

<b>Document Type:</b>	Statistical Analysis Plan
<b>Official Title:</b>	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
<b>NCT Number:</b>	NCT03127722
<b>Document Date:</b>	26 Feb 2021

<b>Title   Statistical Analysis Plan for Essure Study 18894</b>	
<b>BHC Study Drug</b>	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
<b>Study Purpose:</b>	Postmarket surveillance
<b>IMPACT No.:</b>	18894 <b>Protocol Date:</b> 4.0, 31 Jul 2020,
<b>Version, Date:</b>	Final 4.0, 26 Feb 2021
PPD [REDACTED]	PPD [REDACTED]
PPD [REDACTED]	PPD [REDACTED]

**Confidential**

The information provided in this document is strictly confidential and is intended solely for the guidance of the study. Reproduction or disclosure of this document, whether in part or in full, to parties not associated with the study or its use for any other purpose without the prior written consent of the sponsor is not permitted.

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

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

## Statistical Analysis Plan Approval Form

Study Protocol 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

Study Protocol Identifier including Version No. and Date\*

Version 4.0, 31 Jul 2020

Statistical Analysis Plan (SAP) Version and Date

Version 4.0, 26 Feb 2021

SAP includes SAP Table Specifications?

yes ☒ no ☐

\* if no approved Study Protocol is available (e.g. SAP required due to Health Authority request before protocol finalization), mention the approved Study Concept

I have read and approve the SAP / SAP Amendment referred above.

	Name	Signature	Date
<b>Author:</b>			
PPD [redacted]	PPD [redacted]	PPD [redacted]	PPD [redacted]
PPD [redacted]	PPD [redacted]	PPD [redacted]	PPD [redacted]
<b>Approved by:</b>			
PPD [redacted] 1)	PPD [redacted]	PPD [redacted]	PPD [redacted]
PPD [redacted]	PPD [redacted]	PPD [redacted]	PPD [redacted]
PPD [redacted]	PPD [redacted]		
PPD [redacted]	PPD [redacted]		

## Table of Contents

1	Introduction .....	4
1.1	Background .....	4
1.2	Protocol version and amendments .....	4
1.3	Applicable standards .....	4
2	Study objectives .....	4
3	Study design .....	5
4	General statistical considerations .....	6
4.1	Determination of Sample Size .....	6
4.2	General principles .....	6
4.3	Handling of loss to follow-up, premature discontinuation, and censoring .....	7
4.4	Handling of missing data .....	7
4.4.1	Date of last contact .....	7
4.4.2	Study procedure .....	7
4.4.3	Concomitant medication .....	8
4.4.4	Surgical intervention and other concomitant procedures .....	9
4.4.5	Main outcome events .....	9
4.4.6	Other missing values .....	9
4.5	Interim analyses and data monitoring .....	10
4.5.1	Interim and final post market surveillance report .....	10
4.5.2	Data monitoring .....	10
4.6	Data rules .....	10
4.6.1	Baseline .....	11
4.6.2	Subject validity .....	11
4.6.3	Visit labels .....	11
5	Analysis sets .....	12
5.1	Assignment of analysis sets .....	12
5.2	Treatment groups .....	13
6	Statistical methodology .....	13
6.1	Population characteristics .....	13
6.1.1	Background data .....	13
6.1.2	Treatment characteristics .....	14
6.1.3	Risk period definition .....	14
6.2	Adjudication .....	15
6.3	Protocol deviations .....	15
6.4	Outcome endpoints and variables .....	15
6.4.1	Subject Incidence .....	20
6.4.2	Exposure-adjusted subject incidence .....	20
6.4.3	Kaplan-Meier estimates .....	20
6.4.4	Hazard ratios .....	20
6.4.5	Procedure failures that are converted to alternative permanent sterilizations .....	21
6.4.6	Reporting of longitudinal data .....	21
6.5	Additional safety analysis .....	21
6.5.1	Adverse events .....	21
6.5.1	Device events .....	23
6.5.2	Prior and concomitant therapy .....	23
6.6	Confounder or bias adjusted analyses .....	23
6.6.1	Development of propensity score .....	24
6.6.2	Analysis based on different analysis set .....	25
6.7	Subgroup analysis .....	26
6.8	Sensitivity analyses .....	26
7	Interim Analysis .....	26

## Abbreviations

AE	Adverse event
AIC	Akaike information criterion
ANOVA	Analysis of variance
ATC	Anatomic Therapeutic Chemical classification system
bid	bis in die, twice daily
BMI	Body mass index
CI	Confidence interval
CRF	Case Report Form
DMC	Data Monitoring Committee
eg	exempli gratia, for example
FSQ	Fibromyalgia Survey Questionnaire
HC	Health Care
ID	Identifier
ie	Id est, that is
LLT	Low level term
LOS	Length of stay
MDR	Medical Device Reporting
MedDRA	Medical Dictionary for Regulatory Activities
MLG	Medical Labeling Grouping
NA	Not available
PSUR	Periodic Safety Update Report
PS	Propensity score
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SN	Study number
SOC	System Organ Class
SOP	Standard Operating Procedure
TM	Trademark
ULN	Upper limit of normal
WHO	World Health Organization

## **1 Introduction**

This statistical analysis plan describes the study objective, analysis population, and final statistical analysis methods for the study 18894.

### **1.1 Background**

Bayer is conducting this study to yield post-authorization information in Essure and comparator group subjects under real-life conditions.

### **1.2 Protocol version and amendments**

- Protocol, Final version 1.0, 24 JAN 2017
- Protocol, Amendment 1.0, 12 OCT 2017
- Protocol, Amendment 2.0, 25 OCT 2018
- Protocol, Amendment 3.0, 31 JUL 2020
- eCRF, Final version 1.0, 01MAR 2017
- eCRF, Final version 2.0, 07 JUL 2017

### **1.3 Applicable standards**

- Bayer Health Care: Company Sponsored Non-Interventional Studies (NIS), Global Standard Operating Procedure, SOP ID: BSP-SOP-041, Version 2, 2011
- Bayer Health Care: Development Pharma, Standard Operating Procedure, Observational Studies, SOP ID: BPD-SOP-041, Version 3.0, 07 APR 2014
- GNIS Global Standard Tables, Version 1.0, 17 JAN 2012
- Some of the eCRFs were created new and are non-standard
- Some of the eCRFs are modified standard (started with standard and changed)

## **2 Study objectives**

The 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

### **3 Study design**

This study is a multicenter, open-label, non-randomized, continuous enrollment, prospective, observational postmarket surveillance study.

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 ( $\pm 2$  weeks), 12 months ( $\pm 4$  weeks), 24 months ( $\pm 4$  weeks), 36 months ( $\pm 4$  weeks), 48 months ( $\pm 4$  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.

## **4 General statistical considerations**

All issues concerning subject validity, data consistency checks, 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 this Statistical Analysis Plan.

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 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.

### **4.1 Determination of Sample Size**

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).

### **4.2 General principles**

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. The level of precision is defined in the table and figure shells with place holders for decimal places. Selected continuous variables will be categorized in a clinically meaningful way.

Unless specified otherwise, subjects in the analyses will be presented according to their initial index event.

The main analyses will be performed on the full analysis set as well as on a PS confounder-adjusted population of the full analysis set in order to adjust for measured confounding. Main analyses will also be performed in the full analysis set, adjusted full analysis set, reliance set, and adjusted reliance set. Details for derivation and adjustment are described in Sections 5.1 and 6.5.1.

The statistical evaluation will be performed using the software package SAS release 9.3 or higher (SAS Institute Inc., Cary, North Carolina, USA). Where propensity score design is conducted, SAS, the R package or STATA may be used.

All MedDRA terms or standardized MedDRA queries (SMQs) which are mentioned in this document are taken from the most updated MedDRA version. At the time of the analysis MedDRA concepts may have been changed; in this event, the validity of the terms and SMQs will be re-checked.

### **4.3 Handling of loss to follow-up, premature discontinuation, and censoring**

Subjects who leave the study before reaching the study completion assessment five years after start of the sterilization procedure will be included in the analysis populations, since the analyses are based on all subjects who attempt sterilization.

For subjects who attempt two sterilization methods, or have any hysterectomy (subtotal, total or radical), or have Essure complete removal using a salpingectomy, or device removal not accompanied by sterilization procedure, their data will be censored for analysis purpose on the earliest date of second sterilization method, hysterectomy surgery date, or Essure removal date, for the primary analysis.

Data will be collected for all the subjects until the end of study or early termination.

### **4.4 Handling of missing data**

#### **4.4.1 Date of last contact**

If the subject dies, date of last contact will be the death date. Otherwise, date of last contact will be considered as the maximum of

- Date of end of study;
- Latest AE start date;
- Latest date for follow-up visits.

#### **4.4.2 Study procedure**

##### **Definition of index event and start of observation**

Subjects will be allocated to either hysteroscopic sterilization (Essure) or laparoscopic tubal sterilization by decision of the physician/subject on the basis of baseline characteristics, medical history, preferences, and other criteria. The date of the initial procedure is considered the index date for the study (Day 0).

## **Stop dates**

If the stop dates for AEs are completely missing, the event will be considered to be ongoing at the time of end of study. Completely missing stop dates will not be imputed.

Partially missing stop dates will be set to the latest logically possible date:

- In case that only the day is missing, last day of the month will be imputed;
- In case that the day and the month is missing (i.e., only the year is available) the day and month will be imputed as December 31.
- If the imputed dates are after the date of last contact, it will be set to the date of last contact.

### **4.4.3 Concomitant medication**

For concomitant medication, the following imputation rules will be applied:

#### **Start of concomitant medication**

Partially missing start dates for concomitant medication will be set to the earliest logically possible date:

- In case that only the day is missing, the date will be imputed as the first day of the month.
- In case that the day and the month are missing, i.e. only the year is available the day and month will be imputed as January 1.
- In the cases where the start date is missing completely, it will be replaced with the minimum of January 1 of the year of the initial visit

#### **Stop of concomitant medication**

Partially missing stop dates will be set to the latest logically possible date:

- In case that only the day is missing, it will be imputed as the last day of the month;
- In case that only the day and the month are missing (i.e., only the year is available) it will be imputed as December 31.
- If the imputed dates are after the last date of contact, it will be set to the last date of contact.
- If the stop dates are completely missing, the medication will be considered as ongoing at the time of end of study.

#### **4.4.4 Surgical intervention and other concomitant procedures**

For women who undergo surgical intervention (including “insert removal” and hysterectomy) or other concomitant procedures after undergoing the initial sterilization the following imputation rules will be applied:

##### **Definition of surgical intervention**

Partially missing dates for surgical intervention will be set to the earliest logically possible date:

- In case that only the day is missing, the date will be imputed as the first day of the month.
- In case that the day and the month are missing, i.e. only the year is available the day and month will be imputed by January 1.
- If the imputed surgical date is before the index date, it will set to the index date.

#### **4.4.5 Main outcome events**

Incomplete start dates of outcome events for the time to event analyses will be imputed as follows:

- In case that only the day is missing, the date will be imputed as the first day of the month.
- In case that the day and the month are missing (i.e. only the year is available) the day and month will be imputed as January 1.
- In case the event start date is missing completely, index event date will be used as start date.
- If the imputed start date is before the index date, it will set to the index date.

Incomplete stop dates of outcome events for the time to event analyses will be imputed as follows:

- In case that only the day is missing, it will be imputed with last day of the month;
- In case that the day and the month are missing (i.e., only the year is available) it will be imputed as December 31.
- If the imputed dates are after the last date of contact, it will be set to the last date of contact.
- If the stop dates are completely missing, the event will be considered as ongoing at the time of end of study.

#### **4.4.6 Other missing values**

Other missing values will not be imputed. Frequency tables for categorical data will include the number of missing values as additional categories. Percentages will be calculated as proportion of each category including the category of missing values.

## **4.5 Interim analyses and data monitoring**

### **4.5.1 Interim and final post market surveillance report**

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 on September 4, 2016.

Per FDA's final guidance document on Postmarket Surveillance issued on May 16, 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 patients enrolled (to be updated after submission of each interim report).
- Interim summary data and/or analyses thereof when appropriate to protect the public health, for example when interim results raise safety concerns or may otherwise impact treatment.
- Interim summary data and/or analyses thereof when statistically and methodologically appropriate and mutually agreed upon by FDA and Bayer, to be negotiated at such time.

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

When recruitment is finalized, the Propensity Score (PS) development will start. For this purpose, an outcome-blinded party independent to the conduct of the study will receive all baseline data of subjects together with their initial treatment allocation (at index).

The independent party will generate a proposal to proceed on the basis of the data available. This will also include assessments on the overlap of the PS density functions for the treatments, and its impact on the adequacy of analyses planned. The generation of the score will be documented with all decisions taken (variables selected for inclusion in the model, procedures to achieve balance, (matching procedures (caliper distance) and final model).

This proposal will subsequently be discussed with the FDA.

### **4.5.2 Data monitoring**

A DMC will be assembled at the beginning of the study. The DMC members will be independent of the sponsor and have no serious conflict of interest. The roles and responsibilities are defined in the DMC Charter.

## **4.6 Data rules**

Medical texts and device events will be coded with the most recent MedDRA version while concomitant medication will be coded by the WHO drug dictionary.

Concomitant medication comprises all medications which started on or after the index date as well as all medications which begun before the index date with a stop date after the index date or still ongoing at end of study.

#### **4.6.1 Baseline**

Baseline is generally defined as the last available value at or before the index event.

#### **4.6.2 Subject validity**

A subject will be entirely excluded from all analyses if

- she has not signed the informed consent form,

Data of subjects withdrawing their consent for further study participation will be used up to the date of withdrawal.

#### **4.6.3 Visit labels**

##### **General Rules**

For all the variables analyzed by visits, the values at scheduled visits will be used if available. If values at scheduled visits are missing but values are available at an associated unscheduled visit, the value from the closest unscheduled visit will be used to the scheduled visit.

If there are no values at scheduled or unscheduled visits, it will be considered as missing.

A value from the discontinuation visit (for discontinued subjects) will be assigned to the next scheduled visit (for the particular assessment per protocol) after the last visit the subject has completed.

##### **Rules for subjects who have a second placement attempt**

For subjects who have a second placement procedure performed and data are available based on both placement procedures, all study assessments should be performed for the second placement and the analysis will be based on the scheduled visits for the second placement for the summary purpose. Unless otherwise specified. Particularly, the following rules are applied:

- After the second placement procedure, the 1-week post-procedure telephone 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 telephone 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 telephone 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 telephone contact, then the 3-month telephone 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 (ie, 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.
- 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.

## **5 Analysis sets**

### **5.1 Assignment of 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 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 (FAS) 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 Full Analysis Set, but based on propensity score confounder-adjusted population, see Section [6.5.1](#).

#### **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 propensity score confounder-adjusted population, a subject will be included if both she and her matched partner are included in the Reliance Set.

## 5.2 Treatment groups

Subjects will be analyzed in the following two treatment groups:

### Essure

- Subjects who initially attempted the Essure insertion procedure

### Laparoscopic tubal sterilization

- Subjects who initially attempted the laparoscopic tubal sterilization procedure

## 6 Statistical methodology

### 6.1 Population characteristics

#### 6.1.1 Background data

The numbers of subjects enrolled and included in the analysis populations will be tabulated by site. The reasons for subjects excluded from the analysis populations will also be tabulated.

The descriptive analysis will be performed for the baseline variables. All background data such as subject demographics, medical history, index event, risk factors, concomitant diseases and conditions as well as concomitant medication will be described by presenting frequencies and/or summary statistics. [Table 1](#) lists baseline variables to be presented for descriptive analysis. Tables on prior medication, concomitant medication will show frequencies using the WHO Drug Dictionary Version Q1 2016, or later if updated during the study, and the Anatomical Therapeutic Chemical (ATC) Classification codes.

**Table 1 - Baseline Variables**

	Endpoint/Variable
Demography	Age, ethnicity, race, employment status, occupation, hobbies, years of education, university/college degree, health insurance
Reproductive and Menstrual History	Age at menarche, number pregnancies, number ectopic pregnancies, number births, number vaginal births, number caesarean births, Time since last birth/abortion, miscarriage or live birth result in genetic abnormalities, absence of menstrual withdrawal bleeding during last 6 months, dysmenorrhea during last 6 months, intracyclic bleeding during last 6 months, unsuccessfully attempted to conceive, ever experienced premature labor, ever experienced premature delivery, ever experienced premature rupture of membranes, ever had dysmenorrhea, ever had pelvic pain not related to menses, ever had endometriosis, ever had dyspareunia, ever had adenomyosis, ever had fibroids, ever had pelvis inflammatory disease, ever had cone biopsy, ever had loop electrosurgical

	excision procedure, ever had sexually transmitted disease, ever had ovarian cyst, ever had breast cancer, ever had ovarian cancer, prescribed medication to control bleeding in last 2 years, prescribed medication to control lower abdominal pain in last 2 years,
Contraceptive Method at Baseline	Primary method used for contraception, duration of the contraceptive method used.
Abdominal/Pelvic Surgical History	Prior abdominal surgery (other than cesarean section), number of prior abdominal surgeries, time since most recent abdominal surgery, type of abdominal or pelvis surgery
Medical History	Type of medical history, dental history, history of depression, remarkable psychological history, victim of sexual abuse, positive family history of autoimmune disease, history of allergic/hypersensitive reactions, type of allergic/hypersensitive reactions, etiology of allergic/hypersensitive reactions, history of autoimmune like symptoms, type of autoimmune like symptoms, visited specialist, cosmetic permanent implants and/or piercings, medical implants, type of medical implants, dental and tattoo history, wear eyeglasses
Substance Use	Cigarette smoking status, cigarettes per day, duration of cigarette smoker, status of other tobacco habits, type of other habitual tobacco use, alcohol consumption status
Abdominal and Pelvic Exam	remarkable pelvic exam
Prior Medication	Type of medication, main indication for medication
Procedure Physician/Supervising Physician Characteristics	Have experience with Essure, number of Essure System placements in last month, last 12 months, total, successfully completed Essure System training, have experience with laparoscopic tubal sterilization, number of laparoscopic tubal sterilizations in last month, number of laparoscopic tubal sterilizations in last 12 months and total, physician specialty, years after graduating residency, facility/setting and percentages of physician who had a supervising physician for performing the sterilization

P-values for the differences between two groups will be given for flagging of baseline balance uncertainty. For continuous variables the t-test or Wilcoxon test will be used and for categorical variables the Chi-square test will be used.

### 6.1.2 Treatment characteristics

Characteristics describing the procedure will be tabulated by appropriate means.

### 6.1.3 Risk period definition

The safety outcomes analyzed are those occurring in the at-risk-period defined as the time from the index day (Day 0) until a specified censoring date as defined in Section 4.4. The censoring date is the earliest date of second sterilization method, hysterectomy surgery date, Essure removal date, or the date of hormonal manipulation start date for the primary analysis.

For some bleeding analyses the risk period will be restricted. For example, in the Essure group hormonal contraception is expected at least until the subjects are told to rely on Essure for permanent contraception. To have comparable risk periods in the two groups a similar restriction will be applied to the laparoscopic tubal sterilization group.

## 6.2 Adjudication

Adjudication will be discussed by the adjudication committee. Adverse events determined to constitute a validated outcome will be included in the analyses and those determined not to constitute a validated outcome will be excluded. There will also be a tabulation of the original assessment of events (prior to adjudication) considering the adjudicated, validated outcome.

## 6.3 Protocol deviations

Protocol deviations will be listed and summarized for all patients within the Full analysis set.

## 6.4 Outcome endpoints and variables

The main objective of this observational study is to evaluate under routine clinical practice conditions the incidence of important treatment-emergent AEs under hysteroscopic sterilization (Essure) and laparoscopic tubal sterilization. An AE is considered as treatment-emergent when it starts or worsens on or after the index date and up to the date of subject withdrawal or the censoring date, as described in Sections 4.3 and 6.1.3.

The outcome endpoint and variables are presented in Table 2. The descriptive analysis will be performed for all the variables listed below and the comparative analysis will be performed only for the main endpoints.

For the main endpoints, the subject incidence (regardless of the time each subject is “at risk”) is the number of subjects with treatment-emergent events divided by the number of subjects at risk.

Laboratory evaluation results will be compared to their normal ranges. Any values out of normal ranges will be identified. The change from baseline for each laboratory parameter will also be presented for each post-baseline visit.

**Table 2 - Outcome endpoints and variables collected during treatment**

	Endpoint/Variable
Main Endpoints	<ul style="list-style-type: none"> <li>Subjects reporting AEs of chronic lower abdominal and/or pelvic pain after sterilization procedure</li> <li>Subjects reporting AEs of abnormal uterine bleeding after sterilization procedure</li> <li>Subjects with reported allergic/hypersensitive reactions</li> <li>Subjects with newly diagnosed autoimmune disorders</li> </ul>

	Endpoint/Variable
	<ul style="list-style-type: none"> <li>Subjects undergoing invasive gynecologic surgery (e.g., device removal or hysterectomy) after sterilization procedure (excluding second Essure placement attempts)</li> </ul>
Patient Reported Outcomes	<ul style="list-style-type: none"> <li>MOS SF-36 (Version 2) which includes eight distinct health domains (physical function, role-physical, bodily pain, mental health, role-emotional, social functioning, vitality, and general health perceptions) and physical component summary and mental component summary scores</li> <li>PROMIS Scale V1.0—Pain Intensity 3a, raw score, T-Scores, percentages of subjects who had T-Scores more than 50 and 60</li> <li>PROMIS Scale V1.0—Pain Interference 8a, raw score, T-Scores, percentages of subjects who had T-Scores more than 50 and 60</li> <li>AMSS and two intermenstrual bleeding questions used to characterize bleeding in subjects undergoing Essure placement and laparoscopic tubal sterilization, total raw scores and individual score for each question, percentage of subject having total scores greater than 40</li> <li>FSQ: to investigate if scores on this instrument (continuous and categorical) correlate with chronic pelvic pain over the course of the study</li> <li>Supplemental PRO Questionnaires</li> <li>Social Media Questionnaire</li> </ul>
Additional Endpoints	<ul style="list-style-type: none"> <li>New exposure to metals including new cosmetic or medical permanent implants and/or piercings and its material, wear eyeglasses</li> <li>Change from baseline to 1 Year in serum or plasma nickel level, titanium level— both categorical and continuous forms, association with adjudicated hypersensitivity/allergic/autoimmune events</li> <li>Change from baseline to 1 Year in serum or plasma nickel level, titanium level association with adjudicated hypersensitivity/allergic/autoimmune events</li> <li>Proportion of women who crossed over to alternate sterilization method (e.g., Essure subjects who attempted laparoscopic tubal sterilization)</li> </ul>
Essure Insert Placement Procedure <sup>a</sup>	Type of hysteroscopy procedure, reason for second attempt, facility where procedure was performed, premedication, pregnancy test performed within 24 hours of this procedure, hormonal manipulation to promote atrophic or proliferate endometrium, anesthesia used, type of anesthesia used, placement technique, hysteroscopy possible, retroverted uterus, distention medium used, type of distention medium, duration of procedure, Essure procedure attempted, reason Essure procedure not attempted, experienced

	<b>Endpoint/Variable</b>
	AE during hysteroscopy, placement status (by tube), ostium in the field of vision during placement (by tube), if successful - number of Essure trailing coils, number of inserts used (by tube), device type, reasons for unsuccessful placement (by tube), primary reason for unsuccessful placement (by tube), first line confirmation test to be performed, investigator's rating of ease of use of the Essure device, physician's rating of procedure difficulty, experienced AE during Essure implant procedure, Primary method of contraception used just prior to procedure, Primary method of contraception used until reliance assessment, additional procedures performed in conjunction with the Essure procedure
Transvaginal Ultrasound <sup>a</sup>	Reason for TVU, facility where TVU performed, uterine position at time of TVU, insert detected (by tube), implant location (by tube), reason for unsatisfactory placement (by tube), TVU results satisfactory to allow the subject to rely on Essure, individual who performed TVU, individual who interpreted TVU, physician's rating of procedure difficulty, experienced AE during TVU
Hysterosalpingogram <sup>a</sup>	Timing of HSG, reason, HSG indication, TVU/HSG Algorithm requirement, type of difficult placement procedure, facility where HSG performed, uterine position at the time of HSG, insert detected (by tube), implant location (by tube), reason for unsatisfactory location (by tube), tubal occlusion (by tube), HSG results satisfactory to allow the subject to rely on Essure, individual who performed HSG, individual who interpreted HSG, experience AE during HSG
Essure Device Removal <sup>a</sup>	Physician Performing Procedure, Device removal intentional, reason for unintentional removal, primary reason for device removal, additional reasons for procedure, surgical method planned/performed, type of anesthesia, procedure related events, surgery result in permanent sterilization, procedures performed at time of device removal, reason why removal procedures were chosen, types of energy sources, vasoconstrictive agent used during removal, imaging procedures performed to localize inserts prior to removal, number of devices removed, location of device (per device removed), removal status (per device removed),
Reliance Assessment <sup>a</sup>	Timing of reliance assessment visit, imaging used for assessment, whether subject compliant and reason, subject instructed to rely on Essure inserts for contraception
Birth Control Counseling	Time of birth control counseling, reason for counseling on alternate method of birth control, method of birth control discussed with subject
Laparoscopic Tubal Sterilization <sup>b</sup>	Primary method of contraception used just prior to procedure, facility, pregnancy test performed within 24 hours of the procedure, type of procedure planned/performed, surgical method planned/performed, type of anesthesia, intraoperative findings, were both the specific procedure and surgical method completed as initially planned, complications during procedure, additional procedures performed, physician's assessment of

	<b>Endpoint/Variable</b>
	procedural difficulty, assessment of ability to access tubes, bilateral tubal occlusion achieved
Device Event	Any device event, type of device/problem, summary of device events, device event outcome, AE related to device event, device event evaluation
Adverse Events	Any AE, Serious AEs, reason for serious AE, AE of special safety interest, AE intensity, AE related to study procedures or devices, type of procedure/device related to AE, AE outcome, pre-existing condition, concomitant medication, other non-study procedures
Contraceptive Method Post-procedure	Method used for contraception, duration of the contraceptive method used.
Concomitant Medication	Type of medication, main indication for medication
Additional Abdominal or Pelvic Surgery	Type of surgery performed, was surgery done for the purpose of sterilization/ re-sterilization , surgery due to an AE
Allergy/Hypersensitivity Evaluation, Autoimmune Disorder Evaluation, and PRO Alert Response	Symptom subjects reported, adjudication committee form, pathological findings, serum or plasma nickel and titanium levels, NiLPT and chromium LPT results, cytokine samples analysis , type of alert, pain alert response and bleeding response.
Study Completion	Did subject complete study, primary reason for premature discontinuation, time to premature discontinuation
Death	Number subjects died

<sup>a</sup> Only measured for Essure Group

<sup>b</sup> Only measured for laparoscopic tubal sterilization group

For the main outcomes, [Table 3](#) lists the SMQ search terms for abnormal uterine bleeding and lower abdominal and/or 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 (i.e., the stop date of the pain minus start date is longer than 182 days, or by the time of EOS, the subject still has pain ongoing with start date 182 days before EOS).

**Table 3 – Search list for bleeding and pain**

Category	SMQ definition
Abnormal uterine bleeding	Dysfunctional uterine bleeding; Genital hemorrhage; Genital haemorrhage; Menometrorrhagia; Menorrhagia; Metrorrhagia; Polymenorrhagia; Uterine hemorrhage; Uterine haemorrhage; Vaginal hemorrhage; Vaginal haemorrhage; Amenorrhea; Amenorrhoea; Hypomenorrhoea; Hypomenorrhoea; Oligomenorrhoea; Oligomenorrhoea; Bleeding anovulatory; Menstrual disorder; Menstruation delayed; Menstruation irregular.
Lower abdominal and/or pelvic pain	Abdominal pain; Abdominal pain lower; Abdominal tenderness; Abdominal discomfort; Incision site pain; Implant site pain; Medical device discomfort; Medical device pain; Medical device site discomfort; Medical device site pain; Suprapubic pain; Visceral pain; Post ablation tubal ligation syndrome; Pubic pain;; Back pain(excluding LLT upper back pain; including LLT lower back pain); Groin pain; Genito-pelvic pain/ penetration disorder; Uterine cervical pain; Ovulation pain; Pelvic pain; Pelvic discomfort; Dyspareunia; Adnexa uteri pain; Uterine tenderness; Uterine pain; Uterine spasm; Dysmenorrhoea; Menstrual discomfort; Premenstrual cramps;

For allergic/hypersensitive reactions and autoimmune disorders, final determination of whether or not a hypersensitivity/allergic event or autoimmune disorder event has occurred will be based on the determination of the adjudication committee.

For invasive gynecologic surgery, [Table 4](#) lists the terms from eCRF that will be considered as invasive gynecologic surgery.

**Table 4 - Search list for invasive gynecologic surgery**

Terms
Endometrial Ablation
Hysterectomy; subtotal (only uterus removed)
Hysterectomy; Total (uterus and cervix removed)
Hysterectomy; Radical (uterus, cervix, ovaries, oviducts, lymph nodes, & lymph channels removed)
Unilateral/bilateral Salpingectomy(excision of the fallopian tube)
Partial Salpingectomy
Unilateral/bilateral Oophorectomy (excision of the ovary) or removal of the ovarian cyst
Unilateral/bilateral salpingoophorectomy (excision of the ovary and fallopian tube)
Cornual resection
Diagnostic laparoscopy
Salpingotomy
Operative hysteroscopy and specify
Surgery for vascular injury, specify
Surgery for visceral organ injury, specify

Besides all these items from additional pelvic/abdominal surgery eCRF, the following situations will also be considered as invasive gynecologic surgery.

If a subject had Essure removal using Salpingectomy, Hysterectomy and Cornual resection, she will be considered as having invasive gynecologic surgery and classified as “Essure removal using invasive gynecologic surgery”. If a subject had laparoscopic tubal sterilization after she had Essure attempt, she will be considered as having invasive gynecologic surgery and classified as “laparoscopic tubal sterilization after Essure attempt”. If a subject had Essure attempt after she had laparoscopic tubal sterilization, she will be considered as having invasive gynecologic surgery and classified as “operative hysteroscopy, Essure placement after laparoscopic tubal sterilization”.

#### **6.4.1 Subject Incidence**

The subject incidence is defined as the number of subjects with at least one event divided by the number of subjects at risk. Subject incidence will be calculated for each group. The risk difference between two groups will also be calculated. Its associated 95% CI will be derived based on normal approximation.

Additionally for the main endpoints, subject incidence and risk differences will be given for the following time intervals: Day 0, Day 1-7, Day 8-30, Day 31-90, Day 91-180, Day 181-365, Day 366-730, > Day 730.

#### **6.4.2 Exposure-adjusted subject incidence**

The exposure-adjusted subject incidence is defined as the number of subjects with at least one event divided by the total time at risk. For the subject who has at least one event, the risk duration is from the index date to the date of the first event. For the subject who has no events reported, the risk duration is from the index date to the censoring date or end of study date. The exposure adjusted incidence will be calculated for each group. The difference between two groups and its associated 95% CI will be calculated using the method proposed by Liu et.al (2006) [1].

#### **6.4.3 Kaplan-Meier estimates**

Kaplan-Meier estimates for the main endpoints will be given in tables and figures describing the time course until the first event of interest. Subjects who did not experience the event until end of observation are right-censored, see also Section 6.1.3.

Confidence intervals are based on asymptotic method for standard error estimation by Greenwood (1926) [2].

The x-axis of the Kaplan-Meier figures will be restricted to the period in which at least 10% of the subjects are at risk as suggested by Pocock et al. (2002) [3].

#### **6.4.4 Hazard ratios**

Hazard Ratios will be derived for the main endpoints from Cox proportional hazard model with treatment group as an independent variable. Other covariates could include, but are not limited to age, BMI, race, hormonal contraception used at baseline and appropriate pre-existing conditions (bleeding disorder, ovarian pathology, etc.).

#### **6.4.5 Procedure failures that are converted to alternative permanent sterilizations**

A conversion is defined as the change of treatment agent from Essure to laparoscopic tubal sterilization. It is also possible that a subject may convert from an unsuccessful laparoscopic tubal sterilization to Essure.

Subjects will be analyzed according to the group based on the initial index event. All the variables will be summarized from subjects' enrollment till end of study or censoring date. The subjects will be followed for safety monitoring until the end of study no matter if the subjects had attempted alternate permanent sterilization procedure or not.

#### **6.4.6 Reporting of longitudinal data**

Analysis of longitudinal data (e.g., PRO data) will be descriptive.

### **6.5 Additional safety analysis**

In addition to the analysis of the main outcomes (safety variables as described in Section 6.3), the following additional safety analyses will be performed.

#### **6.5.1 Adverse events**

The subject incidence overall and by MedDRA preferred term within the primary system organ class (SOC) will be shown for the following events:

1. any treatment-emergent AE
2. any treatment-emergent serious AE
3. any study procedure-related treatment-emergent AE (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
4. any serious study procedure-related treatment-emergent AE (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
5. any treatment-emergent bleeding event (as reported by investigator)
6. any study procedure-related treatment-emergent bleeding event (as reported by investigator) (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
7. any treatment-emergent serious bleeding event (as reported by investigator)
8. any treatment-emergent serious study procedure-related bleeding event (as reported by investigator) (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)

9. any treatment-emergent pelvic/abdominal pain event, including both chronic and non-chronic (as reported by investigator)
10. any study procedure-related treatment-emergent pelvic/abdominal pain event, including both chronic and non-chronic (as reported by investigator) (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
11. any treatment-emergent serious pelvic/abdominal pain event, including both chronic and non-chronic (as reported by investigator)
12. any treatment-emergent serious study procedure-related pelvic/abdominal pain event, including both chronic and non-chronic (as reported by investigator) (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
13. any treatment-emergent AE excluding bleeding and pelvic/abdominal pain events (as reported by investigator)
14. any study procedure-related treatment-emergent AE excluding bleeding and pelvic/abdominal pain events (as reported by investigator) (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
15. any treatment-emergent serious AE excluding bleeding and pelvic/abdominal pain events (as reported by investigator)
16. any treatment-emergent serious study procedure-related excluding bleeding and pelvic/abdominal pain events (as reported by investigator) (also by specific procedures/devices: related to hysteroscopy, Essure placement, laparoscopy, cauterization/thermal device, Essure insert, clip or ring placement, trochar or veress needle, anesthesia, TVU, HSG, other)
17. any treatment-emergent AE leading to discontinuation
18. any treatment-emergent AE leading to (prolonged) hospitalization
19. any treatment-emergent AE of special interest (identified via a list of pre-specified standardized MedDRA queries)
20. any treatment-emergent AE leading to death.

The SOC and the preferred terms within the SOC will be displayed alphabetically. In addition, a summary table for the event types specified above will be prepared that displays the overall number of events and the incidence proportion.

All subjects with AE will be listed with all details from the AE report form as well as corresponding MedDRA PT and SOC. Subjects who died will be listed with type and duration of treatment, administered concomitant medication (incl. indication) as well as details from all reported AEs. For

subjects with bleeding events data listings will be prepared which present all information from the bleeding questionnaire.

Adverse events which occur after the censoring date will be summarized in a separate table. The subjects will be grouped into three groups based on the censoring reason (i.e., ‘Hysterectomy’ [includes any subject with a subtotal, total or radical hysterectomy], ‘Both Treatment’ [includes subjects who attempted both procedures] and ‘Other’ [includes device removal not accompanied by sterilization procedure; or any other censor event not covered by the Hysterectomy or Both Treatments groups]).

### **6.5.1 Device events**

All device events will be coded using MedDRA.

Frequency tables showing an overall summary of the number of device events and the number of subjects with device events by system organ class (SOC) and preferred term (PT) will be given for the following types of device events:

- All Device Events
- Outcome of Device Event (by device)
- Serious AEs (SAEs) related to the Device Event (by device)

### **6.5.2 Prior and concomitant therapy**

Descriptive analysis will be conducted on the method(s) of contraception used by each subject and the duration of use in the period immediately prior to participation in this study (prior to undergoing permanent sterilization). Summary analysis will be performed on the method of alternative contraception used during the period in which they are unable to rely on Essure or laparoscopic tubal sterilization. All concomitant medications used during the study and prior medications used up to 2 years prior to study participation will be summarized.

## **6.6 Confounder or bias adjusted analyses**

Due to the observational character of this study, the results are prone to bias and confounding. In the study protocol approaches related to study design are given that are intended to reduce bias during study conduct. This section describes how confounding will be addressed in the statistical analysis.

Confounding is a form of systematic bias in which the observed effect measure results from a combination of effect from treatment and effect from correlates of treatment which are independent risk factors for the AE and correlates of exposure. As a consequence, the observed effect measure differs in a systematic way from the true effect measure of the therapy. Therefore, methods to control for confounding will be employed in the analyses. By definition, confounding by indication goes hand in hand with unbalanced covariates, caused by the non-randomized treatment allocation (allocation bias).

To control for measured confounding at baseline in the analyses, the propensity score method as in Rubin (2008) [4] will be used to balance the analysis population with respect to baseline covariates by deriving a PS confounder-adjusted population. Based on all treated subjects (full analysis set, see Section 5.1) this population will be derived as described in Section 6.5.1. The analysis of the PS confounder-adjusted population is described in Section 6.5.2.

### 6.6.1 Development of propensity score

In order to assure that the PS is developed without knowing any outcome variables, the iterative model build process will be conducted by an outcome-blinded independent party which has only access to the treatment variable and the baseline variables listed in [Table 2](#).

The outcome variables will be removed from the data set during PS development; those constructing the score will not have access to any outcome information. Any variable measured after the treatment decision will be considered an outcome, as it could have been affected by the treatment.

The initial sterilization treatment will be considered the “treatment” for the purpose of the PS analyses.

All baseline variables will be considered for inclusion into the model; however the variables in [Table 5](#) have shown previous evidence to likely be included in the model. The decision to keep them or to remove them from the model or to alter the level of scale will be decided during the build of the score using analysis diagnostics as described below. A detailed report on the procedures applied for selection of variables and for considerations for analyses will be provided by the independent party.

**Table 5 - Baseline variables suspected to be included in PS model<sup>a</sup>**

Variables
Age
Race
BMI
US Geographical Region
Insurance type (Government-subsidized program, Commercial/Private , Other)
Hormonal Contraception Use At Baseline
Pre-existing abnormal uterine bleeding
Disorders associated with hysterectomy (fibroids, ovarian pathology, endometriosis, prolapse, hyperplasia)
GI disorders (e.g., IBS)
Pre-existing Autoimmune Disease
Pre-existing Diabetes
Pre-existing Hypertension

<sup>a</sup> Based on internal data on file

The approach to take would be to first construct the PS model and estimate the PS in both groups, assess the overlap, and determine if a PS confounder-adjusted analysis can proceed based on the overlap.

Logistic regression will be used to model the relationship between the background variables and the treatment, and a PS will be estimated for each subject by a fitted value from the logistic regression.

In an effort to improve model fit several steps can be investigated, including dichotomization or grouping of baseline variables intended for inclusion in the model.

In a first step, all above listed potential confounders are to be included in the stepwise model build procedure.

In a second step, all other baseline data plus the list of potential confounders used for model build in the first step will be included in a stepwise logistic regression procedure.

The two models will be compared. If the contribution of the additional data is low, the PS built on the first model will be considered for analysis. The independent party will assess this and propose the final model. This proposal will be discussed with the FDA.

Use of 1-to-1 nearest neighbor matching with a caliper of 0.2 SD of the logit Propensity Score will be the preferred procedure in order to ensure comparability. (Austin 2011 [5], Rosenbaum and Rubin 1985 [6])

Numerical and graphical balance diagnostics will be produced to assess the resulting similarity between treatment groups. Balance will be examined for individual background variables, for logs and squares of continuous background variables, for two-way interactions between background variables, and for other pre-specified combinations of variables. The intent is to properly specify the PS model, but also considering the potential to overfit—as this would reduce PS overlap. Inclusion of factors that are highly predictive of treatment choice but that adversely impact on ability to balance important known confounders should be carefully selected. If such factors exist, they must be reported, as they are also indicative of potential limitations to the interpretation of study results. While the intention to generate an overlap of PS density functions in absence of such predictors of treatment choice would still enable a technical conduct of analyses, it would on the other hand require that these predictors are not outcome associated. Such consideration must be made when omitting strong predictors for treatment choice from the PS Model. A percentage of desired overlap between density functions is not a priori determined. Generally, a loss of patients for the adjusted safety analysis set of less than 15% would be covered by the sample size considerations.

During the iterative process, some subjects may be removed from the analysis population in order to improve the balance between covariates. These subjects will be flagged in the subject listings on AEs.

In case missing data are obtained in the set of confounders, despite the quality assurance measures, it must be decided whether missing data will be utilized as its own category in the PS design or whether subjects with missing data in any variable should be disregarded or imputed in the PS design. This would depend on the magnitude of cases with missing data. The independent party will assess this during PS build and recommend on the procedures for addressing missing data.

#### **6.6.2 Analysis based on different analysis set**

All the baseline characteristics defined in [Table 1](#), main endpoints variables defined in [Table 2](#), and summary AEs will be analyzed using full analysis set, adjusted full analysis set, reliance set and adjusted reliance set with adjusted full analysis set being the primary analysis.

Descriptive analyses of the PRO questionnaires will be done using full analysis set, adjusted full analysis set, reliance set and adjusted reliance set with adjusted full analysis set being the primary analysis.

For other outcome variables listed in [Table 2](#) and AEs by PT and SOC, the analysis will be conducted using the full analysis set and adjusted full analysis set.

For device events, the analysis will be conducted based the full analysis set using all the data till the end of study.

## 6.7 Subgroup analysis

Subgroup analysis will be conducted for main endpoints, summary AEs, and device events for the following groups:

- Types of laparoscopic procedures (Total Salpingectomy, Partial Salpingectomy, Tubal Cauterization, Fallope Ring, Filshie Clip, Hulka Clip and other)
- Age ( $\leq 30$  years,  $> 30$  years)
- Number of births (0, 1-3, 4+)
- FSQ at baseline (FSQ $<13$ , FSQ $\geq 13$ )

## 6.8 Sensitivity analyses

Sensitivity analysis will be performed for the main endpoints and summary AEs. The analysis will include all the data from index date till the end of study no matter if the subject had censoring events or not during the study.

## 7 Interim Analysis

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 at the point 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.

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

1. Demographic information listed in Section 9.3.1.
2. 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.
3. 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.
4. Proportion of subjects with allergic / hypersensitivity reactions possibly attributed to wearing of Essure devices and allergic / hypersensitivity reactions in women undergoing laparoscopic tubal sterilization.
5. Proportion of subjects with newly diagnosed autoimmune disorders in subjects wearing Essure inserts compared to subjects undergoing laparoscopic tubal sterilization.
6. 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.
7. Rates of AEs in subjects undergoing Essure placement and laparoscopic tubal sterilization.
8. The proportion of subjects reporting each protocol deviation.

The propensity score (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. This process may need to be repeated once all subjects complete 3 years of follow-up due to subject drop-out. The first interim analysis will be initiated after the PS matching process has completed. Both 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 and at the end of 3 years of follow-up.

Results of the interim analyses will be summarized in a separate report.

## 8 References

- [1] Liu. G.F., Wang, J., Liu, K and Snaveley, D.B. (2006) Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. *Statistics in Medicine*. 25:1275-1286
- [2] Greenwood M (1926): The natural duration of cancer. Reports on Public Health and Medical Subjects 33, 1–26. Her Majesty’s Stationery Office, London.
- [3] Pocock SJ, Clayton TC, Altman DG (2002): Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. In: *The Lancet* 359 (9318), 1686-1689.
- [4] Rubin DB (2008): For objective causal inference, design trumps analysis. In: *Annals of Applied Statistics*, 2(3), 808-840.
- [5] Austin P (2011): Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. In: *Pharmaceutical Statistics*, 10(2), 150-161.
- [6] Rosenbaum, P. R., & Rubin, D. B. (1985). Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *The American Statistician*, 39, 33–38.