.

For the Essure group only:

12. Subjects who can have only one insert placed (including contralateral proximal tubal occlusion or suspected unicornuate uterus);
13. Subjects who have a known abnormal uterine cavity that makes visualization of the tubal ostia impossible and / or abnormal tubal anatomy or previous tubal ligation (including failed ligation);
14. Subjects who have had total or partial salpingectomies;
15. Subjects who are currently taking corticosteroids or immunosuppressive therapy;
16. Subjects with a known allergy to all contrast media available for use in HSG.

6.3 Justification of selection criteria

This is a post-marketing prospective observational cohort study and, therefore, should follow the current standards of care for both hysteroscopic and laparoscopic tubal sterilization procedures in routine practice.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Section modified by Amendment 1 (Section 16.1), Amendment 2 (Modification 12), and Amendment 4 (Modification 3).

Withdrawal criteria

Subjects *must* be withdrawn from the study if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

Subjects *may* be withdrawn from the study if the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below.

Screening failure

A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure."

Re-screening

For subjects considered screening failures, re-screening to enable the subject's participation at a later time point is allowed once at the discretion of the investigator, provided the subject is eligible at the time of re-screening.

In any case, the investigator has to ensure that the re-screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject will be required to re-sign the ICF, even if it was not changed after the subject's previous screening. Subjects who re-screen will not be required to repeat screening laboratory assessments if the original screening laboratory assessments were collected within 3 months of the new proposed procedure date.

Dropout

A subject who is eligible for study participation and who has a procedure visit date recorded in the electronic case report form (eCRF) (i.e., the subject shows up for the procedure visit) will be considered to have entered the treatment phase. Any termination after this point for any reason is defined as a "dropout." Dropouts will not be allowed to re-screen.

Lost to follow-up

A subject will be considered lost to follow-up if she fails to return for 1 scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and / or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 2 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- Sites are encouraged to continue attempts to contact lost to follow-up subjects annually to determine whether they wish to resume participation in the study.
- Should the subject return to the site at a later time and wish to continue participation in the study, she will no longer be considered lost to follow-up and should complete the next visit due at that time.

General procedures

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records.

The subject may object to the generation and processing of post-withdrawal data as specified in Section 14.6.

Any subject removed (withdrawn) from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 13.

6.4.2 Replacement

Subjects will not be replaced.

6.5 Subject identification

The subject number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center

7. Device

7.1 Device used

- The FDA approved Essure System (ESS305).
- Approved medical devices used for laparoscopic tubal sterilization such as cautery devices, clips, rings, etc.

7.2 Choice of Procedure

The decision to participate in the post-marketing surveillance study must be independent of the subject’s decision to undergo a permanent sterilization procedure and of the type of sterilization procedure selected. This is a non-randomized, continuous enrollment study in which all eligible subjects who desire permanent contraception (female sterilization) via bilateral occlusion of the fallopian tubes with the approved Essure device or laparoscopic tubal sterilization procedure will be asked to enroll.

Part of the counseling process for Essure includes providing the PIB and a patient checklist. Receipt of the PIB and completion of the patient checklist will be part of the inclusion criteria for the Essure group. A similar process will be carried out after signing the informed consent

and prior to performance of the laparoscopic tubal sterilization procedure. These subjects will be provided with a copy of the ACOG brochure on laparoscopic tubal sterilization procedures. In addition, they will receive a patient checklist that is modeled on the final format of the patient checklist that is part of the labeling for Essure.

7.3 Blinding

Not applicable.

7.4 Device logistics and accountability

7.4.1 Device placement compliance

Subjects in the Essure group are required to use alternative contraception until they are told to rely on Essure for contraception (after an Essure Confirmation Test). The Essure device is intended for subjects who desire permanent contraception (female sterilization) and is not intended to be removed.

Subjects who are not told to rely on Essure, regardless of whether or not they have an insert in situ, will continue to be followed in the study for safety data.

8. Non-study therapy

8.1 Prior and concomitant therapy

Information will be collected on the method(s) of contraception each subject has used and the duration of use in the period immediately prior to participation in this study (prior to undergoing permanent sterilization). Data will also be collected on the method of alternative contraception used by Essure subjects during the period in which they are unable to rely on Essure. All concomitant medications used during the study and prior medications used up to 2 years prior to study participation will be collected and entered into the CRF.

Special attention will be given to the following:

- Each woman’s history of use of medication to treat heavy menstrual bleeding or pelvic or abdominal pain;
- Pain medication used or prescribed for the initial sterilization procedures;
- Pain medication used or prescribed for AEs of pain during study participation;
- Use of medication or other treatments to treat AEs of bleeding during study participation;
- Use of any additional contraceptive medications or methods during participation in the study;
- Use of medications to treat any suspected allergic / hypersensitivity reactions;
- Use of medications to treat any suspected immunological disorders.

8.2 Post-study therapy

After the end of this study, further treatment is not necessary since only healthy subjects will be included in the study.

9. Procedures and variables

9.1 Tabular schedule of evaluations – amended

Section modified by Amendment 1 (Section 16.1), Amendment 2 (Modification 3, Modification 4, Modification 5, Modification 13, Modification 14, Modification 16, Modification 17, Modification 20), and Amendment 3 (Modification 2).

Table 9–1 shows the schedule of evaluations for the procedures for the study. Table 9–2 shows the schedule for the PRO procedures.

Due to local regulations impacting the study center due to COVID-19, it is possible that not all planned assessments could be performed or if they had been included in the eCRF, they could not all be verified. The protocol deviations related to COVID-19 will be identified in the by-subject listings.

Table 9–1 Schedule of evaluations

Schedule of evaluations	Screening	Procedure (1st or 2nd)	Post procedure (before discharge)	1 week post procedure (contact)	3 months post procedure (± 2 wk)[a]	12 months (± 4 wk)	24 months (±4 wk)	36 months (±4 wk)	48 months (contact; ±4 wk)	60 months (end of study) (-4 wk, +1 wk)	Premature Discontinuation (Dropout)
Informed consent Inclusion / exclusion criteria Demographic data	●	●[b]									
Provide ACOG brochure and patient checklist for laparoscopic tubal sterilization	●										
Height, smoking history, alcohol, medication history	●										
General medical and surgical history (including history of chronic pain disorders) and gynecological history (including pregnancies, menstrual history, vaginal bleeding, and AUB)	●										
Personal and family history of autoimmune disease, personal history of allergies / hypersensitivities, medical or cosmetic implants, piercings, tattoos with metallic colorants, dental history including orthodonture	●										
Physical examination	●[c]	●[c]									
Height	●[d]	●[d]									
Weight, vital signs	●	●				●	●	●		●	
Whole blood sample for HLA typing[e]	●										
Whole blood sample for NiLPT	●					●					
Serum or plasma sample for nickel level and titanium level[f]	●					●				●	
Frozen serum sample[g]	●					●					
Serum sample for cytokines[g]										●	
Final check of inclusion / exclusion criteria		●									
Pelvic examination	●[c]	●									
Gynecological procedures	●	●	●	●	●	●	●	●	●	●	●
AE assessment	●	●	●	●	●	●	●	●	●	●	●
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●
Alternative contraception (type used)	●	●	●	●	●	→	→	→	→	→	●
Device events		→	→	→	→	→	→	→	→	→	●
New exposure to metals					●	●	●	●	●	●	●
PROCEDURE											
Practitioner Characteristics: experience with the Essure System / LTS, physician specialty		●									
Pregnancy test		●									
LAPAROSCOPIC TUBAL STERILIZATION PROCEDURAL CHARACTERISTICS:											
Type of procedure (cautery, salpingectomy, etc.) and anesthesia used		●									
Length of procedure, length of time in recovery		●									
Number and size of ports placed		●									

Schedule of evaluations	Screening	Procedure (1st or 2nd)	Post procedure (before discharge)	1 week post procedure (contact)	3 months post procedure (± 2 wk)[a]	12 months (± 4 wk)	24 months (±4 wk)	36 months (±4 wk)	48 months (contact; ±4 wk)	60 months (end of study) (-4 wk, +1 wk)	Premature Discontinuation (Dropout)
Concomitant procedures		●									
Assessment of ability to access tubes (easy, moderate, difficult)		●									
Assessment of procedural difficulty		●									
Conversion to laparotomy if needed –data associated with laparotomy		●									
Location of procedure (type of facility)		●									
ESSURE SYSTEM PROCEDURAL CHARACTERISTICS:											
Type of anesthesia, location of procedure		●									
Length of procedure and time in recovery		●									
Physician assessment of procedural difficulty		●									
Reasons for procedural difficulty or complications		●									
Number of attempts at placement		●									
Concomitant procedures		●									
Post-placement insert location, number of trailing coils		●									
Unique Device Identifier		●									
Second attempt if necessary (need to collect all data)		●									
Confirmation test modality (or reason for non-compliance)					●[h]						
Confirmation test results, repeat if necessary					●[h]						
SURGICAL PROCEDURES INCLUDING DEVICE REMOVAL:											
Procedure / method of device removal			→	→	→	→	→	→	→	→	
Complications and outcomes of surgical procedure / device removal (e.g., symptom resolution)			→	→	→	→	→	→	→	→	
Pathology and metallurgic studies			→	→	→	→	→	→	→	→	
INTRA-OPERATIVE AND POST-PROCEDURE:											
Infection, uterine or tubal perforation, device migration, device expulsion, port site hematoma / bleeding			→	→	→	→	→	→	→	→	
Pregnancy including pregnancy outcomes			→	→	→	→	→	→	→	→	●
In cases of potential hypersensitivity / allergy / autoimmune reactions[f,i] / pain AEs, whole blood and serum for laboratory testing including NiLPT, chromium LPT, serum or plasma nickel, serum titanium, HLA panel (autoimmune disease only), and inflammatory cytokines			→[j]	→	→	→	→	→	→	→	

ACOG=American College of Obstetrics and Gynecology, AE=adverse event, AUB=abnormal uterine bleeding, HLA=human leukocyte antigen, HLA-DR = HLA-antigen D Related, LTS = laparoscopic tubal sterilization, NiLPT=nickel lymphocyte proliferation test, wk=week(s).

→ To be done when needed, starting from the time point indicated.

[a] For the Essure group, the 3-month contact window is + 2 weeks, and the results of the confirmation test should be available at the time of the contact.

[b] Final check of inclusion / exclusion criteria should be conducted during the study procedure period.

[c] The physical examination only needs to be performed once, unless the subject history has changed. If not performed prior to the Screening, the physical examination should be performed within 6 weeks prior to the procedure. The results of pelvic examinations performed within the 6 weeks prior to screening can be used unless the subject history has changed.

[d] Height is only measured once, at screening (or at the procedure visit, if it was not already measured at screening).

[e] To characterize nickel hypersensitivity, an HLA panel (HLA-DR subunits B1, B3, B4, and B5) will be performed for all subjects using the baseline sample. To characterize specific autoimmune diseases in subjects with an autoimmune disease diagnosis, an HLA panel will be performed, using any remaining sample. The HLA type to be evaluated will be selected in consultation with an immunologist and / or rheumatologist and will depend on the specific autoimmune disease diagnosed. The HLA panel will be run on the index case as well as a randomly selected control group. If insufficient baseline sample exists, an additional sample may need to be drawn.

[f] Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis. Specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

[g] An inflammatory cytokines panel will be evaluated at baseline, 12 months, and 60 months. The assay will include IFN-γ, IL-10, IL-4, TGF-β, TNF-α, p40 subunit (IL-12, IL-23), p35 subunit (IL-12, IL-35), and IL-17. The assay will use frozen serum sample collected atbaseline and 12 months. A new serum sample will be drawn at 60 months for cytokine analysis. Any leftover baseline and 12-month sample will be stored frozen for future use in subjects with diagnosed autoimmune disease. The 60-month sample will not be frozen.

[h] The visit window for the 3-month contact does not apply to the confirmation test. The confirmation test should be conducted at 3 months post-procedure; however, the exact timing of this test is at the discretion of the investigator.

[i] In cases of suspected autoimmune disorder, additional lab work will be analyzed, as indicated, on previously frozen serum samples (if sufficient sample is available). Any remaining serum sample will remain frozen.

[j] Whole blood and serum or plasma for cases of hypersensitivity, autoimmune reactions, and pain AEs does not need to be taken before discharge; however, whole blood and serum or plasma sampling should occur if symptoms are indicated between discharge and the Week 1 contact.

Table 9–2 Schedule of PRO evaluations

Questionnaire	Baseline	Week 1§	Week 2§	Week 3§	Week 4§	Month 2**	Month 3‡	Month 6‡	Month 9‡	Month 12‡	Month 15‡	Month 18‡	Month 21‡	Month 24‡	Month 27‡	Month 30‡	Month 33‡	Month 36‡	Month 48	Month 60	Premature Discontinuation (Dropout)
PROMIS Scale v1.0 – Pain Intensity 3a*t	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
PROMIS Scale v1.0 – Pain Interference 8a Participant Format*t	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Aberdeen Menorrhagia Severity Scale; and two intermenstrual bleeding questions	●						●	●	●	●	●	●	●	●	●	●	●	●	●	●	
SF-36	●							●		●				●				●		●	
Fibromyalgia Survey Questionnaire	●																				
Supplemental PRO Questionnaires										●				●				●	●	●§§	
Social Media Questionnaire																				●§§	●

PRO=patient reported outcome, PROMIS=patient reported outcome measurement information system, SF-36=Short Form-36.

*All subjects are asked screening question “Did you experience pain in your pelvic area or in your lower abdomen during the past week?” Subjects that answer “Yes” complete both the PROMIS Scale v1.0 – Pain Intensity 3a and PROMIS Scale v1.0 – Pain Interference 8a Participant Format. Subjects that answer “No” do not have to complete the questionnaires.

t In the event a subject spontaneously reports an adverse event of pain, the subject will be given both the PROMIS Scale v1.0 – Pain Intensity 3a and PROMIS Scale v1.0 – Pain Interference 8a Participant Format questionnaires to complete at the time of reporting.

§ Subjects completing ePRO questionnaires will receive email or text reminders to complete questionnaires 2 days prior to the scheduled completion date. The window for completion will be -2 days / +2 days for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. Subjects completing paper questionnaires will not receive automated reminders and every effort will be made to ensure the subject completes the questionnaire within the window.

** Subjects completing ePRO questionnaires will receive email or text reminders to complete questionnaires 5 days prior to the scheduled completion date. The window for completion will be -5 days / +5 days for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. Subjects completing paper questionnaires will not receive automated reminders and every effort will be made to ensure the subject completes the questionnaire within the window.

‡Subjects completing ePRO questionnaires will receive email or text reminders to complete questionnaires 1 week prior to the scheduled completion date. The window for completion will be -1 week / +2 weeks for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. The subject and site will then receive weekly reminders and alerts at +1 week and +2 weeks. Subjects completing paper questionnaires will not receive automated reminders and every effort will be made to ensure the subject completes the questionnaire within the window.

§§ Subjects will complete Supplemental PRO Questionnaires at 12, 24, 36, 48, and 60 months. Subjects will complete a Social Media Questionnaire at 60 months (or Premature Discontinuation visit if applicable).

9.2 Visit description

9.2.1 Screening period

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 4, Modification 13, Modification 14, Modification 15).

A prospective study subject will receive both written and verbal information about the study, and will have an opportunity to ask questions and should have sufficient time to decide whether or not to participate in the study. The original signed and dated Informed Consent Form (ICF) must be retained in the investigator's study file and a copy must be provided to the subject.

All subjects for whom the ICF is completed successfully will be assigned a subject number.

Subject screening must occur within 6 weeks prior to procedure (Essure placement or tubal ligation).

The following procedures will be conducted during the Screening Visit:

- Signed and dated ICF;
- For the laparoscopic tubal group: receipt of the ACOG patient information brochure and completion of patient checklist for laparoscopic tubal sterilization;
- Demographic data collection including:
    - Smoking history;
    - Alcohol consumption;
    - Previous medication.
- Eligibility criteria;
- Physical examination (performed once, within 6 weeks prior to the procedure)
- Height;
- Weight;
- Vital signs (blood pressure [BP], heart rate [HR]);
- Pelvic examination (an examination performed within the 6 weeks prior to Screening may be used unless the subject history has changed).
- General medical and surgical history, including but not limited to:
    - History of chronic pain conditions;
    - Personal and family history of autoimmune disease;
    - History of allergies / hypersensitivities;
    - Medical or cosmetic implants or piercings, including body tattoos with metallic colorants;
    - Dental history including orthodonture.
- Gynecological medical and surgical history, including but not limited to:
    - Pregnancies;

- Gynecological procedures such as endometrial ablation, oophorectomy, any other relevant gynecological events;
- Type of contraception used in the past 6 months;
- Menstrual history;
- Vaginal bleeding and AUB;
- Medication use.

- AE assessment;
- Prior and concomitant medications;
- Baseline blood sample collection, as detailed in Section 9.6.3.1, including:
  - Baseline whole blood for the following assays:
    - Human leukocyte antigen (HLA) typing (obtained from lymphocytes);
    - Nickel lymphocyte proliferation test.
  - Baseline serum or plasma:
    - Serum or plasma will be used to obtain baseline nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.
    - Serum to be frozen. This sample will be used for an inflammatory cytokine panel (for all subjects). Remaining sample will be stored for future baseline analysis for subjects with an autoimmune disease diagnosis. Sites will be responsible for collection and preparation for storage. Further details will be provided in the lab manual to be distributed to sites.

9.2.2 Study procedure period

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 13, Modification 14, Modification 15).

The following will be conducted during the Study Procedure Visit(s):

- Final check of inclusion / exclusion criteria;
- Physical examination (if not performed at or prior to Screening):
- Height (if not measured at Screening);
- Weight (if not performed at or prior to Screening);
- Vital signs (BP, HR) (if not performed at or prior to Screening);
- Pelvic examination (if not performed at or prior to Screening);
- Any unplanned gynecological procedures such as endometrial ablation, salpingectomy, oophorectomy, or any other relevant gynecological events;

- Concomitant medications;
- AE assessment;
- Alternative contraception (type used);
- Pregnancy test within 24 hours of procedure;
- Practitioner characteristics:
    - Experience with Essure System and / or laparoscopic tubal sterilization;
    - Physician specialty.
- Baseline PRO tool measurements:
    - Screening question for lower abdominal / pelvic pain and, if positive:
        - PROMIS Scale v1.0 – Pain Intensity 3a;
        - PROMIS Scale v1.0 – Pain Interference 8a Participant Format;
    - AMSS and 2 intermenstrual bleeding questions;
    - Short form – 36 (SF-36);
    - FSQ.
- Laparoscopic tubal sterilization procedural characteristics:
    - Type of procedure (cautery, salpingectomy, etc.);
        - Use of electrocoagulation, clips rings, type of energy, if used.
    - Anesthesia used;
    - Location of procedure (type of facility);
    - Length of procedure;
    - Recovery time;
    - Number and size of ports placed;
    - Concomitant procedures, if any;
    - Physician assessment of procedural difficulty;
    - Assessment of ability to access tubes (easy, moderate, difficult);
    - Conversion to laparotomy if needed;
        - Collection of data associated with laparotomy.
- Essure System procedural characteristics:
    - Anesthesia used;
    - Location of procedure (type of facility);
    - Length of procedure;
    - Recovery time;
    - Physician assessment of procedural difficulty;
    - Reasons for procedural difficulty or complications (such as poor visualization, anatomical irregularities or tubal spasm);
    - Number of attempts at placement / number of devices used;
    - Concomitant procedures, if any;

- Post-placement insert location, number of trailing coils;
- Unique Device Identifier.

9.2.2.1 Prior to discharge

- For Essure group: Determine contraception method to be used;
- AE assessment;
- Device events (see Section 9.6.1.1 for details);
- Infection, uterine or tubal perforation, device migration, device expulsion, port site hematoma / bleeding.

9.2.2.2 Post Procedure (at any time during study)

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 4, Modification 5).

- Post-operative complications;
- Infection, uterine or tubal perforation, device migration, device expulsion;
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Surgical procedures for removal of Essure insert;
- Methods of device removal (e.g., hysterectomy, salpingectomy, hysteroscopic device removal, laparoscopic device removal);
- Complications and outcomes of device removal (e.g., symptom resolution);
- Pathology and metallurgic analysis of explanted devices and / or tissue specimens;
- Allergic / hypersensitivity reactions, development of autoimmune-like symptoms;
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
    - Serum for inflammatory cytokines panel.
- If indicated for potential autoimmune disorder:
    - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
    - Appropriate HLA panel from previously obtained baseline DNA samples

(or redraw if insufficient sample remains).

- AE assessment;
- Device events (see Section 9.6.1.1 for details);
- Concomitant medication;
- PRO assessment(s):
    - Screening question for lower abdominal / pelvic pain (at 1, 2, 3, and 4 weeks, at 2 and 3 months, and every 3 months thereafter until 36 months post-procedure), and, if positive:
        - PROMIS (3a);
        - PROMIS (8a).
    - AMSS and 2 intermenstrual bleeding questions (at 3 months post-procedure and every 3 months thereafter until 36 months);
    - SF-36 (at 6, 12, 24, and 36 months post-procedure).

9.2.2.3 Second placement and conversion to a secondary procedure

Section modified by Amendment 2 (Modification 16, Modification 22).

Failed primary procedure and conversion to a secondary procedure will be reported.

If a second placement procedure is performed, all study assessments noted in Sections 9.2.2 and 9.2.2.1 should be performed for the second placement.

- After the second placement procedure, the 1-week post-procedure contact assessments should be repeated at 1 week after the second placement procedure. If the second placement procedure is performed before the 1-week post-procedure contact, then the 1-week contact should be performed only once, at 1 week after the second placement procedure.
- If the second placement procedure occurs on or after the 3-month contact, then the 3-month post-procedure assessments should be repeated at 3 months after the second placement procedure.
- If the second placement procedure occurs before the 3-month contact, then the 3-month contact should be rescheduled to occur at 3 months after the second placement procedure only.
- All other post-procedure visits will continue to be scheduled based on the date of the first placement procedure (i.e., 12, 24, and 36 months post-procedure).
- For the PRO evaluations:
    - PROMIS 3a and 8a:
        - After the second placement procedure, PRO evaluations for Week 1, 2, 3, and 4 and Month 2 and 3 should be repeated based upon the date of the second placement procedure. For example: If the subject undergoes the first placement procedure on Day 0 and the second procedure on Day 30, the subject will complete PRO evaluations for Week 1, 2, 3, and 4 based on the first placement

procedure, and then will complete evaluations for Week 1, 2, 3, and 4 and Months 2, and 3 based on the second procedure date. For evaluations that overlap (e.g., the subject has a Month 6 evaluation based on the first placement procedure at the same time at the Month 3 evaluation based on the second placement procedure), only the evaluation based on the second placement procedure should be conducted.

- Evaluations at Month 6 through Month 36 will continue to be scheduled based on the first placement procedure date.

- AMSS – all evaluations will be based on the first placement procedure;
- SF-36 – all evaluations will be based on the first placement procedure.

9.2.2.4 One week post-procedure (contact)

Section modified by Amendment 2 (Modification 4, Modification 16).

The 1-week post-procedure contact is not required to be via telephone and can be a site visit.

- AE assessment;
- Concomitant medication;
- Device events (see Section 9.6.1.1 for details);
- Type of alternative contraception;
- Post-operative complications reported as AEs assessed:
  - Infection, uterine or tubal perforation, device migration, device expulsion;
  - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms;
  - Pregnancy including pregnancy outcomes;
  - Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution).
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
  - Whole blood samples for NiLPT and chromium LPT;
  - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
  - Serum for inflammatory cytokines panel.
- If indicated for potential autoimmune disorder:
  - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain

frozen.

- Appropriate HLA panel from previously obtained baseline DNA samples (or redraw if insufficient sample remains).

9.2.2.5 Confirmation test (Essure group)

Section modified by Amendment 2 (Modification 4, Modification 16).

- Confirmation test modality and results. The confirmation test should be performed according to the IFU. Investigators will be required to obtain images from HSG and TVU studies performed at outside facilities as these must be archived as described in Section 12.6.
- The confirmation test should be completed before performing the 3-month contact.
- Compliance with Confirmation Test for Essure: reasons for non-compliance, including factors such as health insurance coverage, age, gravidity / parity, and difficulty / length of Essure System placement procedure.

9.2.2.6 Three months post-procedure (contact; for laparoscopic group ± 2 weeks; for Essure group + 2 weeks, once confirmation test results are available)

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 4, Modification 15, Modification 16).

The 3 months post-procedure contact is not required to be via telephone and can be a site visit.

- AE assessment, including but not limited to the following AEs of interest:
  - Infection, uterine or tubal perforation, device migration, device expulsion;
  - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.
- Device events;
- Concomitant medications;
- Type of alternate contraception (if applicable);
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
  - Whole blood samples for NiLPT and chromium LPT;
  - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal

analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;

- Serum for inflammatory cytokines panel.

- If indicated for potential autoimmune disorder:
  - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
  - Appropriate HLA panel from previously obtained baseline DNA samples (or redraw if insufficient sample remains).
- PRO assessment(s):
  - Screening question for lower abdominal / pelvic pain, and, if positive:
    - PROMIS (3a);
    - PROMIS (8a).
  - AMSS and 2 intermenstrual bleeding questions.

9.2.2.7 Twelve months post-procedure (± 4 weeks)

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 3, Modification 4, Modification 13, Modification 15).

- AE assessment, including but not limited to the following AEs of interest:
  - Infection, uterine or tubal perforation, device migration, device expulsion;
  - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.
- Device events;
- Concomitant medications;
- Weight and vital signs;
- Type of alternate contraception (if applicable);
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- For all subjects, blood sample collection including:
  - Whole blood for NiLPT;
  - Serum or plasma nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should

be deferred until 96 hours following administration of gadolinium or iodine contrast media.
    - Serum to be frozen. This sample will be used for an inflammatory cytokine panel (for all subjects).
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT.
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
    - Serum for inflammatory cytokines panel.
- If indicated for potential autoimmune disorder:
    - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
    - Appropriate HLA panel from previously obtained baseline DNA samples (or redraw if insufficient sample remains).
- PRO assessment(s)
    - Screening question for lower abdominal / pelvic pain, and, if positive:
        - PROMIS (3a);
        - PROMIS (8a).
    - AMSS and 2 intermenstrual bleeding questions;
    - SF-36;
    - Completion of Supplemental PRO Questionnaires.

9.2.2.8 Twenty-four months post-procedure (± 4 weeks)

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 3, Modification 4, Modification 13).

- AE assessment, including but not limited to the following AEs of interest:
    - Infection, uterine or tubal perforation, device migration, device expulsion;
    - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.
- Device events (see Section 9.6.1.1 for details);
- Concomitant medications;
- Weight and vital signs;
- Type of alternate contraception (if applicable);

- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
    - Serum for inflammatory cytokines panel.
- If indicated for potential autoimmune disorder:
    - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
    - Appropriate HLA panel from previously obtained baseline DNA samples (or redraw if insufficient sample remains).
- PRO assessment(s):
    - Screening question for lower abdominal / pelvic pain, and, if positive:
        - PROMIS (3a);
        - PROMIS (8a).
    - AMSS and 2 intermenstrual bleeding questions;
    - SF-36;
    - Completion of Supplemental PRO Questionnaires.

9.2.2.9 Thirty-six months post-procedure (± 4 weeks)

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 3, Modification 4, Modification 13, Modification 17).

- AE assessment, including but not limited to the following AEs of interest:
    - Infection, uterine or tubal perforation, device migration, device expulsion;
    - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.
- Device events (see Section 9.6.1.1 for details);
- Concomitant medications;
- Weight and vital signs;

- Type of alternate contraception (if applicable);
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- PRO assessment(s):
    - Screening question for lower abdominal / pelvic pain, and, if positive:
        - PROMIS (3a);
        - PROMIS (8a).
    - AMSS and 2 intermenstrual bleeding questions;
    - SF-36;
    - Completion of Supplemental PRO Questionnaires;
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
    - Serum for inflammatory cytokines panel.
- If indicated for potential autoimmune disorder:
    - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
    - Appropriate HLA panel from previously obtained baseline DNA samples (or redraw if insufficient sample remains).

9.2.2.10 Forty-eight months post-procedure (contact; ± 4 weeks)

Section added by Amendment 2 (Modification 3, Modification 4, Modification 17).

The 48-month post-procedure contact is not required to be via telephone and can be a site visit.

- AE assessment, including but not limited to the following AEs of interest:
    - Infection, uterine or tubal perforation, device migration, device expulsion;
    - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.
- Device events (see Section 9.6.1.1 for details);

- Concomitant medications;
- Type of alternate contraception (if applicable);
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- PRO assessment(s):
    - Screening question for lower abdominal / pelvic pain, and, if positive:
        - PROMIS (3a);
        - PROMIS (8a).
    - AMSS and 2 intermenstrual bleeding questions;
    - Completion of Supplemental PRO Questionnaires;
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
    - Serum for inflammatory cytokines panel.
- If indicated for potential autoimmune disorder:
    - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
    - Appropriate HLA panel from previously obtained baseline samples (or redraw if insufficient sample remains).

9.2.2.11 Sixty months post-procedure (-4 wk, +1 wk) (End of Study)

Section added by Amendment 2 (Modification 3, Modification 4, Modification 17, Modification 18).

A subject for whom the 60-month visit is complete is considered a completed subject. Once completed, no additional study-related subject data will be collected. The End of Study form should be filled out at subject's 60-month visit.

- AE assessment, including but not limited to the following AEs of interest:
    - Infection, uterine or tubal perforation, device migration, device expulsion;
    - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.

- Device events (see Section 9.6.1.1 for details);
- Concomitant medications;
- Weight and vital signs;
- Type of alternate contraception (if applicable);
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media;
- If indicated for potential autoimmune disorder:
    - Testing of previously frozen serum samples for autoimmune markers (as indicated, if sufficient serum is available). Any remaining serum will remain frozen.
    - Appropriate HLA panel from previously obtained baseline samples (or redraw if insufficient sample remains).
- Serum for inflammatory cytokine panel (see Section 9.6.3.1)
- PRO assessment(s):
    - Screening question for lower abdominal / pelvic pain, and, if positive:
        - PROMIS (3a);
        - PROMIS (8a).
    - AMSS and 2 intermenstrual bleeding questions;
    - SF-36;
    - Completion of Supplemental PRO Questionnaires;
    - Completion of Social Media Questionnaire.

9.2.2.12 Premature discontinuation (Dropout)

Section added by Amendment 2 (Modification 17).

If discontinuation occurs at the time of a scheduled visit, the appropriate measures/assessments for the timepoint (where possible) will be administered. The Social Media Questionnaire will also be administered (phone contact is acceptable).

If discontinuation occurs outside of a scheduled visit, attempts should be made to collect the following evaluations where possible (either by phone or in person):

- AE assessment, including but not limited to the following AEs of interest:
  - Infection, uterine or tubal perforation, device migration, device expulsion;
  - Allergic / hypersensitivity reactions, development of autoimmune-like symptoms.
- Device events (see Section 9.6.1.1 for details);
- Concomitant medications;
- Type of alternate contraception (if applicable);
- Pregnancy including pregnancy outcomes;
- Gynecological procedures such as endometrial ablation, hysterectomy, salpingectomy, oophorectomy, operative hysteroscopy, any other relevant gynecological events, and complications and outcomes including those associated with device removal (e.g., symptom resolution);
- Any new exposure to metals (e.g., piercings, orthodontics);
- Completion of Social Media Questionnaire.

9.2.3 Patient reported outcome measurements

9.2.3.1 Patient reported outcome data capture system

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 3).

A web-based, electronic data capture system will be available to record PRO measure data in this study. The proposed system will integrate programming that tracks scheduled PRO response compliance with reminder notifications (email or text) to subjects for each scheduled administration of the questionnaires.

The system will provide for a window for completion of PRO instruments at the cross-section, sending the first message to respond to online PRO in anticipation of the ideal scheduled date, according to the windows described in Table 9–2. If the subject fails to respond, a reminder will be sent on the scheduled date encouraging the subject to complete the online questionnaires. If the respondent still fails to respond, a flagged, urgent reminder will be sent both to the subject and to the site investigator, triggering a telephone reminder to the subject to complement the emailed message. Finally, toward the end of the response window, a follow-up email or text will be provided automatically to both the subject and the site prior to closing availability of the questionnaire being implemented indicating a “last chance” for PRO completion if needed.

The system will also be programmed to generate notifications to site investigators triggered by specified subject item response and total score thresholds. For the alerts such as those related to pain and bleeding, site investigators will be required to assess potential AEs for subjects in whom potential AEs have not already been recently assessed.

For subjects who wish to complete the PRO measurements on paper, questionnaires will be mailed to the subject by the site in accordance with the completion windows noted in

Table 9–2. No automated reminders will be sent. Subjects will complete the paper questionnaires and return the questionnaires to Covance via courier. Once received, if the date on the questionnaire is within the appropriate window, the questionnaire data will be entered into the electronic data capture system by an independent data entry group.

If a potential pain event is spontaneously reported outside of a scheduled visit or scheduled PRO tool administration, the pain PRO tools (PROMIS V1.0 – Pain Intensity 3a and PROMIS Scale V1.0 – Pain Interference 8a Participant Format) will be administered off-schedule in order to characterize pain intensity and interference. If a potential bleeding AE is reported at a scheduled visit or if the subject spontaneously reports such an event to the site at some other time, the event will be evaluated per standard AE assessment. In the event of a report outside of a schedule visit or scheduled PRO administration, the Aberdeen Menorrhagia Severity Scale (AMSS) and two intermenstrual bleeding questions will not be re-administered as the recall period for these PRO tools is 3 months and these data are captured during the scheduled PRO tool administration which occurs every 3 months.

9.2.3.2 Patient reported outcome scoring

Section modified by Amendment 2 (Modification 3)

The PRO instruments used to measure key outcomes in this study are scored in the following ways:

PROMIS Scale v1.0—Pain Intensity 3a: For measurements of pain intensity informing the pain event outcome in this study, Bayer will employ individual T-Scores. The T-scores are referenced to the US population and easily derived from totaled raw scores in line with published, publically available PROMIS scoring criteria (4).

The pain intensity score, like other PROMIS instrumentation, was designed using Item Response Theory techniques and can be more precisely scored on the basis of item-level calibrations and response pattern scoring. For analysis other than screening alerts and identification of unreported events, the item-level or “theta” scores may be used as an alternative in exploratory analyses.

PROMIS Scale v1.0—Pain Interference 8a: Scoring for the Pain Interference measure is designed in line with the same criteria as those for Pain Intensity (5). A T-score threshold will be one basis for triggering clinical alerts (see below). Additional exploratory analyses may alternatively use response pattern scoring and using the θ parameter estimate as the individual score.

AMSS: The scoring for the AMSS is outlined in an article reporting the initial validation of the instrument (6). The AMSS was designed using standard Classical Test Theory techniques and all scores are based on raw score totals. Per the initial validation, 13 items are included with a possible raw score total ranging from 0 to 42 points. Individual scores are calculated as the percentage of the maximum possible attained. Clinically meaningful thresholds are discussed below.

MOS SF-36 v2: The SF-36 is a generic health-related quality of life measure that is not focused on a particular disease or condition. This assessment scores eight distinct health domains and provides psychometrically-based physical component summary and mental

component summary scores. Domains include physical function, role-physical, bodily pain, mental health, role-emotional, social functioning, vitality, and general health perceptions.

FSQ: This is a validated questionnaire based on the premise of the importance of an altered central nervous system in processing of pain and other somatic symptoms, or a "centralized pain state" (7). While initially studied in fibromyalgia, research has found that the centralized pain state plays an important role in many chronic pain cohorts, including chronic pelvic pain.

Supplemental PRO Questionnaires: The Supplemental PRO Questionnaires consist of a series of questions covering several different symptoms (depression, anxiety, nausea/vomiting, pruritus, rash, pain in extremities, fatigue, hair loss, dysgeusia, dental problems, weight change). Details about the creation of these questionnaires and information about validation, if applicable, as well as the questionnaires for these events are provided in Appendix 17.8.

9.2.3.3 Patient reported outcome measurement thresholds

Section modified by Amendment 2 (Modification 3).

This study will first employ a medically conservative and sensitive screening threshold to ensure capture of events in subjects that may not report concerns about their pain or bleeding to site investigators. The screening thresholds reflect the clinical judgment of Bayer investigators. Secondly, a more specific preliminary threshold for reporting AEs on the basis of PRO scores alone will be employed. These thresholds reflect scoring derived in instrument development and research experience with the scales.

For the Supplemental PRO Questionnaires related to mental health, a total response greater than or equal to 3 for either set of questions will prompt notification of the investigator; for the Supplemental PRO Questionnaires related to nausea/vomiting, any single response greater than or equal to 3 will prompt notification of the investigator. For the pruritus 5D itch scale, rash, pain in extremities, and fatigue scales, any response greater than or equal to 4 will prompt notification of the investigator. These thresholds were selected to ensure that subjects receive appropriate follow-up if they report medically important symptoms. There are no threshold triggers for hair loss, dysgeusia, dental care, or weight change. Upon notification about a threshold trigger on a Supplemental PRO Questionnaire, an investigator will assess the subject as he/she deems medically appropriate. If after assessment it is concluded that an AE has occurred, it must be captured on the appropriate AE eCRF. Additional information about these questionnaires is provided in Appendix 17.8.

9.2.3.4 Screening thresholds

Section modified by Amendment 1 (Section 16.1).

PROMIS Scale v1.0—Pain Intensity 3a: Any subject response of 3 or higher on Item PAINQU6, "Worst Pain," or a total T-Score above 50 (i.e., above the US population mean) of PRO response will trigger an electronic communication (via email) to the site. If the subject has not previously received medical attention and evaluation for her pain by the site investigator or staff, the investigator will arrange for a timely (as assessed by the investigator

and site expertise) investigation of the subject's pain to determine if the subject is experiencing a pain AE as defined in this protocol.

PROMIS Scale v1.0—Pain Interference 8a: Subjects reporting a rating of 4 ("Quite a bit") or higher on any item or having a T-Score above 50 on the Pain Interference short form will trigger communication about the result to site investigators. A T-score greater than 60 at any cross-section will also trigger a preprogrammed communication to the site investigator. If the subject has not previously had her pain assessed by the site investigator, these scores will signal the need to do so in a timely manner.

AMSS: The following item thresholds reported by a subject at a cross-sectional administration will serve to trigger communication to the site: Question 1 (≥ 2—"Between 8 and 10 days"), Questions 2 to 3 (*no trigger associated*), Question 4 (≥ 2—"Heavy"), Question 5 (≥ 3—"Between 7 and 10 days"), Question 7 (≥ 1—"Soiling / staining of your outer clothes / over garments"), Question 8 (≥ 1—"I could continue to work, but my work suffered"), Question 9 (≥ 1—"Yes, usually or part of one day"), Questions 10 to 11 (≥ 2—"Moderately affected by heavy periods"), Questions 12 to 13 (*no trigger associated*). Additionally, an AMSS total score greater than 40 will serve to trigger communication to the site and the site will determine if the subject requires an unscheduled visit for her complaint.

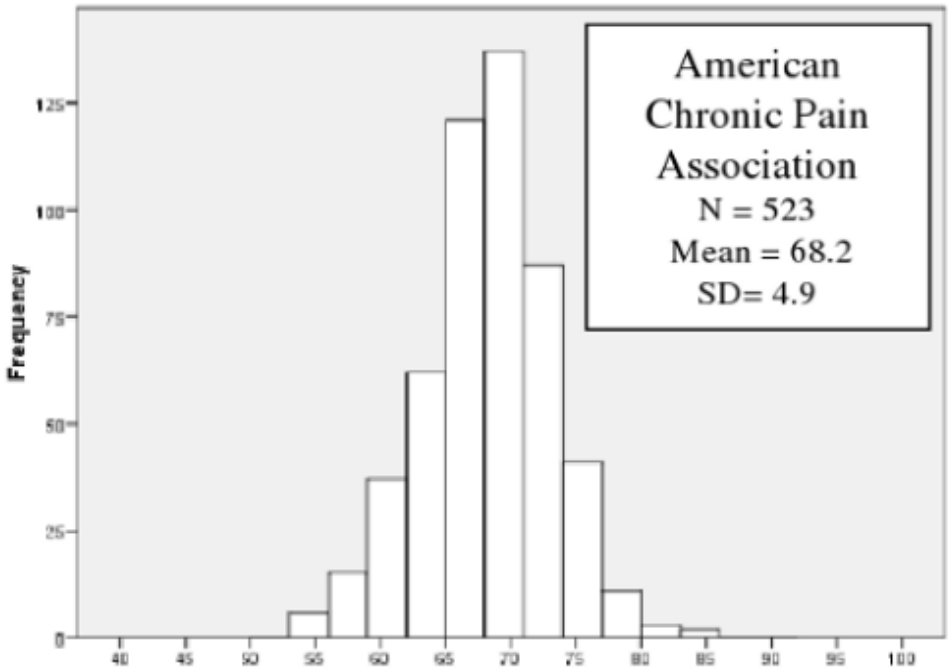
9.2.3.4.1 Self-report event thresholds

PROMIS Scale v1.0—Pain Intensity 3a: A subject T-Score greater than or 60 will be flagged, identified, and reported as a "PRO-identified pain intensity event." This threshold value reflects a score one SD above the US population mean derived in developing the instrument.

PROMIS Scale v1.0—Pain Interference 8a: A subject T-Score greater than or equal to 60 will be flagged, identified, and reported as a "PRO-identified pain interference event." This threshold value reflects a score one SD above the US population mean derived in developing the instrument. Authors showed the distribution of T-Scores in a population of subjects with chronic pain due to various conditions, providing a useful demonstration for the applicability of this cut-point (Figure 9–1).

AMSS: A subject score greater than or equal to 40 points will be flagged, identified, and reported as a "PRO-identified AUB event." The threshold is approximated from 3 "known groups" reported in the research literature, using an estimate below the lower bound of the SD of the largest trial sample where we are most confident about scoring (Table 9–3) (6).

Figure 9–1 Distribution of PROMIS Pain Interference T-Scores in a Population with Chronic Pain



PROMIS=patient reported outcome measurement information system.
Note: Adult respondents having at least one chronic pain condition for the past 3 months, taking the PROMIS web survey posted online. Participants answered the entire candidate 47-item candidate bank from which the short form proposed for use is derived, validated, and normed.

Table 9–3 "Known Group" Means and Supporting Statistics for Estimating Preliminary AMSS Self-Report Event Threshold

Sample	N	[redacted]	SD [Range]	Possible AUB Threshold
Baseline AMSS, premenopausal women with AUB later treated with hydrothermablation (9)	47	47.8	17.4	30.4
Baseline AMSS, premenopausal women with "dysfunctional uterine bleeding" assigned for hysterectomy (10)	114	57.3	15.5	41.8
Baseline AMSS, premenopausal women with "dysfunctional uterine bleeding" assigned for endometrial ablation (10)	123	59.1	15.5	43.6
Baseline AMSS, premenopausal women with "heavy uterine bleeding" related to leiomyomas, later treated with uterine artery embolization (11)	6	53	[51.1-76.7]	51.1
Baseline AMSS, premenopausal women with "heavy uterine bleeding" related to leiomyomas later treated with uterine artery occlusion (11)	8	54	[51.1-69.8]	51.1

AMSS=Aberdeen Menorrhagia Severity Scale, AUB=abnormal uterine bleeding, SD=standard deviation.

9.3 Population characteristics

9.3.1 Demographic

Section modified by Amendment 1 (Section 16.1).

The demographic information listed below should be collected for each subject:

- Age
- Ethnicity
- Race
- Employment status
- Number of years of school and professional education
- College / university degree or equivalent professional qualification (yes, no)
- Health insurance (yes, no)
- Substance use
- Alcohol consumption.

9.3.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent;
- Considered relevant for the subject's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

Section modified by Amendment 2 (Modification 19).

- Height / Weight;
- Surgical history;
- Immunologic or allergic / Hypersensitivity history;
- Reproductive and menstrual history;
- Current contraceptive method;
- Current medications;
- Current or history of eyeglasses, body piercings, permanent implants, and body tattoos with metallic colorant;
- Family history, including autoimmune disorders;
- Type of insurance subject is currently using.

9.4 Efficacy

Not applicable.

9.5 Pharmacokinetics / pharmacodynamics

Not applicable.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 4, Modification 20, Modification 21, Modification 22, Modification 23).

Definition of AE

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) device.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

Adverse device effect (ADE)

An AE related to the use of Essure or medical devices used during laparoscopic sterilization, including AEs resulting from insufficient or inadequate instructions for use, deployment, insert placement, installation or operation or any malfunction of the investigational medical device, use error, or from intentional misuse of the medical device.

In the following differentiation between medical history and AEs, the term "condition" may include abnormal physical examination findings, symptoms, diseases, laboratory, ECG, etc.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – g):

a. Results in death;

b. Is life-threatening;

   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization;

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours;
   - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2);
   - The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE

dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Requires intervention to prevent permanent impairment or damage;

e. Results in persistent or significant disability / incapacity;

Disability means a substantial disruption of a person's ability to conduct normal life's functions;

f. Is a congenital anomaly / birth defect;

g. Is another serious or important medical event as judged by the investigator.

Medical Device Reporting (MDR) event (incident)

A MDR event is defined as follows: (21 CFR 803 Medical Device reporting)

An event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or

- An event that manufacturers or importers become aware of that reasonably suggest that one of their marketed devices:
    - May have caused or contributed to a death or serious injury, or
    - Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Unanticipated ADE (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Device deficiency

Inadequacy of Essure or any other device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error, and inadequate labeling.

Device malfunction

Failure of Essure or any device to meet its performance specifications or otherwise perform as intended when used in accordance with the US IFU.

Device misuse

A misused Essure or laparoscopic tubal ligation device (used by the investigator in a manner that is contradictory to the US IFU) will not be considered a malfunction.

Device events

Examples include, but are not limited to:

- Device breakage;
- Device deficiency (eg, device malfunction, device misuse);
- Device deployment issue;
- Device kink;
- Device issue;
- Device physical property issue (eg, bent insert, bent catheter tips, catheter coiled, device too flexible, stretched coil).

Device failure

Failure of Essure or laparoscopic tubal ligation device to perform or function as intended, including any deviations from the performance specifications or intended use. For the purposes of this study, an unintended pregnancy that occurs in a subject told to rely on an Essure System for contraception is a device failure.

Important Medical Events

The Important Medical Events list (IME) is developed and published by the European Medicines Agency (http://eudravigilance.ema.europa.eu/human/textforIME.asp).

All non-serious AEs reported in this study will be periodically reviewed against the most current IME list. Events that are contained on the IME list will be specifically reviewed and the investigator will be asked to review and confirm whether or not the event meets the criteria for seriousness in his / her opinion. In addition, the following events of special interest will be closely reviewed by the sponsor's study medical expert.

AEs of special safety interest

AEs of special interest are reported in the same time frame as SAEs.

- Unintentional perforations of the uterus, cervix, or fallopian tubes by any surgical instrument or by any sterilization device;
- Expulsion of any sterilization device;
- Device dislocation (devices found in an unintended location);
- Potential new or worsening allergy / hypersensitivity symptoms (e.g., itch [pruritus], rash, hives [urticarial], facial edema, angioedema, allergy to metals, flushing, anaphylaxis), in addition to symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain, joint swelling);
- Potential new or worsening autoimmune reactions;
- Intraoperative bleeding or complications after undergoing hysteroscopic sterilization with Essure or laparoscopic tubal sterilization, including additional surgical procedures to manage the complications;
- Chronic pelvic pain. Per the definition by the American College of Obstetricians and Gynecologists, chronic pelvic pain is pain in the pelvic area that lasts for 6 months or

longer. In those subjects reporting new or worsening lower abdominal / pelvic pain at any time during the study, either spontaneously or in response to the regularly scheduled PRO tool, evaluation of the event will note if duration of the pain meets this definition.

- Pregnancy (refer to Section 9.6.2);
- Upper genital tract infection (for example, endometritis, salpingo-oophoritis, salpingitis).

Allergic / hypersensitivity reactions

For potential allergic / hypersensitivity reactions, investigators will be instructed that an evaluation should be performed in any subject presenting with urticaria, angioedema, unexplained rash, unexplained itching, flushing, or anaphylaxis. Evaluation will also be performed in subjects who present with other symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain, joint swelling). This evaluation will include a NiLPT, which is a measure of sensitized T-cell reactivity to nickel in culture; a chromium LPT, which is a measure of sensitization to chromium; serum or plasma nickel level; and serum or plasma titanium level and an inflammatory cytokines panel. For NiLPT and chromium LPT, both the continuous score as well as the positive / negative score (based on established cut-offs for negative responses) will be recorded. The results of these lab tests will be forwarded to the sponsor directly by the central lab and will be made available to the adjudication committee. In addition, any subject presenting with an AE of pelvic / lower abdominal pain and any subject presenting with symptoms she believes are due to a hypersensitivity or allergic reaction will also be evaluated, including a NiLPT, chromium LPT, serum or plasma nickel level, and serum or plasma titanium level and an inflammatory cytokines panel. If removal of a device or any other surgery is performed, pathological evaluation and metallurgic studies (if applicable) will be included. After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not a hypersensitivity / allergic reaction has occurred, all information will be forwarded to the adjudication committee in a blinded fashion. In cases of pathological evidence, blinding may not be possible. Final determination of whether or not a hypersensitivity / allergic event has occurred will be based on the determination of this committee. Once adjudicated events are available, the following comparisons will be possible:

- Pathological findings (if sufficient specimens are obtained) in subjects with Essure and adjudicated hypersensitivity reactions can be compared to pathological findings in subjects with Essure without hypersensitivity reactions as well as to pathological findings in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- Levels of inflammatory markers and HLA type in subjects with Essure and adjudicated hypersensitivity reactions can be compared to corresponding findings in subjects with Essure without hypersensitivity reactions as well as to laboratory results in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions). Serum cytokine values will be classified as below the normal range, within the normal range, or above the normal range, as appropriate. These values will be used to provide descriptive summaries of change of categories between baseline and

Year 1 and between baseline and Year 5. For these analyses the safety population will be used to present data by treatment groups and by symptomatic/asymptomatic subjects. Secondary analyses can also be performed in subjects who report positively to events on the Supplementary PRO tools (e.g. fatigue, headache) versus those who do not. These comparisons will not rely on device removal.

- Serum or plasma nickel and titanium levels in subjects with Essure and adjudicated hypersensitivity reactions can be compared to serum or plasma nickel and titanium levels in subjects with Essure without hypersensitivity reactions as well as to serum or plasma nickel and titanium levels in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions). Secondary analyses can also be performed in subjects who report positively to events on the Supplementary PRO tools (e.g. fatigue, headache) versus those who do not. These comparisons will not rely on device removal.
- NiLPT and chromium LPT results (both the continuous measurement as well as the positive / negative assessment) in subjects with Essure and adjudicated hypersensitivity reactions can be compared to NiLPT and chromium LPT results in subjects with Essure without hypersensitivity reactions as well as to NiLPT and chromium LPT results in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions). Secondary analyses can also be performed in subjects who report positively to events on the Supplementary PRO tools (e.g. fatigue, headache) versus those who do not. These comparisons will not rely on device removal.
- An individual subject's serum or plasma nickel and titanium levels and NiLPT can be compared to baseline levels in order to assess any change. In addition, in cases of removal, subsequent post-removal levels can also be compared.

Autoimmune diseases

For autoimmune disorders, any subject presenting with symptoms indicating a potential autoimmune disorder should be evaluated per standard medical practice. All effort will be made to obtain records of any diagnostic workup conducted by outside physicians. A NiLPT, chromium LPT, serum or plasma nickel level, and serum or plasma titanium level and serum inflammatory cytokines will also be drawn by the study site. An appropriate human leukocyte antigen (HLA) panel will be run on previously obtained baseline samples if sufficient sample exists. An additional whole blood sample will be drawn for HLA if needed. Frozen serum will be used in cases of suspected autoimmune disorders (for both the index case as well as a randomly selected control group). If sufficient frozen sample exists, it will be adequate to be used for tests used to diagnose autoimmune conditions (e.g., anti-citrullinated protein antibody in cases of suspected rheumatoid arthritis, thyroid peroxidase antibody for suspected autoimmune thyroid diseases, and antinuclear antibody in cases of suspected lupus erythematosus). Based on epidemiology, the number of subjects who develop an autoimmune disease during the study is expected to be very small. If removal of a device or any other surgery is performed, pathological evaluation and metallurgic studies (if applicable) will be included.

After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not an autoimmune disorder exists, all information will be forwarded to the adjudication committee in a blinded fashion. In cases of pathological evidence, blinding may not be possible. Final determination of whether or not an autoimmune disorder has occurred will be based on the determination of this committee. Once adjudicated events are available, the following comparisons will be possible:

- Pathological findings (if sufficient specimens are obtained) in subjects with Essure and adjudicated autoimmune disorders can be compared to pathological findings in subjects with Essure without autoimmune disorders as well as to pathological findings in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders).
- Levels of inflammatory markers and HLA type in subjects with Essure and adjudicated autoimmune disorders can be compared to these findings in subjects with Essure without autoimmune disorders as well as to laboratory results in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders). Secondary analyses can also be performed in subjects who report positively to events on the Supplementary PRO tools (e.g. fatigue, headache) versus those who do not. These comparisons will not rely on device removal.
- Serum or plasma nickel and titanium levels in subjects with Essure and adjudicated autoimmune disorders can be compared to serum or plasma nickel and titanium levels in subjects with Essure without autoimmune disorders as well as to serum or plasma nickel and titanium levels in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders). Secondary analyses can also be performed in subjects who report positively to events on the Supplementary PRO tools (e.g. fatigue, headache) versus those who do not. These comparisons will not rely on device removal.
- NiLPT and chromium LPT results (both the continuous measurement as well as the positive / negative assessment) in subjects with Essure and adjudicated autoimmune disorders can be compared to NiLPT and chromium LPT results in subjects with Essure without autoimmune disorders as well as to NiLPT and chromium LPT results in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders). Secondary analyses can also be performed in subjects who report positively to events on the Supplementary PRO tools (e.g. fatigue, headache) versus those who do not. These comparisons will not rely on device removal.
- An individual subject's serum or plasma nickel and titanium levels and NiLPT can be compared to baseline levels in order to assess any change. In addition, in cases of removal, subsequent post-removal levels can also be compared.

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild;
- Moderate;
- Severe.

9.6.1.2.3 Action taken with study device

Not applicable.

9.6.1.2.4 Treatment(s) of adverse events

Section modified by Amendment 1 (Section 16.1).

- None;
- Remedial drug therapy;
- Additional surgical procedure;
- Change in surgical procedure;
- Other.

9.6.1.2.5 Outcome

- Recovered / resolved;
- Recovering / resolving;
- Recovered / resolved with sequelae;
- Not recovered / not resolved;
- Fatal;
- Unknown.

9.6.1.2.6 Causal relationship

Section modified by Amendment 1 (Section 16.1).

The assessment of the causal relationship between an AE and the sterilization procedure is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

Causality should be assessed separately for each procedure as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study procedures (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study procedure.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study procedure or device in question.

Possible answers are “yes” or “no”.

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g., mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study procedure or device.

Important factors to be considered in assessing the relationship of the AE to study procedure include:

- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the indication being treated and any other disease the subject may have.
- Concomitant medication or treatment: Any drugs the subject is taking or the procedure the subject receives should be examined to determine whether any of them might have caused the event in question.
- Exposure to physical and / or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The assessment is not possible.

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective CRF pages all AEs occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

“Death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of underlying AE(s).

For all SAEs, the sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study procedure.

Investigator responsibility

Investigators must record and document all AEs on the AE CRF.

- If the AE is an SAE or MDR (including device or procedure-related AEs / effects and deaths), it must be reported immediately (within 24 hours) to the relevant institutional review board (IRB) / Ethics Committee (per local requirements) and to the sponsor by the investigator and recorded on the CRF. The investigator will send to the sponsor,

all appropriate paper work (discharge summaries, office notes, etc.) that might be pertinent. Reports relating to the subjects' subsequent medical course must be submitted to the sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

- If the AE is also a UADE, it must be reported to the sponsor and the reviewing IRB / Ethics Committee (per local requirements) as soon as possible but no longer than 3 working days after becoming aware of the event. The investigator will send to the sponsor all appropriate paperwork (discharge summaries, office notes, etc.) that might be pertinent. Reports related to the subject's subsequent medical course must be submitted to the sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Sponsor responsibility

- The Sponsor will be responsible for categorizing SAEs / serious adverse device effect (SADEs) in terms of expectedness, seriousness, and causal relationship to the Essure device when all necessary data are available.

MDR / SADE Reporting – Because this study involves using a commercially approved device in accordance with labeling, the device is subject to MDR regulations, 21 CFR 803 / MEDDEV 2.7.3. The sponsor will review all AEs and follow the guidelines of the MDR regulations for those events that can be attributed solely to the insert placement procedure and device wearing and report based on local regulations.

9.6.1.4 Reporting of serious adverse events

Section modified by Amendment 2 (Modification 24).

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs and SADEs / incidents. This information, including all relevant contact details, is summarized in the investigator site file (ISF). This information will be updated as needed.

All SAEs / MDRs occurring during the observation period defined in Section 9 must immediately (within 24 hours of the investigator's awareness) be reported to the sponsor's designated recipient. A SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the sponsor's designated recipient.

Each SAE / MDR must be followed up until resolution or stabilization by submission of updated reports to the designated recipient. Any SAE / MDR occurring after the protocol-defined observation period will be processed by the sponsor's designated recipient according to all applicable regulations.

In addition, device failures, malfunctions or MDRs must be reported to sponsor's designated recipient within 24 hours via fax or email. In case of a device failure, malfunction, or SADE related to the device, the device must be returned to the sponsor's product surveillance department for analysis.

Ectopic pregnancies and spontaneous abortions are always to be considered SAEs and reported as such to the sponsor's designated recipient within 24 hours.

Notification of the independent ethics committee (IECs) / IRBs

Notification of the IECs / IRBs about all relevant events (e.g., SAEs / MDRs, UADEs, device failures, device malfunctions) in the study will be performed by the sponsor and / or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs / MDRs, UADEs, device failures, device malfunctions) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g., SAEs / MDRs, ADEs, UADEs, device failures, device malfunctions) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this medical device study, the applicable reference document is the most current version of the US IFU.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Device removal and surgical pathology

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 5).

Each time a surgical procedure is performed (Essure or laparoscopic tubal ligation), additional information will be collected about the circumstances surrounding the surgery (e.g., date of placement, reason for removal, procedure details, any energy sources used, vasoconstrictive agent used, imaging to assist with confirming the location of the insert, and the location and status of the device removed). Subjects who have had surgical intervention or their device removed will continue to be followed for the collection of safety and laboratory data.

Prior to any planned surgical removal of an Essure insert, salpingectomy, or hysterectomy, the investigator must contact the sponsor in order to arrange for handling of the pathology specimen. This is important as improper handling of specimens may preclude the performance of metallurgic analyses.

Whenever possible, and if clinically and surgically appropriate, if the decision is to remove the fallopian tube, this should be done with the Essure insert or sterilization device, if

applicable (e.g., Falope ring, Filshie clip) in situ. In the case of Essure, this can be accomplished by making a circumferential incision around the proximal tube near the cornua, then pulling the proximal most portion of the insert from the cornua (while the remainder of the insert remains in the tube that is removed), or with a cornual resection. Physician judgment as to the appropriate procedure for the subject will take precedence over obtaining a pathology specimen. If a hysterectomy is clinically and surgically appropriate, it should be performed with the tubes attached to the uterus, if possible.

In the Essure group, ideal specimens will have the Essure insert in situ as this will provide the most complete information; however, all tubes, regardless of presence of the insert, should be submitted for examination. In addition, all inserts, regardless of whether they are in situ or previously removed, should be submitted. Processing for tubes with and without inserts in situ will need to be slightly different.

In the laparoscopic sterilization group, ideal specimens will be fallopian tubes with sterilization devices in situ, if applicable (e.g., Falope ring, Filshie clip); however, all tubes should be submitted regardless of presence of a previously applied sterilization device.

After removal of the specimen, the pathologist should provide a gross description of the specimen and obtain photographs of both the anterior and posterior aspects of the specimen. If the specimen consists of the fallopian tube only, the proximal portion of the tube, the portion of the tube containing the insert / device / or cauterized section, together with a 2 cm section immediately distal to the insert / device or cauterized section, should be removed (as one specimen) and placed in formalin. If the specimen also has the uterine cornua attached to the tube, the cornua should also be included as part of the specimen. If the tube is attached to the uterus, the cornua should be removed from the uterus along with the portions of the tube noted above. In the case of Essure, if the insert has already been removed from the tube, the surgeon should tie a single non-metallic suture around the tube indicating the proximal location of where the insert was located in the tube and a double non-metallic suture around the tube indicating the distal location of where the insert was located in the tube (if applicable / possible). This is necessary for subsequent metallurgic testing in the event the insert is missing from the tube. The specimen will then be placed in formalin and sent to a central gynecologic pathology laboratory for processing. Any explanted Essure inserts should also be placed in formalin and sent.

Once at the central processing location, in the case of Essure, the specimen will be divided into 3 sections: the first section will be kept within the gynecologic pathology laboratory for additional processing, the second section will be sent to a specialized laboratory for methacrylate embedding, and a third section will be sent to a specialized laboratory for metallurgic testing. If the insert has been removed from the tube, an x-ray of the tube will be necessary to ensure no fragment of insert remains in the tube. If there are no metallic components in the tube, methacrylate embedding will be unnecessary.

For the basic gynecology histology section, in a portion of the tube containing the Essure insert, the tissue will be carefully micro-dissected free from the insert and then embedded in paraffin and sectioned prior to histologic examination. Sectioning will include areas of the tube containing the insert as well as a section of the tube at least 1 to 1.5 cm distal to the insert as an internal control. A second portion of the tube containing the Essure insert will be

sent to a specialized pathology laboratory for methacrylate embedding and sectioning. This will allow for subsequent histologic examination of the specimen with the insert in situ. Sections will be made both of the tube with the insert in situ as well as a portion of the tube distal to the insert for comparison.

A standardized scoring protocol based on ISO 10-993, part 6 criteria will be used to assess inflammatory response. The H&E, Movat's pentachrome, and CD68 immunostaining will be performed on both methacrylate and paraffin embedded specimens. If on stained slides there appears to be a moderate or extensive inflammatory reaction, immunohistochemical staining for additional markers will be performed. These will be performed on both methacrylate and paraffin embedded specimens; however, some stains may not be possible on methacrylate embedded specimens.

Due to the number of expected pathological specimens, evaluation will be qualitative. Comparisons can be made between the area of the tube containing the insert versus the area of the tube distal to the insert. Any additional qualitative comparisons will be entirely dependent on availability of specimens in each of the potential comparator groups. If sufficient samples exist, it may be possible to compare histology findings in women who have removals due to pain and / or other AEs to women who have their tubes removed for other unrelated issues. In addition, if available, tubal histology in the Essure group can be qualitatively compared to tubal histology in the laparoscopic sterilization group.

The third portion of the tube will be sent to a specialized laboratory for metallurgic testing to determine nickel and titanium content / presence in the adjacent tissue both in the tissue immediately adjacent to the insert as well as in tissue distal to the insert. This will be accomplished through inductively coupled plasma mass spectrometry (ICPMS). Information derived from ICPMS will be correlated with blood levels of nickel and titanium taken from the subject at various times both pre- and post-implant removal. Tissue nickel and titanium concentrations will be compared in the section of tube containing the insert versus the section of tube distal to the insert. Additional qualitative comparisons will be entirely dependent on the availability of specimens. If appropriate specimens are available, tissue nickel and titanium concentrations in women with complaint of pain or hypersensitivity / allergic reactions can be compared to tissue nickel and titanium concentrations in women who have their tubes removed for other (non-AE associated) reasons. In the case of tubes where the insert has been previously removed, surgeons will be asked to indicate the location of the insert by tying non-metallic suture at each end, as described above. In addition to assessing metal concentrations in tissue, metallurgic examination will also look at Essure inserts. The ideal insert is one that is micro-dissected in the laboratory as this will have the least deformation / artifact. The inserts will be examined to look for pitting and loss of material. In cases of inserts already removed from the tube, examination will be restricted to areas not exposed to deformation.

In the case of laparoscopic tubal sterilization, specimens will be embedded in paraffin prior to sectioning for histology and stained and examined in the same way as noted above for the Essure group. If a device (e.g., Falope ring, Filshie clip) is attached to the tube, it will be carefully removed prior to processing. There will be no need for methacrylate embedding or metallurgic testing in the case of laparoscopic sterilization.

In all cases, histologic evaluation will be performed by 2 pathologists (3 in the event of disagreement between the initial 2 pathologists) blinded as to subject symptoms and will be evaluated using a standardized grading system. The final score for a specimen will be the average of the three readings, rounded to nearest whole number. Specifically, the pathologists will not know if the sample belongs to a subject reporting hypersensitivity / immunologic symptoms or to a subject undergoing surgical removal for a reason unrelated to hypersensitivity / immunologic symptoms. As noted above, if histology reveals a moderate or extensive inflammatory response, additional immunohistochemical staining will be performed as appropriate. Given the number of expected samples, no statistical comparisons will be possible and results will be presented descriptively.

If Essure insert removal is conducted at a site that is not participating in this study, the investigator should make all efforts possible to obtain as much information as possible regarding insert removal including surgical pathology. The subject will be asked to sign a release to have all relevant documents transferred to the study site and Adjudication Committee and the site personnel will submit relevant, available data..

9.6.2 Pregnancies

Section modified due to Amendment 2 (Modification 21).

If a subject becomes pregnant (i.e., an unintended pregnancy) at any time following the visit in which she is told to rely on Essure, the pregnancy will be counted as a device failure. Following the resolution of the pregnancy, subject will be asked to undergo an HSG. Subject will also be counseled that she can no longer rely on Essure for contraception.

If a subject becomes pregnant (i.e., an unintended pregnancy) at any time following her sterilization procedure, the pregnancy will be counted as a sterilization failure. The pregnancy will be followed to resolution. The subject will then be managed as per local standard of care, at the discretion of the treating physician.

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study (i.e., after signing of the informed consent). The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. For a study subject, the outcome of the pregnancy should be followed up carefully and the outcome of the pregnancy for both the mother and the child are to be reported using the Pregnancy Form provided.

9.6.3 Further safety

9.6.3.1 Laboratory evaluations

Section modified by Amendment 2 (Modification 4).

Several different laboratory assays will be conducted on whole blood or serum/plasma samples throughout the study. A summary of the samples to be collected and assays to be performed include:

- HLA typing (obtained from lymphocytes)
  Certain HLA types are associated with specific autoimmune diseases. In addition, preliminary research indicates that some HLA types may be related to an increased

risk of nickel hypersensitivity reactions. A whole blood sample will be collected at baseline and will be used to characterize nickel hypersensitivity and to evaluate HLA in subjects diagnosed with an autoimmune disease.

  - To characterize nickel hypersensitivity, an HLA panel, including HLA-antigen D Related (HLA-DR) subunits B1, B3, B4, and B5 (which are related to potential reactions to nickel) will be run on the baseline sample for all subjects. Any remaining specimen will be stored frozen for future additional HLA typing, only for subjects diagnosed with an autoimmune disease.
  - To characterize specific autoimmune diseases in subjects with an autoimmune disease diagnosis, the HLA type specific to that autoimmune disease will be run. The HLA type to be evaluated will be selected in consultation with an immunologist and / or rheumatologist and will depend on the specific autoimmune disease diagnosed. For each HLA type that is evaluated, a randomly selected control group of subjects without the specific autoimmune disease will be identified, and the HLA type run in the index case will be run as a control sample. The size of this control group will depend on the frequency of the specific HLA type in the population.

- Nickel lymphocyte proliferation test (NiLPT)
  The NiLPT is a measure of sensitization to nickel. A whole blood sample will be collected and sent by the site to a single specialty laboratory, and must be received in the laboratory within 24 hours. This test will be drawn and run at baseline and at 12 months in all subjects. In addition, if at any point in the study a subject develops symptoms that could be due to hypersensitivity or autoimmune process, including pelvic pain, an unscheduled NiLPT sample will be drawn. The continuous score and the positive / negative score (based on a cutoff for negative response of Stimulation Index (SI) < 5.7) will be recorded.
- Chromium lymphocyte proliferation test (LPT)
  The LPT is a measure of sensitization to chromium. This test requires whole blood and must be received in the laboratory within 24 hours. Due to the very low positivity rate for this test, it will only be drawn if a subject develops symptoms that could be due to hypersensitivity or autoimmune process, including pelvic pain.
- Serum nickel level
  This test will be drawn and run at baseline, at 12 months, and at 60 months in all subjects. In addition, if at any point in the study a subject develops symptoms that could be due to hypersensitivity or autoimmune process, including pelvic pain, an unscheduled serum nickel level will be re-drawn. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.
- Serum titanium level
  This test will be drawn and run at baseline and at 1 year in all subjects. In addition, if at any point in the study a subject develops symptoms that could be due to hypersensitivity or autoimmune process, including pelvic pain; an unscheduled serum titanium level will be re-drawn. Gadolinium and iodine-based contrast material are

known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

- Serum
  Serum will be collected at baseline and at 1 year on all subjects. This serum will be frozen. For all subjects, this serum will be used to run a baseline and one-year inflammatory cytokine panel (to include IFN- γ, IL-10, IL-4, TGF- β, TNF-α , p40 subunit (IL-12, IL-23), p35 subunit (IL-12, IL35), and IL-17). Any remaining serum will be frozen. It will be used if a subject develops an autoimmune disease. In these cases, the serum can be used to obtain baseline levels for the particular diagnosed autoimmune condition (e.g. a Rheumatoid Factor if subject is diagnosed with rheumatoid arthritis; thyroid peroxidase antibody if subject is diagnosed with autoimmune thyroid disease. Given the number of potential diseases, it is not possible to establish a baseline for every potential autoimmune disease). If any serum remains after running these tests, it will remain frozen.

  At 60 months, additional serum will be drawn. This will be sent for a repeat inflammatory cytokine panel.

9.6.3.2 Physical examination

Section modified by Amendment 1 (Section 16.1) and Amendment 2 (Modification 14).

A detailed physical examination including height, weight, vital signs (BP, HR), smoking history, alcohol consumption, previous medications, and a pelvic examination will be conducted. Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.6.1.1).

9.7 Appropriateness of procedures / measurements

Section modified by Amendment 1 (Section 16.1).

All safety variables and validated PRO instruments, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant. As described in Table 9–2, subjects completing PRO assessments electronically will receive alerts to complete the scheduled questionnaires prior to the scheduled completion date for each questionnaire. If the questionnaire is not completed by the scheduled date, the subject will receive a second reminder and an alert will be sent to the site. The subject and site will then receive up to 2 additional reminders if the questionnaires are not completed. Subjects completing PRO assessment on paper will not receive alerts.

10. Statistical methods and determination of sample size

10.1 General considerations

All issues concerning subject validity, data consistency checks, permissible data modifications, as well as coding of medical terms and concomitant medication, will be

described in detail in the Data Management Plan. All statistical issues including calculated variables are detailed in the Statistical Analysis Plan (SAP).

The study is observational and does not allow a randomized decision for treatment allocation. Therefore, the allocation of procedure to a subject is driven by preferences, medical decision, medical circumstances, and other information the treating physician requires for the selection of the best option. Allocation bias must therefore be assumed, with consequent potential for confounding. Under such conditions, formal statistical hypotheses of no treatment effect would include an unknown size of bias, as the size of the confounding remains unknown a priori. In particular, the confounding may nullify differences between groups, due to the size of the confounding that cannot be attenuated through analytical methods, but also may inflate differences.

Attempts can be made by analytical procedures to adjust for measured confounding, but still, in this setting, unmeasured confounding cannot be quantified. Several scenarios of analyses are therefore planned to be employed, addressing several of these sources of confounding

It is expected that, due to the recent media attention given to the Essure procedure, there will be significant confounding between the 2 treatment groups leading to channeling bias that will be insurmountable with any analytical method.

The analysis must therefore be considered exploratory in nature.

10.2 Analysis sets

The goal of this study is to assess the various aspects of safety of the procedures studied. Assuming there is adequate overlap in the propensity score (PS) distribution to enable comparisons in the PS confounder-adjusted population between treatment groups, the Adjusted Full Analysis Set will be the primary analysis set.

Safety analysis set

A subject will be included in the safety analysis set if the subject came to the sterilization procedure visit.

Full analysis set

A subject will be included in the Full Analysis Set if she has selected a treatment and, at the time of the procedure, an Essure device has been introduced into the hysteroscope or has an incision / puncture for laparoscopy.

Adjusted Full Analysis Set

Same as the Full Analysis Set, but based on PS confounder-adjusted population. For additional details, see the SAP.

Reliance Set

A subject will be included in the Reliance Set if she has been told to rely on the sterilization method selected at the index event.

Adjusted Reliance Set

Among the PS confounder-adjusted population, a subject will be included if both she and her matched partner are included in the Reliance Set.

10.3 Endpoints and planned statistical analyses

Section modified by Amendment 2 (Modification 3, Modification 25).

The following endpoints will be summarized as part of this study:

- The proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after insertion of Essure System compared to the proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after laparoscopic tubal sterilization. In both groups, AEs due to other apparent etiologies will be identified and excluded.
- The proportion of subjects reporting AEs of AUB after insertion of Essure System compared to the proportion of subjects reporting AEs of AUB after laparoscopic tubal sterilization. In both groups, AEs due to other apparent etiologies will be identified and excluded.
- Proportion of subjects with allergic / hypersensitivity reactions possibly attributed to wearing of Essure devices and allergic / hypersensitivity reactions in women undergoing laparoscopic tubal sterilization.
- Proportion of subjects with newly diagnosed autoimmune disorders in subjects wearing Essure inserts compared to subjects undergoing laparoscopic tubal sterilization.
- Proportion of subjects undergoing invasive gynecologic surgery after Essure placement (excluding second placement attempts), including Essure insert removal compared to the proportion of subjects undergoing gynecologic surgery after laparoscopic tubal sterilization.
- Patient reported outcome measures:
    - MOS SF-36 (Version 2);
    - PROMIS Scale V1.0—Pain Intensity 3a;
    - PROMIS Scale V1.0—Pain Interference 8a Participant Format;
    - AMSS and two intermenstrual bleeding questions used to characterize bleeding in subjects undergoing Essure placement and laparoscopic tubal sterilization;
    - FSQ: to investigate if scores on this instrument (continuous and categorical) correlate with chronic pelvic pain over the course of the study;
    - Supplemental PRO Questionnaires – a series of PRO tools used to actively solicit information on AEs commonly found in MDR reports with Essure;
    - Social Media Questionnaire – to elicit information about sources of influence on medical decisions, in particular, use of social media.

- Rates of AEs in subjects undergoing Essure placement and laparoscopic tubal sterilization;
- Characteristics of physicians performing the procedures;
- Characteristics of subjects undergoing Essure Confirmation Test compared to subjects who do not comply with the requirement for Essure confirmation testing.

Statistical analyses will be explorative and descriptive in nature and no confirmatory hypothesis tests are intended to be performed; p-values will be interpreted as a metric for uncertainty. Therefore, no adjustment for multiplicity will be necessary.

All endpoints and variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, lower and upper quartiles, median, and maximum will be calculated for continuous data. Frequency tables will be generated for categorical data. They will include the number of missing values as additional categories. Relative frequencies will be shown as percentages which will be calculated as a proportion including the category of missing values. Incidence rates and proportions will be used to summarize main endpoints and other variables. For time-to-event endpoints, hazard ratios derived from a Cox regression model, and Kaplan-Meier estimates will be provided.

If not specified otherwise, the analyses are presented in a way that events will be assigned to the treatment which was given initially at the index event.

The main analyses will be performed on a PS confounder-adjusted population of the Full Analysis Set in order to adjust for measured confounding as well as on the Full Analysis Set population. After all subjects have been enrolled, an outcome-blinded independent party, which only has access to the treatment variable and baseline variables, will perform the PS matching. All baseline variables will be considered for inclusion into the model; however, the following variables have shown previous evidence to likely be included in the model: age, race, BMI, US geographical region, insurance, hormonal contraception use at baseline, pre-existing pain disorders (pelvic pain, low back pain, chronic headache, fibromyalgia), disorders associated with hysterectomy (fibroids, ovarian pathology, endometriosis, prolapse, hyperplasia), gastrointestinal disorders (e.g., irritable bowel syndrome), pre-existing autoimmune disease, pre-existing diabetes, and pre-existing hypertension.

For subjects with a second placement procedure, any PROMIS 3a and 8a PRO data collected after baseline and up to and including Month 3 will be repeated based on the timing of the second placement procedure (See Section 9.2.2.3 for additional details). For summaries by time point (e.g., Week 1), only the final evaluation will be included in the analyses. For time-to-event endpoints or proportion of subjects meeting a given criterion, all collected data will be used.

10.4 Determination of sample size

Section modified by Amendment 2 (Modification 6).

Overall enrollment will be dependent on availability of Essure.

Recruitment in the Essure arm is planned to continue as long as Essure is being implanted.

Enrollment in the laparoscopic tubal sterilization arm will be ceased once its enrollment reaches approximately 2:1 ratio laparoscopic tubal sterilization : Essure (anticipated).

10.5 Planned interim analyses - amended

Section added by Amendment 2 (Modification 26) and Amendment 3 (Modification 1). Section modified by Amendment 4 (Modification 2 and Modification 4)

Three interim analyses will be performed. The first will be initiated at the end of enrollment, the second will be initiated after all subjects complete 1 year of follow-up, and the third will be initiated at the point all subjects complete 3 years of follow-up. The purpose of these analyses is to formally review study data, at the request of FDA.

The following will be summarized as part of these interim analyses:

- Demographic information listed in Section 9.3.1.
- The proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after insertion of Essure System compared to the proportion of subjects reporting AEs of chronic lower abdominal and / or pelvic pain after laparoscopic tubal sterilization.
- The proportion of subjects reporting AEs of AUB after insertion of Essure System compared to the proportion of subjects reporting AEs of AUB after laparoscopic tubal sterilization.
- Proportion of subjects with allergic / hypersensitivity reactions possibly attributed to wearing of Essure devices and allergic / hypersensitivity reactions in women undergoing laparoscopic tubal sterilization.
- Proportion of subjects with newly diagnosed autoimmune disorders in subjects wearing Essure inserts compared to subjects undergoing laparoscopic tubal sterilization.
- Proportion of subjects undergoing invasive gynecologic surgery after Essure placement (excluding second placement attempts), including Essure insert removal compared to the proportion of subjects undergoing gynecologic surgery after laparoscopic tubal sterilization.
- Rates of AEs in subjects undergoing Essure placement and laparoscopic tubal sterilization.
- Device removals, and outcomes and resolutions, when associated with an AE.

The PS model will be developed, after all subjects have been enrolled, by an outcome-blinded independent party which will only have access to baseline characteristics and sterilization group. Balance of the PS baseline characteristics will be assessed at the 3-year interim analysis and end of study; if necessary, the process will be reevaluated to ensure balance of baseline characteristics throughout the study. The first interim analysis will be initiated after the PS matching process has completed. All 3 interim analyses will be performed on a PS-matched population in order to adjust for measured confounding as well as on the total population. In other words, the main analysis sets are the Adjusted Full Analysis Set (PS-matched population among subjects where a sterilization procedure of choice was

attempted) and the Full Analysis Set (sterilization procedure of choice was attempted) for the interim analyses. A Reliance Set will consider women relying on the sterilization method selected at the index event.

For all the outcomes and variables, a descriptive analysis will be performed and no statistical comparison will be made. For continuous data, N, mean, standard deviation, min, and max will be provided and for categorical data, frequency and percentages will be provided. Unless otherwise specified, the analyses will be presented in a way that events will be assigned to the treatment which was given initially at the index event.

Summaries for the interim analyses will use all data up to the data cutoff dates, which will be at the time enrollment ends, after all subjects complete 1 year of follow-up, and at the end of 3 years of follow-up. Serology data (cytokines, nickel and titanium levels, and nickel LPT results) will be summarized in the interim analysis to be performed at the end of 3 years of follow-up. The interim analysis report will also include a description of the pathologic and histologic findings of fallopian tubes, and individual dossiers provided to the Adjudication Committee in cases of potential hypersensitivity/allergy/autoimmune reactions.

Results of each interim analysis will be summarized in a separate report.

The interim analysis reports will be submitted no later than 3 months after database lock for each interim analysis data cutoff date.

11. Interim and final post market surveillance report

Section added by Amendment 2 (Modification 26). Section modified by Amendment 4 (Modification 1)

Bayer will submit an interim postmarket surveillance report every 6 months for the first 2 years of the postmarket surveillance and annually thereafter from the date of approval of the 522 postmarket surveillance study plan which was anticipated to be 04 SEP 2016.

Per FDA's final guidance document on Postmarket Surveillance issued on 16 MAY 2016 (located at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268141.pdf), after approval of the study plan, FDA may post surveillance plan parameters related to the study design and objectives on the FDA postmarket surveillance webpage (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm). Furthermore, the FDA may post the following information from interim postmarket surveillance reports in the following conditions:

- Number of study sites enrolled (to be updated after submission of each interim report);
- Number of subjects enrolled (to be updated after submission of each interim report);
- Interim summary data and / or analyses thereof when appropriate to protect the public health, e.g., when interim results raise safety concerns or may otherwise impact treatment. In the event that posting the interim results is appropriate to protect the public health, the public release of data will be coordinated between Bayer and FDA.

- Interim summary data and / or analyses thereof, to be performed at the end of 3 years of follow-up. The interim data for public release will be agreed to between Bayer and FDA.

The final report will be submitted no later than 3 months after postmarket surveillance study completion (as defined by database lock).

12. Data handling and quality assurance

12.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered / transmitted to a validated database or data system (CIE / TOSCA; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE system contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made, and the date and time it was made. This information is available both at the investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site.

Data recorded from screening failures

At minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth / age; if applicable race / ethnicity);
- Date of informed consent;
- Relevant inclusion / exclusion criteria;
- Reason for premature discontinuation;
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the eCRF in addition to the data specified above:

- All information related to the SAE such as:
    - The SAE itself;
    - Concomitant medication;
    - Medical history;
    - Other information needed for SAE complementary page.

12.2 Monitoring

In accordance with applicable regulations, Good Clinical Practice (GCP), and sponsor's / Contract Research Organization's (CRO) procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor / designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete. Supporting data may be requested (e.g., blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected;
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol);
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

12.3 Data processing

Data will be collected as described in Section 12.1. Clinical data management will be performed in accordance with applicable sponsor's / CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other

sources (e.g., interactive voice response system, laboratory, electronic PRO, adjudication committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

12.4 Missing data

The investigator should show due diligence and explore all possible options to reach a subject who fails to return to a visit. The site must document all attempts to try to contact the subject in the medical records / source documents.

The following measure will be implemented to minimize the amount of missing data.

- If the subject does not attend the visits in person, the investigator should make every effort to contact the subject via phone.

12.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor / inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

12.6 Archiving

Essential documents, including images from TVU and HSG confirmation tests, shall be archived safely and securely by the investigator in such a way that ensures that they are readily available upon authorities' request.

Subject (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The ISF is not to be destroyed without the sponsor's approval.

The contract with the investigator / institution will contain all regulations relevant for the study center.

13. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms, centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g., SAEs);
    - Results of any interim analysis;
    - Results of parallel clinical studies;
    - Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate, dropout rate, data quality, protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his / her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC(s) / IRB(s), competent authority(ies), study center, head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.4.1.

14. Ethical and legal aspects

14.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's ISF.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained, and delegated individual of the investigational site.

The PI of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must

be signed by the PI and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

14.2 Data Monitoring Committee – amended

Section modified by Amendment 4 (Modification 1).

The role of the DMC has concluded, as of Amendment 4.

14.3 Adjudication Committee

Section modified by Amendment 2 (Modification 27).

An adjudication committee for allergy / hypersensitivity and immunology / autoimmune events will be formed. This will consist of a group of experts in allergy / immunology who are also experienced in evaluating immunological symptoms in subjects with medical devices. A gynecologist will be included. For possible hypersensitivity/allergic reactions, the committee will develop a list of Medical Dictionary for Regulatory Activities (MedDRA) terms that could represent hypersensitivity or allergy, irrespective of treatment group or investigator's assessment of relatedness. This list will be provided to investigators and will be stored in the ISF. All events with these terms will be sent to the committee for adjudication. In addition to the list of MedDRA terms, all subjects who are evaluated for pelvic pain will also be reviewed by the adjudication committee to assess whether or not an element of hypersensitivity could have played a role in the subject's pain. In the event that a subject reports that an AE is an allergic reaction, the AE will be investigated by the adjudication committee, regardless of whether the AE term is on the pre-established list.

For each case, the committee will receive:

- information from the eCRFs (blinded as to group assignment);
- baseline and supplemental study laboratory values;
- medical records (e.g. medical history or relevant medical information), consultant reports, other diagnostic studies (e.g. laboratory, radiological), and operative reports, as applicable, as well as any pathology reports.

In addition, all cases with a suspected or confirmed diagnosis of an autoimmune disease will be evaluated by the committee. The records listed above will be provided to the committee. In cases of suspected or confirmed autoimmune diseases, the adjudication committee may also request that previously collected baseline and/or one-year frozen serum be used to run additional tests. Results of HLA type will also be provided to the committee.

The committee will operate based on the allergy / immunology adjudication committee charter.

14.4 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and / or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

14.5 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s) / IRBs will be obtained for all participating centers / countries before start of the study, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment, or renewal of the IEC / IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IEC / IRB, head of the study center / medical institution) must supply to the sponsor, upon request, a list of the IEC / IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC / IRB / sponsor approval / favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment should be submitted to the IEC / IRB / head of medical institution / sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 13.

14.6 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and ICF provided by the sponsor or the study center. A sample subject information and ICF is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB / IEC has been obtained.

Each subject / legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Table 9–1.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine, or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may she enter the study. Additionally, the investigator or delegate will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the ISF or, if locally required, in the subject's note / file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The ICF and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written ICF. The investigator will inform the subject / legal representative or proxy consenter of changes in a

timely manner and will ask the subject to confirm her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC / IRB's approval or favorable opinion in advance of use.

14.7 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, while free to utilize study data derived from his / her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

14.8 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

14.9 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

15. Reference list

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16. Protocol amendments

16.1 Amendment 1

Amendment 1 (dated 12 OCT 2017) is an amendment to the original protocol dated 24 JAN 2017. Changes to the protocol include:

- Clarification of when subjects will be considered dropouts;
- Added that samples for nickel and titanium level testing may be from plasma;
- Separated HLA typing from other serum samples in Schedule of Evaluations;
- Moved assessment of practitioner characteristics from Screening to the procedure visit;
- Added new SAE definition for required intervention;
- Modified AE of special interest definitions to be applicable to both treatment groups;
- Added new AE of special interest: autoimmune reaction;
- Added text for attempted contact of subjects who are lost to follow-up;
- Clarified the windows for the PRO assessments;
- Clarified reminders for subjects completing PRO assessments electronically versus paper;
- Moved baseline assessment of PRO measurements from screening to procedure visit;
- Added response option for treatment of AEs;
- Clarification of causal relationship of AEs;
- Added the screening question for lower abdominal / pelvic pain and intermenstrual bleeding questions to protocol appendices;
- Removed requirement that PRO assessments that occur in conjunction with a study visit must be completed at the study visit;
- Added registration number;
- Corrected description of PROMIS and AMSS screening thresholds;
- Corrected demographics information;
- Added detail to scoring of inflammatory response and histologic evaluation;
- Corrected text errors;
- Amended exclusion criterion #3 to allow screening procedures to begin while subjects are < 6 weeks post-partum / post pregnancy termination.

16.1.1 Overview of changes

Modification 1

Clarification of when subjects will be considered dropouts.

Rationale:

Clarification was needed to when a subject who withdraws prematurely from the study would be considered a 'dropout' as opposed to a 'screen failure' so that the subjects would be appropriately assigned to an analysis set. The original protocol did not provide a clear definition.

Sections affected include:

- 6.4.1 – Withdrawal.

Modification 2

Added that samples for nickel and titanium level testing may be from plasma and an additional consideration for interference with gadolinium or iodine-based contrast media.

Rationale:

Increased flexibility for site standard practices. Additionally, as gadolinium or iodine-based contrast media are known to interfere with trace metal analysis, a recommendation to defer serum/plasma nickel and titanium testing for 96 hours following administration of gadolinium or iodine contrast media has been inserted.

Sections affected include:

- 5.2.1 – Main endpoints;
- Table 9-1 – Schedule of evaluations;
- Table 9-1 – footnote 'e';
- 9.2.1 – Screening period;
- 9.2.2.2 – Post procedure (at any time during the study);
- 9.2.2.6 – Three months post procedure (phone contact; for laparoscopic group ± 2 weeks; for Essure group + 2 weeks, once confirmation test results are available);
- 9.2.2.7 – Twelve months post procedure (± 4 weeks);
- 9.2.2.8 – Twenty-four months post-procedure (± 4 weeks);
- 9.2.2.9 – Thirty-six months post procedure (- 4 weeks, + 1 week) – End of Study;
- 9.4.1.1 – Definitions.

Modification 3

Separated HLA typing from other serum samples in the Schedule of Evaluations.

Rationale:

Modified to increase clarity of the Schedule of Evaluations.

Sections affected include:

- Table 9-1 – Schedule of evaluations.

Modification 4

Moved assessment of practitioner characteristics from Screening to the procedure visit.

Rationale:

This assessment was determined to be more appropriate for the procedure visit.

Sections affected include:

- Table 9-1 – Schedule of evaluations;
- 9.2.1 – Screening period;
- 9.2.2 – Study procedure period.

Modification 5

Added new SAE definition for required intervention.

Rationale:

It was determined that a study-specific SAE definition was required.

Sections affected include:

- 9.4.1.1 – Definitions.

Modification 6

Modified AE of special interest definitions to be applicable to both treatment groups.

Rationale:

As the FDA has requested information on the comparison of AE rates between the treatment groups, it was determined that AEs of special interest should generally apply to both groups.

Sections affected include:

- 9.4.1.1 – Definitions.

Modification 7

Added new AE of special interest: autoimmune reaction.

Rationale:

Autoimmune reactions were always intended as an AE of special interest; however, it was determined that the original definitions did not clearly include symptoms for autoimmune reactions.

Sections affected include:

- 9.4.1.1 – Definitions.

Modification 8

Added text for attempted contact of subjects who are lost to follow-up.

Rationale:

Text for lost to follow-up subjects was missing from the original protocol.

Sections affected include:

- 6.4.1 – Withdrawal.

Modification 9

Clarified the windows for the PRO assessments.

Rationale:

The original protocol contained windows for the PRO assessments that were not appropriate for the Weeks 1 to 4 and Month 2 assessments.

Sections affected include:

- Table 9-2 – Schedule of PRO evaluations; footnotes;
- 9.2.3.1 – Patient reported outcome data capture system;
- 9.5 – Appropriateness of procedures / measurements.

Modification 10

Clarified reminders for subjects completing PRO assessments electronically versus paper.

Rationale:

The original protocol assumed all subjects would complete PRO assessments electronically. A paper version will now be available. Subjects completing the PRO assessments on paper will not be sent automated reminders.

Sections affected include:

- Table 9-2 – Schedule of PRO evaluations; footnotes;
- 9.2.2.2 – Post procedure (at any time during study);
- 9.2.2.7 – Twelve months post procedure (± 4 weeks);
- 9.2.2.8 – Twenty-four months post procedure (± 4 weeks);
- 9.2.2.9 – Thirty-six months post procedure (-4 weeks, +1 week);
- 9.2.3.1 - Patient reported outcome data capture system;
- 9.5 – Appropriateness of procedures / measurements.

Modification 11

Moved baseline assessment of PRO measurements from screening to procedure visit.

Rationale:

The baseline PRO assessments are conducted at the procedure visit, prior to the procedure. The original protocol was in error.

Sections affected include:

- 9.2.1 – Screening period;
- 9.2.2 – Study procedure period.

Modification 12

Added response option for treatment of adverse events.

Rationale:

Language updated to match the eCRF.

Sections affected include:

- 9.4.1.2.4 – Treatment(s) of adverse events.

Modification 13

Clarification of causal relationship of AEs.

Rationale:

Updated protocol language to reflect that causal relationship of AEs in this study can be related to the procedure or the device.

Sections affected include:

- 9.4.1.2.6 – Causal relationship.

Modification 14

Added the screening question for lower abdominal / pelvic pain and intermenstrual bleeding questions to protocol appendices.

Rationale:

The original protocol did not contain samples of the screening question for lower abdominal / pelvic pain or the two intermenstrual bleeding questions. These were added to the protocol appendices for clarity.

Sections affected include:

- 17.1 – Screening question for lower abdominal / pelvic pain;
- 17.5 – Intermenstrual bleeding questions.

Modification 15

Removed requirement that PRO assessments that occur in conjunction with a study visit must be completed at the study visit.

Rationale:

To make completion of the questionnaires as flexible as possible for subjects, the requirement for the assessments to be completed at the study visit at baseline and 12, 24, and 36 months post procedure has been removed.

Sections affected include:

- 9.2.2.6 – Three months post procedure (phone contact; for laparoscopic group ± 2 weeks; for Essure group + 2 weeks, once confirmation test results are available);
- 9.2.3.1 – Patient reported outcome data capture system.

Modification 16

Added registration number.

Rationale:

Registration number is now available.

Sections affected:

- Title page.

Modification 17

Corrected description of PROMIS and AMSS screening thresholds.

Rationale:

There was redundant text in the screening threshold description for the PROMIS Scale v 1.0 (Pain Intensity 3a) and incorrect text in the screening threshold description for the AMSS.

Sections affected:

- 9.2.3.4 – Screening Thresholds.

Modification 18

Corrected demographics information.

Rationale:

The collection of tobacco use noted in demographics did not match the CRF.

Sections affected:

- 9.3.1 – Demographic.

Modification 19

Added detail to scoring of inflammatory response and histologic evaluation.

Rationale:

Following an advisory board meeting, it was determined that additional detail and some minor correction was needed for the scoring of inflammatory response and histologic evaluation.

Sections affected:

- 9.4.1.6 – Device removal and surgical pathology.

Modification 20

Corrected text errors.

Sections affected:

- 9.4.3 – Further safety.

Modification 21

Amended exclusion criterion #3 to allow screening procedures to begin while subjects are < 6 weeks post-partum / post pregnancy termination.

Rationale:

Text change will allow subjects to begin screening procedures before the 6-week post-partum / post pregnancy termination as long as the PRO assessments and sterilization procedure are conducted at > 6 weeks post-partum / post pregnancy termination.

Sections affected include:

- 1 – Synopsis (Diagnosis and criteria for exclusion);
- 6.2 – Exclusion criteria.

16.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "old text." Additions are underlined in the "new text." Corrections of typing errors or omissions are not highlighted in this amendment.

Title page: Registration

This section was changed as a result of Modification 16.

Old text:

Registration:	~~EudraCT no.:~~	Version no.:	1.0

New text:

Registration:	NCT03127722	Version no.:	

Section 1 Synopsis (Diagnosis and criteria for exclusion); Section 6.2 Exclusion criteria

These sections were changed as a result of Modification 21.

New text:

1. Subjects post-partum or having undergone pregnancy termination ≤ 6 weeks prior to scheduled procedure (Note: subjects may be screened and consented for the study prior to 6 weeks post-partum / post pregnancy termination; however, PRO tools must be administered > 6 weeks post-partum / pregnancy termination and the sterilization procedure must occur > 6 weeks post-partum / pregnancy termination);

Section 5.2.1 Main endpoints

This section was changed as a result of Modification 2.

New text:

In addition, this evaluation will include collection and submission of blood and serum or plasma samples to a central laboratory for a nickel lymphocyte proliferation test (NiLPT), which is a measure of sensitization to nickel, a chromium lymphocyte proliferation test (LPT), which is a measure of sensitization to chromium, serum or plasma nickel level, and serum or plasma titanium level.

New text:

In addition, this evaluation will include collection and submission of blood and serum samples to a central laboratory for a NiLPT, which is a measure of sensitization to nickel, a chromium LPT, which is a measure of sensitization to chromium, serum or plasma nickel level, and serum or plasma titanium level.

New text:

Blood samples for NiLPT, chromium LPT, serum or plasma nickel level, and serum or plasma titanium level will also be collected by the study site.

Section 6.4.1 Withdrawal – Screening failure

This section was changed as a result of Modification 1.

New text:

Re-screening

New text:

Subjects who re-screen will not be required to repeat screening laboratory assessments if the original screening laboratory assessments were collected within 3 months of the new proposed procedure date.

Section 6.4.1 Withdrawal – Dropout

This section was changed as a result of Modification 1.

Old text:

A subject who is eligible for study participation ~~or in whom a sterilization procedure was attempted~~ will be considered to have entered the treatment phase. Any termination after this point for any reason is defined as a "dropout."

New text:

A subject who is eligible for study participation and who has a procedure visit date recorded in the electronic case report form (eCRF) (i.e., the subject shows up for the procedure visit) will be considered to have entered the treatment phase. Any termination after this point for any reason is defined as a "dropout." Dropouts will not be allowed to re-screen.

Section 6.4.1 Withdrawal – Lost to follow-up

This section was changed as a result of Modification 8.

New text:

Lost to follow-up

A subject will be considered lost to follow-up if she fails to return for 1 scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and / or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 2 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- Should the subject return to the site at a later time and wish to continue participation in the study, she will no longer be considered lost to follow-up and should complete the next visit due at that time.

Section 9.1 Tabular schedule of evaluations

These changes were made as a result of Modifications 2, 3, and 4.

Old text:

Schedule of evaluations	Screen-ing	Proce-dure (1st or 2nd)	Post procedure (before discharge)	1 week post procedure (phone)	3 months post procedure (± 2 wk)[a]	12 months (± 4 wk)	24 months (±4 wk)	36 months (-4 wk, +1 wk)
Informed consent Inclusion / exclusion criteria Demographic data	•							
Provide ACOG brochure and patient checklist for laparoscopic tubal sterilization	•							
Height, smoking history, alcohol, medication history	•							
General medical and surgical history (including history of chronic pain disorders) and gynecological history (including pregnancies, menstrual history, vaginal bleeding, and AUB)	•							
Personal and family history of autoimmune disease, personal history of allergies / hypersensitivities, medical or cosmetic implants, piercings, tattoos with metallic colorants, dental history including orthodonture	•							
Physical examination including vital signs	•	•						
Weight	•	•				•	•	•
Whole blood sample for ~~HLA typing~~[b] ~~and~~ NiLPT; serum sample for nickel level and titanium level	•					•		
Frozen serum sample	•					•	•	
Final check of inclusion / exclusion criteria		•						
Gynecological examination	•	•						
Gynecological procedures	•	•	•	•	•	•	•	•
AE assessment	•	•	•	•	•	•	•	•

Schedule of evaluations	Screen-ing	Proce-dure (1st or 2nd)	Post procedure (before discharge)	1 week post procedure (phone)	3 months post procedure (± 2 wk)[a]	12 months (± 4 wk)	24 months (±4 wk)	36 months (-4 wk, +1 wk)
Concomitant medication	●	●	●	●	●	●	●	●
Alternative contraception (type used)	●	●	●	●	●	→	→	→
Device events		→	→	→	→	→	→	→
New exposure to metals					●	●	●	●
Practitioner Characteristics: experience with the Essure System / LTS, physician specialty	●							
~~PROCEDURE~~								
Pregnancy test		●						

New text:

Schedule of evaluations	Screen-ing	Proce-dure (1st or 2nd)	Post procedure (before discharge)	1 week post procedure (phone)	3 months post procedure (± 2 wk)[a]	12 months (± 4 wk)	24 months (±4 wk)	36 months (-4 wk, +1 wk)
Informed consent Inclusion / exclusion criteria Demographic data	●							
Provide ACOG brochure and patient checklist for laparoscopic tubal sterilization	●							
Height, smoking history, alcohol, medication history	●							
General medical and surgical history (including history of chronic pain disorders) and gynecological history (including pregnancies, menstrual history, vaginal bleeding, and AUB)	●							
Personal and family history of autoimmune disease, personal history of allergies / hypersensitivities, medical or cosmetic implants, piercings, tattoos with metallic colorants, dental history including orthodonture	●							
Physical examination including vital signs	●	●						
Weight	●	●				●	●	●
Whole blood sample for HLA typing	●							
Whole blood sample for NiLPT; serum or plasma sample for nickel level and titanium level[b]	●					●		
Frozen serum sample	●					●	●	
Final check of inclusion / exclusion criteria		●						
Gynecological examination	●	●						
Gynecological procedures	●	●	●	●	●	●	●	●
AE assessment	●	●	●	●	●	●	●	●
Concomitant medication	●	●	●	●	●	●	●	●
Alternative contraception (type used)	●	●	●	●	●	→	→	→
Device events		→	→	→	→	→	→	→
New exposure to metals					●	●	●	●
PROCEDURE								

Schedule of evaluations	Screen-ing	Proce-dure (1st or 2nd)	Post procedure (before discharge)	1 week post procedure (phone)	3 months post procedure (± 2 wk)[a]	12 months (± 4 wk)	24 months (±4 wk)	36 months (-4 wk, +1 wk)
Practitioner Characteristics: experience with the Essure System / LTS, physician specialty		•						
Pregnancy test		•						

Table 9-1 Schedule of evaluations – footnotes

This change was made as a result of Modifications 2 and 3.

Deleted text:

~~[b] HLA will only be done at baseline.~~

New text:

[b] Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis. Specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

[d] Whole blood and serum or plasma for cases of hypersensitivity, autoimmune reactions, and pain AEs does not need to be taken before discharge; however, whole blood and serum or plasma sampling should occur if symptoms are indicated between discharge and the Week 1 contact.

Table 9-2 Schedule of PRO evaluations

This change was made as a result of Modifications 9 and 10.

Old text:

Questionnaire	Baseline	Week 1	Week 2	Week 3	Week 4	Month 2	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36
PROMIS Scale v1.0 – Pain Intensity 3a*t‡	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PROMIS Scale v1.0 – Pain Interference 8a Participant Format*t‡	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Aberdeen Menorrhagia Severity Scale; and two intermenstrual bleeding questions ‡	x						x	x	x	x	x	x	x	x	x	x	x	x
SF-36‡	x							x		x				x				x
Fibromyalgia Survey Questionnaire	x																	

New text:

Questionnaire	Baseline	Week 1§	Week 2§	Week 3§	Week 4§	Month 2**	Month 3‡	Month 6‡	Month 9‡	Month 12‡	Month 15‡	Month 18‡	Month 21‡	Month 24‡	Month 27‡	Month 30‡	Month 33‡	Month 36‡
PROMIS Scale v1.0 – Pain Intensity 3a*t	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PROMIS Scale v1.0 – Pain Interference 8a Participant Format*t	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Aberdeen Menorrhagia Severity Scale; and two intermenstrual bleeding questions	●						●	●	●	●	●	●	●	●	●	●	●	●
SF-36	●							●		●				●				●
Fibromyalgia Survey Questionnaire	●																	

Table 9-2 Schedule of PRO evaluations – footnotes

This change was made as a result of Modifications 9 and 10.

Old text:

ǂSubjects will receive email or text reminders to complete questionnaires 1 week prior to the scheduled completion date. The window for completion will be -1 week / +2 weeks for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. The subject and site will then receive weekly reminders and alerts at +1 week and +2 weeks.

New text:

§ Subjects completing ePRO questionnaires will receive email or text reminders to complete questionnaires 2 days prior to the scheduled completion date. The window for completion will be -2 days / +2 days for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. Subjects completing paper questionnaires will not receive automated reminders and every effort will be made to ensure the subject completes the questionnaire within the window.

** Subjects completing ePRO questionnaires will receive email or text reminders to complete questionnaires 5 days prior to the scheduled completion date. The window for completion will be -5 days / +5 days for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. Subjects completing paper questionnaires will not receive automated reminders and every effort will be made to ensure the subject completes the questionnaire within the window.

ǂSubjects completing ePRO questionnaires will receive email or text reminders to complete questionnaires 1 week prior to the scheduled completion date. The window for completion will be -1 week / +2 weeks for all questionnaires. If the questionnaire(s) are not completed by the scheduled completion date, another reminder will be sent and an alert will be sent to the site. The subject and site will then receive weekly reminders and alerts at +1 week and +2 weeks. Subjects completing paper questionnaires will not receive automated reminders and every effort will be made to ensure the subject completes the questionnaire within the window.

Section 9.2.1 Screening period

This change was made as a result of Modification 4.

Deleted text:

- ~~Practitioner characteristics:~~
  - ~~Experience with Essure System and/or laparoscopic tubal sterilization~~
  - ~~Physician specialty.~~

Section 9.2.1 Screening period

This change was made as a result of Modification 2.

Old text:

- Baseline serum:
  - Serum will be used to obtain baseline ~~serum~~ nickel and ~~serum~~ titanium levels.

New text:

- Baseline serum or plasma:
  - Serum or plasma will be used to obtain baseline nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

Section 9.2.1 Screening period

This change was made as a result of Modification 11.

Deleted text:

- ~~Baseline PRO tool measurements:~~
  - ~~Screening question for lower abdominal/pelvic pain and, if positive:~~
    - ~~PROMIS Scale v1.0 – Pain Intensity 3a~~
    - ~~PROMIS Scale v1.0 – Pain Interference 8a Participant Format.~~
  - ~~AMSS and two intermenstrual bleeding questions~~
  - ~~SF-36~~
  - ~~FSQ~~

Section 9.2.2 Study procedure period

This change was made as a result of Modification 4.

Added text:

- Practitioner characteristics:
  - Experience with Essure System and / or laparoscopic tubal sterilization;
  - Physician specialty.

Section 9.2.2 Study procedure period

This change was made as a result of Modification 11.

Added text:

- Baseline PRO tool measurements:
    - Screening question for lower abdominal / pelvic pain and, if positive:
        - PROMIS Scale v1.0 – Pain Intensity 3a;
        - PROMIS Scale v1.0 – Pain Interference 8a Participant Format.
    - AMSS and two intermenstrual bleeding questions;
    - SF-36;
    - FSQ.

Section 9.2.2.2 Post Procedure (at any time during study)

This change was made as a result of Modification 2.

Old text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT
    - Samples for ~~serum~~ nickel and ~~serum~~ titanium levels

New text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

Section 9.2.2.2 Post Procedure (at any time during study)

This change was made as a result of Modification 10.

Deleted text:

- PRO assessment(s) ~~(electronically)~~:

Section 9.2.2.6 Three months post procedure (phone contact: for laparoscopic group ± 2 weeks; for Essure group + 2 weeks, once confirmation test results are available)

This change was made as a result of Modification 2.

Old text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:

- Whole blood samples for NiLPT and chromium LPT
- Samples for ~~serum~~ nickel and ~~serum~~ titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

New text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
  - Whole blood samples for NiLPT and chromium LPT;
  - Serum or plasma samples for nickel and titanium levels.

Section 9.2.2.6 Three months post procedure (phone contact: for laparoscopic group ± 2 weeks; for Essure group + 2 weeks, once confirmation test results are available)

This change was made as a result of Modification 15.

Added text:

- PRO assessment(s):
  - Screening question for lower abdominal / pelvic pain, and, if positive:
    - PROMIS (3a);
    - PROMIS (8a).
  - AMSS and two intermenstrual bleeding questions;
  - SF-36.

Section 9.2.2.7 Twelve months post procedure (± 4 weeks)

This change was made as a result of Modification 2.

Old text:

- For all subjects: blood sample collection including:
  - Whole blood for NiLPT
  - Serum nickel and ~~serum~~ titanium levels
  - Serum to be frozen

New text:

- For all subjects: blood sample collection including:
  - Whole blood for NiLPT;
  - Serum or plasma nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

- Serum to be frozen.

Section 9.2.2.7 Twelve months post procedure (± 4 weeks)

This change was made as a result of Modification 10.

Deleted text:

- PRO assessment(s) ~~(electronically)~~:

Section 9.2.2.8 Twenty-four months post procedure (± 4 weeks)

This change was made as a result of Modification 2.

Old text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
  - Whole blood samples for NiLPT and chromium LPT
  - Samples for ~~serum~~ nickel and ~~serum~~ titanium levels

New text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
  - Whole blood samples for NiLPT and chromium LPT;
  - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

Section 9.2.2.8 Twenty-four months post procedure (± 4 weeks)

This change was made as a result of Modification 10.

Deleted text:

- PRO assessment(s) ~~(electronically)~~:

Section 9.2.2.9 Thirty-six months post procedure (-4 weeks, +1 week) – End of Study

This change was made as a result of Modification 10.

Deleted text:

- PRO assessment(s) ~~(electronically)~~:

Section 9.2.2.9 Thirty-six months post procedure (-4 weeks, +1 week) – End of Study

This change was made as a result of Modification 2.

Old text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT
    - Samples for ~~serum~~ nickel and ~~serum~~ titanium levels

New text:

- If indicated for potential hypersensitivity reaction / pain AEs / allergy / autoimmune disorder:
    - Whole blood samples for NiLPT and chromium LPT;
    - Serum or plasma samples for nickel and titanium levels. Gadolinium and iodine-based contrast material are known to interfere with trace metal analysis; therefore, specimen collection for serum/plasma nickel and titanium should be deferred until 96 hours following administration of gadolinium or iodine contrast media.

9.2.3.1 Patient reported outcome data capture system

This change was made as a result of Modifications 9, 10, and 15.

Old text:

A web-based, electronic data capture system will be ~~used~~ to record PRO measure data in this study. The proposed system will integrate programming that tracks scheduled PRO response compliance with reminder notifications (email or text) to subjects for each scheduled administration of the questionnaires.

The system will provide for a ~~3-week~~ window for completion of PRO instruments at the cross-section, sending the first message to respond to online PRO ~~with one-week's~~ anticipation of the ideal scheduled date. If the subject fails to respond ~~within the week~~, a reminder will be sent on the scheduled date encouraging the subject to complete the online questionnaires. If the respondent fails to respond ~~within the second week~~, a flagged, urgent reminder will be sent both to the subject and to the site investigator, triggering a telephone reminder to the subject to complement the emailed message. Finally, toward the end of the ~~third week~~, a follow-up email or text will be provided automatically to both the subject and the site prior to closing availability of the questionnaire being implemented indicating a "last chance" for PRO completion if needed.

The system will also be programmed to generate notifications to site investigators triggered by specified subject item response and total score thresholds. These advisories will require site investigators to assess potential pain or bleeding events for subjects in whom they have not already been recently assessed.

~~The PRO assessments will be collected according to the schedule in Table 9-2. If a PRO assessment is scheduled to occur concurrently with a study visit (ie, Screening and 12, 24, and 36 months post-procedure), the subject will be asked to complete the PRO assessments on an electronic device at the visit.~~

If a potential pain event is spontaneously reported outside of a scheduled visit or scheduled PRO tool administration, the pain PRO tools (PROMIS V1.0 – Pain Intensity 3a and PROMIS Scale V1.0 – Pain Interference 8a Participant Format) will be administered off-schedule in order to characterize pain intensity and interference. If a potential bleeding AE is reported at a scheduled visit or if the subject spontaneously reports such an event to the site at some other time, the event will be evaluated per standard AE assessment. In the event of a report outside of a schedule visit or scheduled PRO administration, the Aberdeen Menorrhagia Severity Scale (AMSS) and two intermenstrual bleeding questions will not be re-administered as the recall period for these PRO tools is 3 months and this data is captured during the scheduled PRO tool administration which occurs every 3 months.

New text:

A web-based, electronic data capture system will be available to record PRO measure data in this study. The proposed system will integrate programming that tracks scheduled PRO response compliance with reminder notifications (email or text) to subjects for each scheduled administration of the questionnaires.

The system will provide for a window for completion of PRO instruments at the cross-section, sending the first message to respond to online PRO in anticipation of the ideal scheduled date, according to the windows described in Table 9-2. If the subject fails to respond, a reminder will be sent on the scheduled date encouraging the subject to complete the online questionnaires. If the respondent still fails to respond, a flagged, urgent reminder will be sent both to the subject and to the site investigator, triggering a telephone reminder to the subject to complement the emailed message. Finally, toward the end of the response window, a follow-up email or text will be provided automatically to both the subject and the site prior to closing availability of the questionnaire being implemented indicating a “last chance” for PRO completion, if needed.

The system will also be programmed to generate notifications to site investigators triggered by specified subject item response and total score thresholds. These advisories will require site investigators to assess potential pain or bleeding events for subjects in whom they have not already been recently assessed.

For subjects who wish to complete the PRO measurements on paper, questionnaires will be mailed to the subject by the site in accordance with the completion windows noted in Table 9-2. No automated reminders will be sent. Subjects will complete the paper questionnaires and return the questionnaires to Covance via courier. Once received, if the date on the questionnaire is within the appropriate window, the questionnaire data will be entered into the electronic data capture system by an independent data entry group.

If a potential pain event is spontaneously reported outside of a scheduled visit or scheduled PRO tool administration, the pain PRO tools (PROMIS V1.0 – Pain Intensity 3a and PROMIS Scale V1.0 – Pain Interference 8a Participant Format) will be administered off-schedule in order to characterize pain intensity and interference. If a potential bleeding AE is reported at a scheduled visit or if the subject spontaneously reports such an event to the site at some other time, the event will be evaluated per standard AE assessment. In the event of a report outside of a schedule visit or scheduled PRO administration, the Aberdeen Menorrhagia Severity Scale (AMSS) and two intermenstrual bleeding questions will not be

re-administered as the recall period for these PRO tools is 3 months and this data is captured during the scheduled PRO tool administration which occurs every 3 months.

Section 9.2.3.4 Screening thresholds

This change was made as a result of Modification 17.

Deleted text:

PROMIS Scale v1.0—Pain Intensity 3a: Any subject response of 3 or higher on Item PAINQU6, "Worst Pain," or a total T-Score above 50 (i.e., above the US population mean) of PRO response will trigger an electronic communication (via email) to the site. If the subject has not previously received medical attention and evaluation for her pain by the site investigator or staff, the investigator will arrange for a timely (as assessed by the investigator and site expertise) investigation of the subject's pain to determine if the subject is experiencing a pain AE as defined in this protocol. ~~Similarly, a subject not previously having received attention for her pain by the site investigator who reports a T-Score greater than or equal to 60 (i.e., one standard deviation [SD] above the US population mean) at a single cross-section will be contacted in a timely manner to determine if the subject is suffering an AE.~~

Section 9.2.3.4 Screening thresholds

This change was made as a result of Modification 17.

Old text:

AMSS: The following item thresholds reported by a subject at a cross-sectional administration will serve to trigger communication to the site: Question 1 (≥ 2—"Between 8 and 10 days"), Questions 2 to 3 (~~*missing data*~~), Question 4 (≥ 2—"Heavy"), Question 5 (≥ 3—"Between 7 and 10 days"), Question 7 (≥ 1—"Soiling / staining of your outer clothes / over garments"), Question 8 (≥ 1—"I could continue to work, but my work suffered"), Question 9 (≥ 1—"Yes, usually or part of one day"), Questions 10 to 11 (≥ 2—"Moderately affected by heavy periods"), Questions 12 to 13 (~~*missing data*~~). Additionally, an AMSS total score greater than 40 will serve to trigger communication to the site and the site will determine if the subject requires an unscheduled visit for her complaint.

New text:

AMSS: The following item thresholds reported by a subject at a cross-sectional administration will serve to trigger communication to the site: Question 1 (≥ 2—"Between 8 and 10 days"), Questions 2 to 3 (*no trigger associated*), Question 4 (≥ 2—"Heavy"), Question 5 (≥ 3—"Between 7 and 10 days"), Question 7 (≥ 1—"Soiling / staining of your outer clothes / over garments"), Question 8 (≥ 1—"I could continue to work, but my work suffered"), Question 9 (≥ 1—"Yes, usually or part of one day"), Questions 10 to 11 (≥ 2—"Moderately affected by heavy periods"), Questions 12 to 13 (*no trigger associated*). Additionally, an AMSS total score greater than 40 will serve to trigger communication to the site and the site will determine if the subject requires an unscheduled visit for her complaint.

Section 9.3.1 Demographic

This change was made as a result of Modification 18.

Old text:

- ~~Tobacco~~ use

New text:

- Substance use;

Section 9.4.1.1 Definitions (Definition of serious adverse event [SAE])

This change was made as a result of Modification 5.

Added text:

d. Requires intervention to prevent permanent impairment or damage.

Section 9.4.1.1 Definitions (AEs of special safety interest)

This change was made as a result of Modifications 6 and 7.

Old text:

~~For Essure:~~

- Perforations of the uterus, cervix, or fallopian tubes ~~by the Essure insert(s) or the Essure delivery system~~
- Expulsion of ~~Essure inserts~~
- Device dislocation
- Potential allergy / hypersensitivity ~~to Essure inserts~~ (e.g., itch [pruritus], rash, hives [urticarial], facial edema, angioedema, allergy to metals), in addition to symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain).

~~For laparoscopy tubals:~~

- Failed ~~laparoscopy/conversion to laparotomy~~
- Additional surgical procedures for example to treat intraoperative bleeding or complications.

~~For both groups:~~

- Chronic pelvic pain. Per the definition by the American College of Obstetricians and Gynecologists, chronic pelvic pain is pain in the pelvic area that lasts for 6 months or longer. In those subjects reporting lower abdominal / pelvic pain at any time during the study, either spontaneously or in response to the regularly scheduled PRO tool, evaluation of the event will note if duration of the pain meets this definition.
- Pregnancy (refer to Section 9.4.2)
- Upper genital tract infection (for example: endometritis, salpingooophoritis, salpingitis).

New text:

- Unintentional perforations of the uterus, cervix, or fallopian tubes by any surgical instrument or by any sterilization device;
- Expulsion of any sterilization device;
- Device dislocation (devices found in an unintended location);
- Potential new or worsening allergy / hypersensitivity symptoms (e.g., itch [pruritus], rash, hives [urticarial], facial edema, angioedema, allergy to metals, flushing, anaphylaxis), in addition to symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain, joint swelling).
- Potential new or worsening autoimmune reactions;
- Failed primary procedure / conversion to secondary procedure;
- Additional surgical procedures for example to treat intraoperative bleeding or complications;
- Chronic pelvic pain. Per the definition by the American College of Obstetricians and Gynecologists, chronic pelvic pain is pain in the pelvic area that lasts for 6 months or longer. In those subjects reporting new or worsening lower abdominal / pelvic pain at any time during the study, either spontaneously or in response to the regularly scheduled PRO tool, evaluation of the event will note if duration of the pain meets this definition.
- Pregnancy (refer to Section 9.4.2);
- Upper genital tract infection (for example: endometritis, salpingooophoritis, salpingitis).

Section 9.4.1.1 Definitions (Allergic / hypersensitivity reactions)

This change was made as a result of Modifications 2 and7.

Old text:

For potential allergic / hypersensitivity reactions, investigators will be instructed that an evaluation should be performed in any subject presenting with urticaria, angioedema, unexplained rash, ~~or~~ unexplained itching. Evaluation will also be performed in subjects who present with other symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain). This evaluation will include a NiLPT, which is a measure of sensitized T-cell reactivity to nickel in culture; a chromium LPT, which is a measure of sensitization to chromium; serum nickel level; and serum titanium level. For NiLPT and chromium LPT, both the continuous score as well as the positive / negative score (based on established cut-offs for negative responses) will be recorded. The results of these lab tests will be forwarded to the sponsor directly by the central lab and will be made available to the adjudication committee. In addition, any subject presenting with an AE of pelvic / lower abdominal pain and any subject presenting with symptoms she believes are due to a hypersensitivity or allergic reaction will also be evaluated, including an NiLPT,

chromium LPT, serum nickel level, and serum titanium level. If removal of a device or any other surgery is performed, pathological evaluation and metallurgic studies (if applicable) will be included. After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not a hypersensitivity / allergic reaction has occurred, all information will be forwarded to the adjudication committee in a blinded fashion. In cases of pathological evidence, blinding may not be possible. Final determination of whether or not a hypersensitivity / allergic event has occurred will be based on the determination of this committee. Once adjudicated events are available, the following comparisons will be possible:

- Pathological findings in subjects with Essure and adjudicated hypersensitivity reactions can be compared to pathological findings in subjects with Essure without hypersensitivity reactions as well as to pathological findings in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- Serum nickel and titanium levels in subjects with Essure and adjudicated hypersensitivity reactions can be compared to serum nickel and titanium levels in subjects with Essure without hypersensitivity reactions as well as to serum nickel and titanium levels in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- NiLPT and chromium LPT results (both the continuous measurement as well as the positive / negative assessment) in subjects with Essure and adjudicated hypersensitivity reactions can be compared to NiLPT and chromium LPT results in subjects with Essure without hypersensitivity reactions as well as to NiLPT and chromium LPT results in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- An individual subject's serum nickel and titanium levels and NiLPT can be compared to baseline levels in order to assess any change. In addition, in cases of removal, subsequent post-removal levels can also be compared.

New text:

For potential allergic / hypersensitivity reactions, investigators will be instructed that an evaluation should be performed in any subject presenting with urticaria, angioedema, unexplained rash, unexplained itching, flushing, or anaphylaxis. Evaluation will also be performed in subjects who present with other symptoms that could possibly be related to an inflammatory reaction (e.g., hair loss, fatigue, muscle pain, joint pain, joint swelling). This evaluation will include a NiLPT, which is a measure of sensitized T-cell reactivity to nickel in culture; a chromium LPT, which is a measure of sensitization to chromium; serum or plasma nickel level; and serum or plasma titanium level. For NiLPT and chromium LPT, both the continuous score as well as the positive / negative score (based on established cut-offs for negative responses) will be recorded. The results of these lab tests will be forwarded to the sponsor directly by the central lab and will be made available to the adjudication committee. In addition, any subject presenting with an AE of pelvic / lower abdominal pain and any subject presenting with symptoms she believes are due to a hypersensitivity or allergic reaction will also be evaluated, including a NiLPT, chromium LPT, serum or plasma nickel

level, and serum or plasma titanium level. If removal of a device or any other surgery is performed, pathological evaluation and metallurgic studies (if applicable) will be included. After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not a hypersensitivity / allergic reaction has occurred, all information will be forwarded to the adjudication committee in a blinded fashion. In cases of pathological evidence, blinding may not be possible. Final determination of whether or not a hypersensitivity / allergic event has occurred will be based on the determination of this committee. Once adjudicated events are available, the following comparisons will be possible:

- Pathological findings in subjects with Essure and adjudicated hypersensitivity reactions can be compared to pathological findings in subjects with Essure without hypersensitivity reactions as well as to pathological findings in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- Serum or plasma nickel and titanium levels in subjects with Essure and adjudicated hypersensitivity reactions can be compared to serum or plasma nickel and titanium levels in subjects with Essure without hypersensitivity reactions as well as to serum or plasma nickel and titanium levels in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- NiLPT and chromium LPT results (both the continuous measurement as well as the positive / negative assessment) in subjects with Essure and adjudicated hypersensitivity reactions can be compared to NiLPT and chromium LPT results in subjects with Essure without hypersensitivity reactions as well as to NiLPT and chromium LPT results in laparoscopic tubal ligation subjects (with and without adjudicated hypersensitivity reactions).
- An individual subject's serum or plasma nickel and titanium levels and NiLPT can be compared to baseline levels in order to assess any change. In addition, in cases of removal, subsequent post-removal levels can also be compared.

Section 9.4.1.1 Definitions (Autoimmune diseases)

This change was made as a result of Modification 2.

Added text:

> For autoimmune disorders, any subject presenting with symptoms indicating a potential autoimmune disorder should be evaluated per standard medical practice. All effort will be made to obtain records of any diagnostic workup conducted by outside physicians. A~~n~~ NiLPT, chromium LPT, serum or plasma nickel level, and serum or plasma titanium level will also be drawn by the study site. Frozen serum will be used in cases of suspected autoimmune disorders (both for the index case as well as a randomly selected control group). The quantity of serum will be adequate to be used for tests used to diagnose autoimmune conditions (e.g., anti-citrullinated protein antibody in cases of suspected rheumatoid arthritis, thyroid peroxidase antibody for suspected autoimmune thyroid diseases, and antinuclear antibody in cases of suspected lupus erythematosus). If removal

of a device or any other surgery is performed, pathological evaluation and metallurgic studies (if applicable) will be included.

After the evaluation of the subject is complete, regardless of investigator's assessment as to whether or not an autoimmune disorder exists, all information will be forwarded to the adjudication committee in a blinded fashion. In cases of pathological evidence, blinding may not be possible. Final determination of whether or not an autoimmune disorder has occurred will be based on the determination of this committee. Once adjudicated events are available, the following comparisons will be possible:

- Pathological findings in subjects with Essure and adjudicated autoimmune disorders can be compared to pathological findings in subjects with Essure without autoimmune disorders as well as to pathological findings in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders).
- Serum or plasma nickel and titanium levels in subjects with Essure and adjudicated autoimmune disorders can be compared to serum or plasma nickel and titanium levels in subjects with Essure without autoimmune disorders as well as to serum or plasma nickel and titanium levels in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders).
- NiLPT and chromium LPT results (both the continuous measurement as well as the positive / negative assessment) in subjects with Essure and adjudicated autoimmune disorders can be compared to NiLPT and chromium LPT results in subjects with Essure without autoimmune disorders as well as to NiLPT and chromium LPT results in laparoscopic tubal ligation subjects (with and without adjudicated autoimmune disorders).
- An individual subject's serum or plasma nickel and titanium levels and NiLPT can be compared to baseline levels in order to assess any change. In addition, in cases of removal, subsequent post-removal levels can also be compared.

Section 9.4.1.2.4 Treatment(s) of adverse events

This change was made as a result of Modification 12.

Added text:

- None;
- Remedial drug therapy;
- Additional surgical procedure;
- Change in surgical procedure;
- Other.

Section 9.4.1.2.6 Causal relationship

This change was made as a result of Modification 13.

New text:

The assessment is based on the question whether there was a “reasonable causal relationship” to the study procedure or device in question.

New text:

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study procedure or device.

Section 9.4.1.6 Device removal and surgical pathology

This change was made as a result of Modification 19.

Added text:

A standardized scoring protocol based on ISO 10-993, part 6 criteria will be used to assess inflammatory response. The H&E, Movat’s pentachrome, and CD68 immunostaining will be performed on both methacrylate and paraffin embedded specimens. If on stained slides there appears to be ~~a~~an moderate or extensive inflammatory reaction, immunohistochemical staining for additional markers will be performed. These will be performed on both methacrylate and paraffin embedded specimens; however, some stains may not be possible on methacrylate embedded specimens. It will then be possible to compare histology findings in women who have removals due to pain and / or other AEs to women who have their tubes removed for other unrelated issues. Comparisons will also be made between the area of the tube containing the insert versus the area of the tube distal to the insert. Finally, tubal histology in the Essure group can be compared to tubal histology in the laparoscopic sterilization group.

Old text:

In all cases, histologic evaluation will be performed by ~~2~~ pathologists blinded as to subject symptoms and will be evaluated using a standardized grading system. Specifically, the pathologists will not know if the sample belongs to a subject reporting hypersensitivity / immunologic symptoms or to a subject undergoing surgical removal for a reason unrelated to hypersensitivity / immunologic symptoms. ~~If there is disagreement on the reading, a third pathologist will be used.~~ As noted above, if histology reveals a~~n~~ inflammatory response, additional immunohistochemical staining will be performed as appropriate.

New text:

In all cases, histologic evaluation will be performed by 3 pathologists blinded as to subject symptoms and will be evaluated using a standardized grading system. The final score for a specimen will be the average of the three readings, rounded to nearest whole number. Specifically, the pathologists will not know if the sample belongs to a subject reporting hypersensitivity / immunologic symptoms or to a subject undergoing surgical removal for a reason unrelated to hypersensitivity / immunologic symptoms. As noted above, if histology reveals a moderate or extensive inflammatory response, additional immunohistochemical staining will be performed as appropriate.

Section 9.4.3 Further safety

This change was made as a result of Modification 20.

Added text:

A detailed physical examination including height, weight, vital signs (BP, HR), smoking history, alcohol consumption, previous medications, and a gynecological examination will be conducted. Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.4.1.1).

Section 9.5 Appropriateness of procedures / measurements

This change was made as a result of Modifications 9 and 10.

Old text:

All safety variables and validated PRO instruments, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant. As described in Table 9-2, subjects will receive alerts to complete the scheduled questionnaires ~~1 week~~ prior to the scheduled completion date for each questionnaire. If the questionnaire is not completed by the scheduled date, the subject will receive a second reminder and an alert will be sent to the site. The subject and site will then receive ~~weekly~~ reminders ~~/ alerts at +1 week and +2 weeks~~ if the questionnaires are not completed.

New text:

All safety variables and validated PRO instruments, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant. As described in Table 9-2, subjects completing PRO assessments electronically will receive alerts to complete the scheduled questionnaires prior to the scheduled completion date for each questionnaire. If the questionnaire is not completed by the scheduled date, the subject will receive a second reminder and an alert will be sent to the site. The subject and site will then receive up to 2 additional reminders if the questionnaires are not completed. Subjects completing PRO assessment on paper will not receive alerts.

Section 17.1 Screening question for lower abdominal / pelvic pain

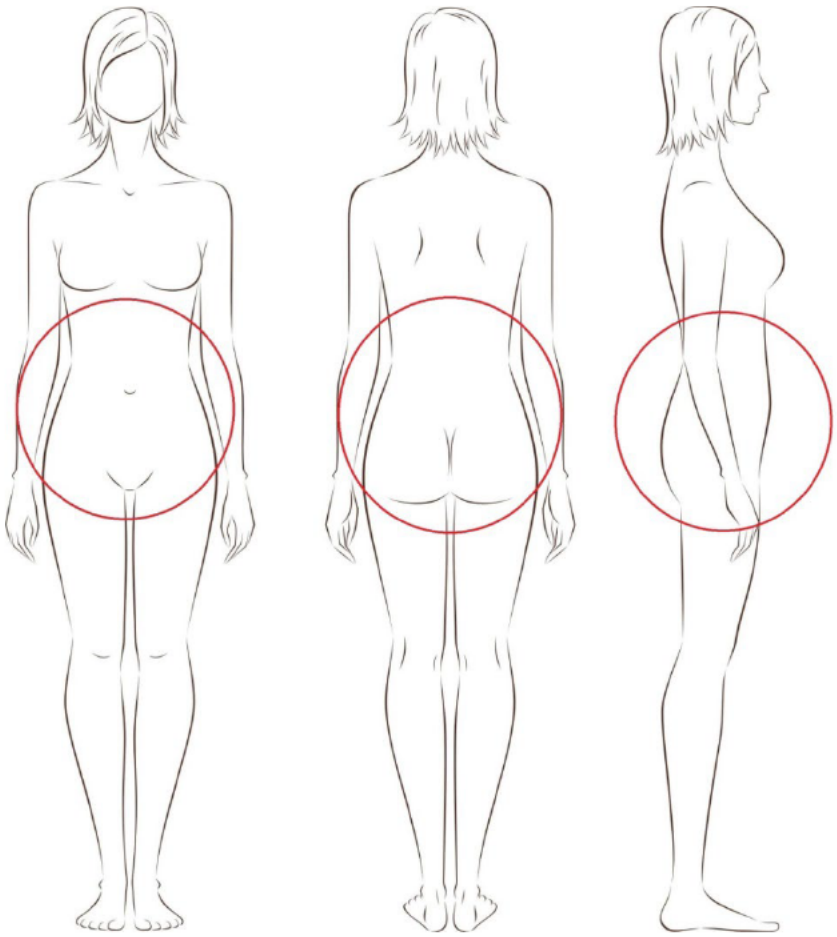
This change was made as a result of Modification 14.

Added text:

17.1 Screening question for lower abdominal / pelvic pain

Pain Screener

Did you experience pain in your pelvic area or in your lower abdomen during the past 7 days?	❍ Yes ❍ No



Section 17.5 Intermenstrual questions

This change was made as a result of Modification 14.

Added text:

17.5 Intermenstrual questions

Intermenstrual questions

At any time during the last 3 months did you experience any bleeding or spotting in between your periods?	❍ No ❍ Yes
• If yes, how much did it interfere with your normal daily activities?	❍ Not at all ❍ Mildly ❍ Moderately ❍ Severely

16.2 Amendment 2

Amendment 2 (dated 25 OCT 2018) is an amendment to Protocol Amendment 1 dated 12 OCT 2017. Changes to the protocol include:

- Updated name of Medical Director;
- Increased the number of targeted sites participating in the study;
- Added new PRO questionnaires;
- Clarified existing and added new laboratory evaluations for hypersensitivity reactions and potential autoimmune disorders;
- Clarified pathological evaluations and metallurgic studies;
- Changed determination of sample size;
- Separated the variable of "hypersensitivity / allergy / autoimmune disorder" into "hypersensitivity / allergy" and "autoimmune disorder"
- Amended inclusion criterion #2 to clarify age restrictions;
- Amended inclusion criterion #3 to remove weight restrictions;
- Clarification of intrauterine device procedure;
- Clarification of exclusion of subjects with diseases or conditions that might interfere with the conduct of the study or interpretation of the results;
- Clarified re-screening procedure;
- Clarified and corrected the schedule of evaluations;
- Replaced "gynecological examination" with "pelvic examination;"
- Clarified and corrected procedures during the screening period and study visits;
- Removed post-procedure contact method;
- Added 48-month contact, 60-month visit, and premature discontinuation (dropout) visit;
- Corrected name of End of Study form;
- Amended baseline characteristics;
- Added device events to safety definitions;
- Clarified that only unintended pregnancies are to be considered device failures;
- Removed "failed primary procedure / conversion to secondary procedure" as an AE of special interest;
- Clarified procedure complications;
- Added detail to reporting of SAEs;
- Updated insurance type response at baseline;
- Added 2 interim analyses;
- Updated adjudication committee details.

Editorial corrections such as abbreviations and capitalization changes will not be detailed.

16.2.1 Overview of changes

Modification 1

Updated name of PPD .

Rationale:

At the time of final approval of this protocol amendment, the PPD was PPD PPD .

Sections affected include:

- Signature of the sponsor's medically responsible person

Modification 2

Increased the number of targeted sites participating in the study.

Rationale:

The number of targeted sites for participation increased from "50 to 75" to "up to 90" sites.

Sections affected include:

- 5.1 – Design overview.

Modification 3

Added new PRO questionnaires and a Social Media Questionnaire.

Rationale:

A Social Media Questionnaire will be used to elicit information about sources of influence on medical decisions. Supplemental PRO Questionnaires will be used to solicit information on possible AEs and to help control potential bias in AE reporting. Text was also added to define triggers for Supplemental PRO Questionnaires. Text was added to clarify that the supplemental PRO tools are used to investigate potential symptoms of hypersensitivity. A larger sample size can be obtained if laboratory test results are used rather than relying on surgical specimens. If only pathology is used, samples from only a subset of patients would be obtained.

Sections affected include:

- 2 – Synopsis (Methodology)
- 5.2.1 – Main endpoints;
- 9.1 – Tabular schedule of evaluations;
- 9.2.2.7 – Twelve months post-procedure (± 4 weeks);
- 9.2.2.8 – Twenty-four months post-procedure (± 4 weeks);
- 9.2.2.9 –Thirty-six months post-procedure (± 4 weeks);
- 9.2.2.10 – Forty-eight months post-procedure (contact;± 4 weeks);
- 9.2.2.11 – Sixty months post-procedure (-4weeks, +1 week) – End of Study;
- 9.2.3.1 – Patient reported outcome data capture system;

- 9.2.3.2 – Patient reported outcome scoring;
- 9.2.3.3 – Patient reported outcome measurement thresholds;
- 10.3 – Endpoints and planned statistical analyses;
- 17.8 – Supplemental PRO Questionnaires;
- 17.9 – Social Media Questions.

Modification 4

Clarified existing and added new laboratory evaluations for hypersensitivity reaction and potential autoimmune disorders**.**

Rationale:

As described in the original protocol, if a subject is diagnosed with an autoimmune disease during the course of the study, her specimen is planned to be used to run an appropriate HLA type. This will be done in consultation with an immunologist and/or rheumatologist and will depend on the specific autoimmune disease diagnosed. A group of control subjects (without the specific autoimmune disease) will be identified and the same HLA type will be run. The size of this control sample will depend on the frequency of the specific HLA type in the population.

An addition to the protocol is the use of HLA type in the evaluation of nickel hypersensitivity. This is distinct from the use of HLA type in autoimmune disease. Recently, it has been found that individuals with the HLA types DRB1, B3, B4 and B5 may be at increased risk of experiencing a reaction to nickel if they have been sensitized. This is very early data, but this presents an opportunity to explore this concept in Study 18894. Accordingly, the existing HLA baseline specimen will be used to run these HLA types on all subjects. If sufficient sample remains, it will be held to use in cases of autoimmune disease (as originally planned); otherwise, it will be re-drawn if additional sample is needed.

Up to Integrated Protocol Version 2.0, serum nickel and titanium levels were evaluated at baseline and 12 months. An additional serum nickel and serum titanium assay will now also be performed at 60 months. Of note, considering that ion release is highest in the first days/weeks following implantation and then reaches very low, steady state release of ions, changes to serum nickel and titanium levels at 5 years would very likely represent exposure to an alternate source of nickel or titanium, and not due to Essure. However, as a blood draw has been added at 60 months, serum nickel and titanium levels will be repeated at 60 months per request of the FDA.

Up to Integrated Protocol Version 2.0, a serum sample was drawn, frozen, and stored for future use in subjects who develop autoimmune diseases during the study (in order to look at their baseline serology). As of Integrated Protocol Version 3.0, this sample will be used to evaluate an inflammatory cytokine panel on all subjects. The panel includes IFN-γ, IL-10, IL-4, TGF-β, TNF-α, p40 subunit (IL-12, IL-23), p35 subunit (IL-12, IL-35), and IL-17. The inflammatory cytokines panel will be run at baseline, 12 months, and 60 months for additional characterization of allergic/hypersensitivity reactions.

Overall, the descriptions of the laboratory tests to evaluate hypersensitivity reactions were clarified in a new subsection of Section 9.6.3 (Further safety), within the descriptions of

safety procedures and variables. The existing descriptions of physical examinations were organized as a separate subsection.

Sections affected include:

- 5.2.1 – Main endpoints;
- 9.1 – Tabular schedule of evaluations;
- 9.2.1 – Screening period;
- 9.2.2.2 – Post-Procedure (at any time during study);
- 9.2.2.4 – One week post-procedure;
- 9.2.2.6 – Three months post-procedure;
- 9.2.2.7 – Twelve months post-procedure (± 4 weeks);
- 9.2.2.8 – Twenty-four months post-procedure (± 4 weeks);
- 9.2.2.9 – Thirty-six months post-procedure (± 4 weeks);
- 9.2.2.10 – Forty-eight months post-procedure (contact; ± 4 weeks);
- 9.2.2.11 – Sixty months post-procedure (-4 wk, +1 wk) (End of Study);
- 9.6.1.1 – Definitions;
- 9.6.3 – Further safety (including new subsection: 9.6.3.1 Laboratory evaluations).

Modification 5

Clarified pathological evaluations and metallurgic studies.

Rationale:

It was determined that the planned methods for characterizing allergic/hypersensitivity reactions, i.e., pathological evaluations and metallurgic studies, will be insufficient, and a laboratory marker strategy was added, as described in Modification 4, for characterizing allergic/hypersensitivity reactions. Some text related to pathological evaluations was edited for clarity as a result of the new assay.

Additional instruction was provided to sites, to place explanted Essure inserts in formalin before sending to pathology laboratory for processing, for consistency.

It was clarified that initially 2 pathologists will evaluate the histological sample, and a 3rd pathologist will evaluate only if the 2 initial results disagree.

Sections affected include:

- 5.2.1 – Main endpoints;
- 9.1 – Tabular schedule of evaluations;
- 9.2.2.2 – Post procedure (at any time during study).

Modification 6

Changed determination of sample size.

Rationale:

Per Bayer decision, the Essure permanent birth control device in the US will no longer be distributed or sold after 31 DEC 2018. Enrollment and sample size will not be set to a fixed number; instead, enrollment at each site will be dependent on availability of Essure. Enrollment in the laparoscopic tubal sterilization arm will be ceased once its enrollment reaches approximately 2:1 laparoscopic tubal sterilization:Essure (anticipated).

Sections affected include:

- 2 – Synopsis (Number of subjects)
- 5.3 – Managing differences in recruitment rates
- 10.4 – Determination of sample size

Modification 7

Separated the variable of "hypersensitivity / allergy / autoimmune disorder" into "hypersensitivity / allergy" and "autoimmune disorder"

Rationale:

For improved clarity and readability, the description of the variable "hypersensitivity / allergy / autoimmune disorder" was updated; the variable of "hypersensitivity / allergy / autoimmune disorder" was separated into "hypersensitivity / allergy" and "autoimmune disorder". There was no modification to study objectives or analysis as a result of this editorial change.

Sections affected include:

- Synopsis – Main variable(s)
- 5.2.1 – Main endpoints

Modification 8

Amended inclusion criterion #2 to clarify age restrictions.

Rationale:

There are no age restrictions in the Instructions For Use for this product.

Sections affected include:

- 2 – Synopsis (Diagnosis and criteria for inclusion);
- 6 – Study Population;
- 6.1 – Inclusion criteria.

Modification 9

Amended inclusion criterion #3 to remove weight restrictions.

Rationale:

There are no weight restrictions in the Instructions For Use for this product.

Sections affected include:

- 2 – Synopsis (Diagnosis and criteria for inclusion);
- 6.1 – Inclusion criteria.

Modification 10

Clarification of intrauterine device procedure.

Rationale:

Intrauterine device removal/placement is not considered a concomitant procedure.

Sections affected include:

- 2 – Synopsis (Diagnosis and criteria for exclusion);
- 6.2 – Exclusion criteria.

Modification 11

Clarification of exclusion of subjects with diseases or conditions that might interfere with the conduct of the study or interpretation of the results.

Rationale:

Subjects with pre-existing conditions such as pelvic pain, autoimmune disease, or menorrhagia may be included at the discretion of the principal investigator.

Sections affected include:

- 2 – Synopsis (Diagnosis and criteria for exclusion);
- 6.2 – Exclusion criteria.

Modification 12

Clarified re-screening procedure.

Rationale:

For subjects considered screening failures, re-screening to enable the subject's participation at a later time point is allowed once.

Sections affected include:

- 6.4.1 – Withdrawal.

Modification 13

Clarified and corrected schedule of evaluations.

Rationale:

Footnotes were added to clarify that the final check of inclusion / exclusion criteria should be conducted during the study procedure period. The physical examination only needs to be performed once, within 6 weeks prior to the procedure unless the subject history has changed. Vital signs are grouped with weight rather than physical examination in the Table. Height was also listed, and a footnote was added to clarify that it will be measured only once, at

screening. Results of pelvic examinations performed within the 6 weeks prior to screening can be used unless the subject history has changed. The frozen serum sample was not a requirement at 24 months and was removed from the Table.

Sections affected include:

- 9.1 – Tabular schedule of evaluations;
- 9.2.1 – Screening period;
- 9.2.2 – Study procedure period;
- 9.2.2.7 – Twelve months post procedure (± 4 weeks);
- 9.2.2.8 – Twenty-four months post-procedure (± 4 weeks);
- 9.2.2.9 – Thirty-six months post procedure (± 4 weeks).

Modification 14

Replaced “gynecological examination” with “pelvic examination.”

Rationale:

In the context of this protocol, a gynecologic examination refers to a pelvic examination, and the text was amended for clarity.

Sections affected include:

- 9.1 – Tabular schedule of evaluations;
- 9.2.1 – Screening period;
- 9.2.2 – Study procedure period;
- 9.6.3.2 – Physical examination

Modification 15

Clarified and corrected procedures during the screening period and study visits.

Rationale:

Any unplanned gynecological procedures will be conducted during the Study Procedure Visit. The AE assessment, alternative contraception (type used) were added to the text for consistency with the Schedule of evaluations at the Study Procedure Visit. The SF-36 was removed from text at three months post-procedure, and AMSS and two intermenstrual bleeding questions added to the text, for consistency with the Schedule of PRO evaluations. Weight and vital signs are measured at each in-person visit.

Sections affected include:

- 9.2.1 – Screening period;
- 9.2.2 – Study procedure period;
- 9.2.2.6 – Three months post-procedure.

Modification 16

Removed post-procedure contact method.

Rationale:

Contact with subject post-procedure is no longer required to be via telephone. The type of contact can include telephone, visit, etc.

Sections affected include:

- 9.1 – Tabular schedule of evaluations;
- 9.2.2.3 – Second placement and conversion to a secondary procedure;
- 9.2.2.4 – One week post-procedure;
- 9.2.2.5 – Confirmation test (Essure group);
- 9.2.2.6 – Three months post-procedure.

Modification 17

Added 48-month contact, 60-month visit, and premature discontinuation (dropout) visit.

Rationale:

Per discussions with the FDA, the existing follow-up period was extended to 5 years. Text was added to clarify the procedure in cases of premature discontinuation (dropout) from the study.

Sections affected include:

- 2 – Synopsis – Test device, Duration of treatment; Methodology; Time point / frame of measurement for primary variable(s);
- 9.1 – Tabular schedule of evaluations;
- 9.2.2.9 – Thirty-six months post-procedure (±4 weeks)
- 9.2.2.10 – Forty-eight months post-procedure (±4 weeks)
- 9.2.2.11 – Sixty months post-procedure (-4 weeks, +1 week) (End of Study)
- 9.2.2.12 – Premature Discontinuation (Dropout) (new section)

Modification 18

Corrected name of End of Study form.

Rationale:

The Study Completion/Termination Visit form referenced in the original protocol should be the End of Study form.

Sections affected include:

- 9.2.2.11 – Sixty months post-procedure (±4weeks).

Modification 19

Amended baseline characteristics.

Rationale:

Eyeglasses have been added to the list of baseline characteristics.

Sections affected include:

- 9.3.3 – Other baseline characteristics.

Modification 20

Added device events to safety definitions.

Rationale:

Text for device events was missing from the original protocol.

Sections affected include:

- 9.6.1.1 – Definitions.

Modification 21

Clarified that only unintended pregnancies are to be considered device failures.

Rationale:

Intentional pregnancy, for example in the case of surrogacy, are not device failures.

Sections affected include:

- 9.6.1.1 – Definitions
- 9.6.2 – Pregnancies

Modification 22

Removed “failed primary procedure / conversion to secondary procedure” as an AESI and reported as an outcome variable.

Rationale:

The variable “Failed primary procedure/ conversion to secondary procedure” is not per se an AE but is an outcome variable. Therefore, it has been moved to Section 9.2.2.3 under “Second placement and conversion to a secondary procedure”.

Sections affected include:

- 9.2.2.3 – Second placement and conversion to a secondary procedure;
- 9.6.1.1 – Definitions.

Modification 23

Clarified procedure complications

Rationale:

To avoid any confusion on treatment of intraoperative, which is a concomitant disease, the item was modified.

Sections affected include:

- 9.6.1.1 – Definitions.

Modification 24

Added detail to reporting of SAEs.

Rationale:

All SAEs require 24-hour reporting. Clarification was needed that SAEs are reported to the Sponsor's designated recipient, not the sponsor.

Sections affected include:

- 9.6.1.4 – Reporting of serious adverse events.

Modification 25

Updated insurance type response at baseline.

Rationale:

The existing response (Medicaid versus commercial) was updated to be consistent with the eCRF (eCRF response: Yes or No).

Sections affected include:

- 10.3 – Endpoints and planned statistical analyses

Modification 26

Added 2 interim analyses

Rationale:

Per discussions with the FDA, an interim analysis is planned to be performed once enrollment has ended, and a second interim analysis once subjects have completed 3 years of follow-up. A new section was added to the protocol to describe these 2 interim analyses.

Sections affected include:

- 2 – Synopsis (Plan for statistical analysis)
- 10.5 – Planned interim analyses (new section);
- 11 – Interim and final post market surveillance report.

Modification 27

Updated adjudication committee details.

Rationale:

The full list of medical coding terms triggering adjudication committee review was not available at the time the original protocol was issued. The list will be distributed outside of the protocol. Text was also amended to clarify the responsibility of the adjudication committee in the event that an AE is possibly due to hypersensitivity or an allergic reaction.

Sections affected include:

- 14.3 – Adjudication Committee.

16.2.2 Changes to the protocol text

Changes to Protocol Amendment 2 are detailed in a separate Tracked Changes document.

16.3 Amendment 3

Amendment 3 (dated 31 JUL 2020) is an amendment to Protocol Amendment 2 dated 25 OCT 2018. Changes to the protocol include:

- Additional interim analysis
- Protocol deviations due to COVID-19

Editorial corrections such as abbreviations and capitalization changes will not be detailed.

16.3.1 Overview of changes

Modification 1 Additional interim analysis

An additional interim analysis will be initiated after all subjects complete 1 year of follow-up (1-year interim analysis).

Rationale: The 1-year interim analysis has been added at the request of the FDA.

Sections affected include:

- Section 2.0 Synopsis - Plan for statistical analysis
- Section 10.5 Planned interim analyses

Modification 2 Protocol deviations due to COVID-19

Text was added to describe how the potential impact of COVID-19 to study conduct and data collection processes will be managed.

Sections affected include:

- Section 2.0 Synopsis - Methodology
- Section 9.1 Tabular schedule of evaluations

16.3.2 Changes to the protocol text

Changes to Protocol Amendment 3 are detailed in a separate Tracked Changes document.

16.4 Amendment 4 – New

Amendment 4 (dated 28 JUN 2022) is an amendment to Protocol Amendment 3 dated 31 JUL 2020. Changes to the protocol include:

- Conclusion of DMC role
- Year 3 interim analysis details related to serology and pathology findings

Editorial corrections such as abbreviations and capitalization changes will not be detailed.

16.4.1 Overview of changes

Modification 1 Conclusion of DMC role

Text referring to DMC has been deleted. The role of the DMC was concluded as agreed among the FDA, DMC, and Bayer.

Sections affected include:

- Section 2.0 Synopsis – Data Monitoring Committee
- Section 11 Interim and final post market surveillance report
- Section 14.2 Data Monitoring Committee

Modification 2 Evaluation of propensity score baseline characteristics at interim analysis and end of study.

Sections affected include:

- Section 2.0 Synopsis – Plan for statistical analysis
- Section 10.5 Planned interim analyses

Rationale: The balance of propensity score characteristics will be assessed at the 3-year interim analysis and end of study to ensure balance of baseline characteristics throughout the study.

Modification 3 Note added that sites are encouraged to contact subjects lost to follow-up annually regarding continued participation in the study.

Sections affected include:

- Section 6.4 – Withdrawal of subjects from study

Modification 4 Year 3 interim analysis details related to device removals, serology, and pathology/histologic findings.

Sections affected include:

- 10.5 Planned interim analyses

Device removals (including outcomes/resolutions), serology data, pathologic/histologic findings of fallopian tubes, and individual dossiers for cases of potential hypersensitivity/allergy/autoimmune reactions will be included in the interim analysis at the end of the 3-year follow-up period.

Rationale: The inclusion of device removals, serology data, and pathologic/histologic findings in the 3-year follow-up analysis has been added at the request of the FDA.

16.4.2 Changes to the protocol text

Changes to Protocol Amendment 4 are detailed in a separate Tracked Changes document.

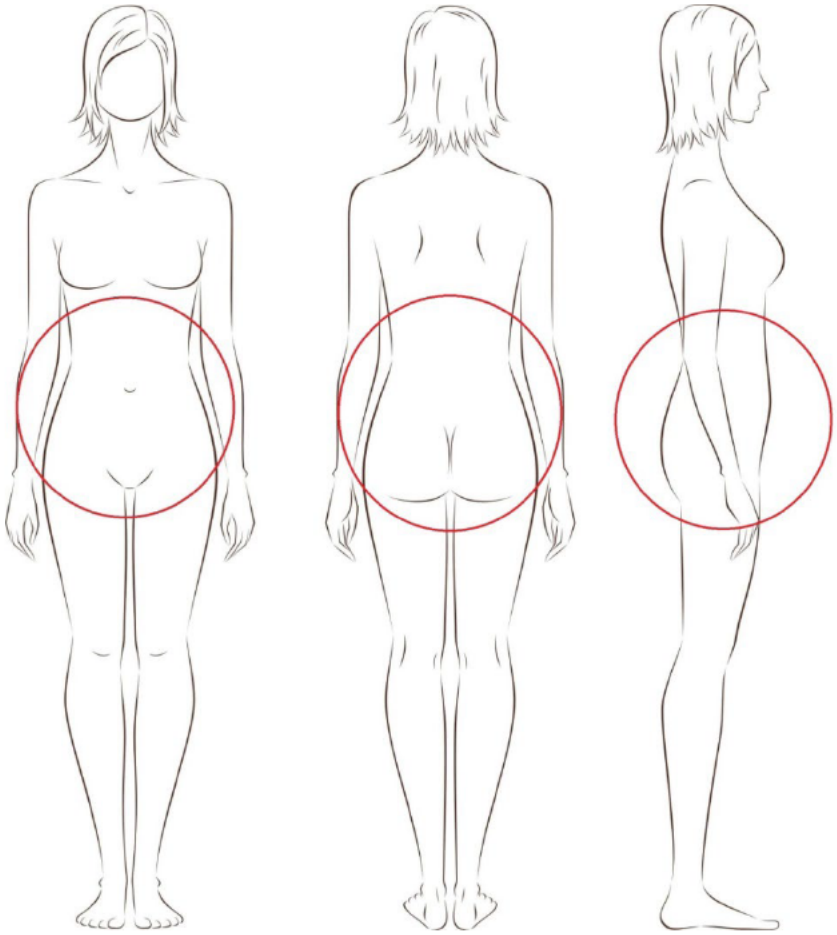
17. Appendices

17.1 Screening question for lower abdominal / pelvic pain

Pain Screener

Section modified by Amendment 1 (Section 16.1).

Did you experience pain in your pelvic area or in your lower abdomen during the past 7 days?	❍ Yes ❍ No



17.2 PROMIS scale version 1.0 – Pain Intensity Short Form 3a

Please respond to each item by marking one box per row.

	In the past 7 days…	Had no pain	Mild	Moderate	Severe	Very severe
PAINQ3	How intense was your pain at its worst?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINQU8	How intense was your average pain?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		No pain	**Mild**	**Moderate**	**Severe**	**Very severe**
PAINQU21	What is your level of pain right now?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

17.3 PROMIS scale version 1.0 – Pain Interference Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
1	How much did pain interfere with your day to day activities?	☐	☐	☐	☐	☐
2	How much did pain interfere with work around the home?.....	☐	☐	☐	☐	☐
3	How much did pain interfere with your ability to participate in social activities?	☐	☐	☐	☐	☐
4	How much did pain interfere with your household chores?.....	☐	☐	☐	☐	☐
5	How much did pain interfere with the things you usually do for fun?	☐	☐	☐	☐	☐
6	How much did pain interfere with your enjoyment of social activities?.....	☐	☐	☐	☐	☐
7	How much did pain interfere with your enjoyment of life?.....	☐	☐	☐	☐	☐
8	How much did pain interfere with your family life?.....	☐	☐	☐	☐	☐

17.4 Aberdeen Menorrhagia Severity Scale

The following questions ask you about your period during the last three months. Please give a single answer for every question.

1. On average, during the last three months, for how many days did your period last?

○ Less than 3 days
○ Between 3 and 7 days
○ Between 8 and 10 days
○ More than 10 days

2. On average, during the last three months, were your periods regular or irregular?

○ Regular
○ Irregular

3. On average, during the last three months, how many days were there from the first day of a period to the first day of the next period?

○ Less than 21 days
○ Between 21 and 35 days
○ More than 35 days

4. On average, during the last three months, would you describe your periods as?

○ Light
○ Moderate
○ Heavy
○ Very Heavy

5. On average, during the last three months, for how many days of each period was the bleeding heavy?

○ Not heavy
○ Between 1 and 3 days
○ Between 4 and 6 days
○ Between 7 and 10 days
○ More than 10 days

6. On average, during the last three months, have your periods been associated with any pain?

○ No pain at all
○ Slight pain
○ Moderate pain
○ Severe pain
○ Very severe pain

7. On average, during the last three months, have you had any problems with soiling / staining any of the following because of your periods?

○ Soiling / staining of your outerclothes / overgarments
○ Soiling / staining of your bed linen
○ Soiling / staining of your upholstery

8. On average, during the last three months, have your periods prevented you from carrying out your work, housework or other daily activities?

○ No, not at all
○ I could continue to work, but my work suffered
○ Yes, usually with no more than one day with each period
○ Yes, usually more than one day with each period

9. On average, during the last three months, have you been confined to bed with each period?

○ No, not at all
○ Yes, usually for part of one day
○ Yes, usually for the whole of one day
○ Yes, usually for more than one day 0

10. On average, during the last three months, have your leisure activities been affected by your heavy periods? (including sport, hobbies, social life)

○ Not affected by heavy periods
○ Mildly affected by heavy periods
○ Moderately affected by heavy periods
○ Severely affected by heavy periods
○ Heavy periods have prevented any social life at all

11. On average, during the last three months, has your sex life been affected by your heavy periods?

○ Not affected by heavy periods
○ Mildly affected by heavy periods
○ Moderately affected by heavy periods
○ Severely affected by heavy periods
○ Heavy periods prevented any sex life at all
○ Does not apply

12. On average, how many pads might you use on the heaviest day of your period?

○ No pads at all
○ Between 1 and 5 pads
○ Between 6 and 10 pads
○ Between 11 and 15 pads
○ More than 15 pads

13. At any time during the last three months, did you require more than one form of protection at the same time (Not including mini pads or mini pant-liners)?

○ No
○ Tampon and pad together
○ Two pads together
○ Tampon and two pads together
○ More protection than this (i.e., disposable nappies, towels etc.)

17.5 Intermenstrual questions

Intermenstrual questions

Section modified by Amendment 1 (Section 16.1).

At any time during the last 3 months did you experience any bleeding or spotting in between your periods?	❍ No ❍ Yes
• If yes, how much did it interfere with your normal daily activities?	❍ Not at all ❍ Mildly ❍ Moderately ❍ Severely

17.6 Short Form – 36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

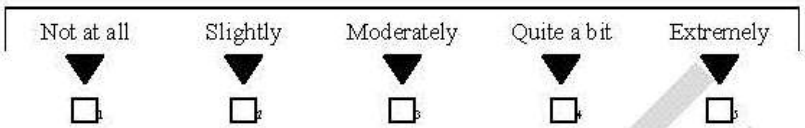
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

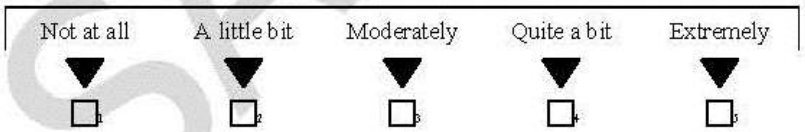
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

17.7 Fibromyalgia Survey Questionnaire

17.8 Supplemental PRO Questionnaires

Section added by Amendment 2 (Modification 3).

17.8.1 Mental Health Questions – Patient Health Questionnaire-2 (Validated)

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care. 2003;41:1284-92.

Thibault JM, Prasaad Steiner, RW. Efficient identification of adults with depression and dementia. American Family Physician. 2004;7(6)

1. **Over the past two weeks, how often have you been bothered by any of the following problems?**

   - **Little interest or pleasure in doing things.**
     - 0 = Not at all
     - 1 = Several days
     - 2 = More than half the days
     - 3 = Nearly every day

   - **Feeling down, depressed, or hopeless.**
     - 0 = Not at all
     - 1 = Several days
     - 2 = More than half the days
     - 3 = Nearly every day

   Total point score: _____

   Score interpretation:

Score	Probability of major depressive disorder	Probability of any depressive disorder
1	15.4%	36.9%
2	21.1%	48.3%
3	38.4%	75.0%
4	45.5%	81.2%
5	56.4%	84.6%
6	78.6%	92.9%

A total response ≥ 3 for the set of questions above will result in notification to the investigator.

2. **Over the last two weeks, how often have you been bothered by the following problems?**
   - **Feeling nervous, anxious or on edge**
     - 0 = Not at all
     - 1 = Several days

- 2 = More than half the days
- 3 = Nearly every day

- **Not being able to stop or control worrying**
  - 0 = Not at all
  - 1 = Several days
  - 2 = More than half the days
  - 3 = Nearly every day

A total response ≥ 3 for the set of questions above will result in notification to the investigator.

17.8.2 Pruritus – 5D Itch Scale (Validated) *Modified for study purpose*

Elman S, Hynan LS, Gabriel V et al. The 5-D itch scale a new measure of pruritus. British Journal of Dermatology. 2010;162(3):587-93.

1. **In the past 12 months, have you experienced any unexplained itching?**
   - Yes/No
2. **If yes, please rate the impact of your unexplained itching on the following activities since the last year.**
   - Sleep (includes falling asleep and staying asleep)
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Leisure/Social
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Housework/Errands
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Work/School
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity

4. Frequently affects this activity
5. Always affects this activity

Preliminary threshold of any response ≥ 4 will result in notification to the investigator. This will also trigger need for labs.

17.8.3 Rash

Developed through POET Internal Discussions

1. **In the past 12 months, have you had an unexplained rash?**
   - Yes/No
2. **If yes, please rate the impact of your unexplained rash on the following activities since the last year.**
   - Sleep (includes falling asleep and staying asleep)
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Leisure/Social
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Housework/Errands
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Work/School
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity

Preliminary threshold of any response ≥ 4 will result in notification to the investigator. This will also trigger need for labs.

17.8.4 Pain in extremities

Developed through POET Internal Discussions

1. **In the last 12 months, have you experienced unexplained pain in your arms and/or legs (e.g. joints or muscles)?**
   - Yes/No
2. **If yes, please rate the impact of the unexplained pain you feel in your arms and/or legs (e.g. joints or muscles) on the following activities.**
   - Sleep(includes falling asleep and staying asleep)
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Leisure/Social
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Housework/Errands
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity
   - Work/School
     1. Never affects this activity
     2. Rarely affects this activity
     3. Occasionally affects this activity
     4. Frequently affects this activity
     5. Always affects this activity

Preliminary threshold of any response ≥ 4 will result in notification to the investigator. This will also trigger need for labs.

17.8.5 Hair Loss

Developed through POET Internal discussions

1. **In the past 12 months, have you experienced hair loss?**
   - Yes/No
2. **If yes, what is the severity of your hair loss?**
   - 1 (minimal)

- 2 (mild)
- 3 (moderate)
- 4 (severe)
- 5 (very severe)

17.8.6 Nausea/Vomiting

Developed through POET Internal Discussions

1. **In the past 12 months, did you have any unexplained nausea/vomiting?**
   - Yes/No
2. **If yes, how bothersome has this unexplained nausea/vomiting been to your quality of life?**
   - 1 (minimal)
   - 2 (mild)
   - 3 (moderate)
   - 4 (severe)
   - 5 (very severe)

Preliminary threshold of any response ≥ 3 will result in notification to the investigator.

17.8.7 Dysgeusia (distortion of sense of taste)

Developed through POET Internal Discussions

1. **In the past 12 months, have you experienced changes in your perception of taste?**
   - Yes/No
2. **If yes, how bothersome has this experience been?**
   - 1 (minimal)
   - 2 (mild)
   - 3 (moderate)
   - 4 (severe)
   - 5 (very severe)

17.8.8 Fatigue – Fatigue Assessment Scale (Validated) *Modified for study purpose*

Michielsen H, De Vries J, Heck G. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. Journal of Psychosomatic Research. 2003;54(1):345-52.

1. **I am bothered by fatigue**
   1. Never
   2. Sometimes

3. Regularly
4. Often
5. Always

2. I get tired very quickly

1. Never
2. Sometimes
3. Regularly
4. Often
5. Always

3. I don't do much during the day

1. Never
2. Sometimes
3. Regularly
4. Often
5. Always

4. I have enough energy for everyday life

1. Never
2. Sometimes
3. Regularly
4. Often
5. Always

Preliminary threshold of any response ≥ 4 will result in notification to the investigator.

17.8.9 Dental Care

Developed through POET Internal Discussions

1. In the past 12 months, have you experienced any of the following dental problems? (check all that apply)

- Tooth removal
- Tooth loss
- Tooth pain
- Tooth decay (cavities)
- Gum problems

17.8.10 Weight change

Developed through POET Internal Discussions

1. How has your weight changed over the past 12 months?

- Weight loss of more than 10 pounds

- Weight loss of 5 – 10 pounds
- Weight loss of less than 5 pounds
- No change in weight
- Weight gain of less than 5 pounds
- Weight gain of 5 – 10 pounds
- Weight gain of more than 10 pounds

17.9 Social Media Questions

Section modified by Amendment 2 (Modification 3).

Social Media Questions *To be asked at 60 months (or Premature Discontinuation visit if applicable)*

Please answer the following questions about your experiences during the time you have participated in this study.

1. **In general, how much do the following influence your health care related decisions:**

	No Influence	Little Influence	Moderate Influence	Large Influence	Very Large Influence
Your Physician	0	1	2	3	4
Your Social Media feed (e.g. Facebook, Instagram, Twitter, Internet Forums, Blogs)	0	1	2	3	4
Your own Internet Research of medical sites (e.g. Medscape, Mayo Clinic, etc.)	0	1	2	3	4
Television and/or Radio	0	1	2	3	4
Family and Friends	0	1	2	3	4
Other: (specify)	0	1	2	3	4

2. **How much did the following influence your decision on which sterilization technique (Essure or laparoscopic tubal sterilization) to choose:**

	No Influence	Little Influence	Moderate Influence	Large Influence	Very Large Influence
Your Physician	0	1	2	3	4
Your own Social Media feed (e.g. Facebook, Instagram, Twitter, Internet Forums, Blogs)	0	1	2	3	4
Your own Internet Research of medical sites (e.g. Medscape, Mayo Clinic, etc.)	0	1	2	3	4
Television and/or Radio	0	1	2	3	4
Family and Friends	0	1	2	3	4
Other: (specify)	0	1	2	3	4

3. **How would you best describe your social media use (e.g. Facebook, Instagram, Twitter, Internet Forums, Blogs)?**
    a. none
    b. 0–2 hours per day
    c. > 2–4 hours per day
    d. > 4–6 hours per day
    e. > 6–8 hours per day
    f. > 8 or more hours per day

4. **How much has social media (e.g. Facebook, Instagram, Twitter, Internet Forums, Blogs) influenced whether or not you reported side effects after your sterilization procedure?**
    a. (no influence)
    b. (minimal influence)
    c. (moderate influence)
    d. (large influence)
    e. (very large influence)

5. **How much has internet research (e.g. Medscape, Mayo clinic, etc.) influenced whether or not you reported side effects after your sterilization procedure?**
    a. (no influence)
    b. (minimal influence)
    c. (moderate influence)
    d. (large influence)
    e. (very large influence)

6. **Were you ever encouraged to report side effects by someone outside of the study (e.g. family, friends, social media contact, etc.) after your sterilization procedure?**
    a. Yes
    b. No