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Cover page of the integrated protocol

A Study to Evaluate the Effectiveness of Essure Post-NovaSure Radiofrequency Endometrial Ablation Procedure Following a Successful Essure Confirmation Test

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

- **Original protocol,** Version 0, dated 22 DEC 2011
- **Amendment no. 1** (described in Section 13.1)
  forming integrated protocol Version 1.0, dated 03 FEB 2012
- **Amendment no. 2** (described in Section 13.1)
  forming integrated protocol Version 2.0, dated 15 FEB 2012
- **Amendment no. 3** (described in Section 13.1)
  forming integrated protocol Version 3.0, dated 19 DEC 2012
- **Amendment no. 4** (described in Section 13.2)
  forming integrated protocol Version 4.0, dated 12 DEC 2014
- **Amendment no. 5** (described in Section 13.3)
  forming integrated protocol Version 5.0, dated 03 DEC 2015
  (approved by the FDA on 12 MAY 2016)
- **Amendment no. 6** (described in Section 13.4)
  forming integrated protocol Version 6.0, dated 12 JUL 2016
  (approved by the FDA on 29 SEP 2016)

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

Title page - *amended*

A Study to Evaluate the Effectiveness of Essure Post-NovaSure Radiofrequency Endometrial Ablation Procedure Following a Successful Essure Confirmation Test

Essure-NovaSure PAS

Test device:	BAY 1454032		
Study purpose:	The purpose of the study is to evaluate the effectiveness and safety of the Essure System when a NovaSure endometrial ablation (EA) procedure is performed following a successful Essure Confirmation Test.		
Clinical study phase:	Post-approval study (PAS)	Date:	12 JUL 2016
EudraCT no.:	Not applicable	Version no.:	6.0
Study no.:	16975		
Sponsor:	Bayer HealthCare, LLC[1] 100 Bayer Boulevard Whippany, NJ 07981 USA		
Sponsor's medical expert:	PPD Bayer HealthCare, LLC 100 Bayer Boulevard P.O. Box 915 Whippany, NJ 07981 USA Telephone: PPD		

The study will be conducted in compliance with the protocol, ISO 14155, ICH- GCP and any applicable regulatory requirements.

[1] Per Amendment 4 and 6
[2] Per Amendment 4

Signature of the sponsor's medically responsible person

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

Name: PPD Role: PPD

Date: 20 October 2016

PPD

Signature of principal investigator

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

Name:

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.

Synopsis[3] - amended

Title	A Study to Evaluate the Effectiveness of Essure Post-NovaSure Radiofrequency Endometrial Ablation Procedure Following a Successful Essure Confirmation Test (Essure-NovaSure PAS)
Short title	Essure-NovaSure PAS
Clinical study phase	Post-approval study (PAS)
Study objectives	The objectives of this study are to: • Evaluate the contraceptive failure rate of Essure when NovaSure is performed following a successful Essure Confirmation Test, and • Monitor the incidence of adverse events and/or complications associated with the performance of NovaSure in the presence of Essure micro-inserts.
Test device	BAY 1454032 (Essure 305)
Indication	The Essure® System is indicated for women who desire non-incisional permanent birth control (female sterilization) by occlusion of the fallopian tubes. The NovaSure endometrial ablation (EA) procedure is indicated for the treatment of menorrhagia.
Diagnosis and main criteria for inclusion	• Subject is between 21-50 years of age • Subject is between 90-300 lbs (40-136 kg) • Subject has a successful Essure Confirmation Test showing bilateral satisfactory micro-insert location (when using transvaginal ultrasound [TVU]) or both bilateral satisfactory location and tubal occlusion (when using a modified hysterosalpingogram [HSG]) documented in her subject record.[4] • Subject is experiencing menorrhagia due to benign causes • Subject is willing to use NovaSure as endometrial ablation procedure for menorrhagia • Subject is willing to accept the risk of pregnancy while relying on the Essure micro-inserts for prevention of pregnancy following a NovaSure ablation procedure for menorrhagia • Subject is willing and able to give written Informed Consent prior to participation in the post-approval study, in accordance with regulatory requirements • Subject is willing and able to complete all follow-up visits as required by the post-approval study protocol • Subject is willing and able to allow their data to be shared with the post-approval study Sponsor, Institutional Review Board / Ethics Committee and the Food and Drug Administration of the United States (FDA)

[3] New section from sponsor template; populated per Amendment 4.
[4] The definition of the Essure confirmation test modified per Amendment 6 to include transvaginal ultrasound.

Study design	Prospective, multi-center, single-arm observational study
Methodology	In this study, the NovaSure EA procedure following successful placement of a commercially available Essure device is the treatment being administered. The Essure device, with the exception of relatedness to adverse events (AE), and placement procedure are not being evaluated. One week (plus or minus two days) from the date of NovaSure EA, the subject will return to the physician's office for a physical exam, to inquire whether or not any adverse events occurred since the NovaSure procedure and to conduct a subject interview to obtain information on subject satisfaction and comfort with wearing the Essure micro-inserts post-NovaSure EA. One, two-, and three- years (± 28 days) from the date of the NovaSure EA procedure, the subject will be contacted by the physician's office to have a telephone follow-up visit. During each of these visits, designated study staff will conduct a subject interview to confirm subject is not currently pregnant or has not been pregnant in the previous year, to inquire whether or not any adverse events occurred over the past year, to obtain information on subject satisfaction and comfort with wearing the micro-inserts post-NovaSure EA procedure and to discuss whether or not subject has had or will have any extirpative surgery.
Type of control	Not applicable
Number of subjects	Approximately 220
Primary variable	Occurrence of confirmed pregnancy at 1 year and 3 years among subjects relying on Essure micro-inserts for permanent birth control when NovaSure EA is performed following a successful Essure Confirmation Test.
Plan for statistical analysis	The primary effectiveness endpoint of this study is the 1-year and 3-year pregnancy rates. The rates will be calculated as described below. Each woman-month of follow-up represents a "Bernoulli trial" of the Essure device. A woman contributes as many women-months as her participation in the post-approval study. Upon observing f failures in w women-months, the posterior distribution of the monthly failure rate, r, is calculated as: r = beta(a+f, b+w-f) where a and b = 0.5, representing a non-informative prior distribution. The upper Bayesian credible interval of **r** is easily calculated from the inverse beta function. A 1-year failure rate can be calculated as: 1-year rate = $1-(1-r)^{12}$ The 1-year rate will be calculated when all participating women have reached at least 1 year of follow-up. As an additional related calculation, we will determine the 3-year failure as: 3-year rate = $1-(1-r)^{36}$

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List of abbreviations[5] - *amended*

ADE	Adverse device event
ADL	activities of daily living
AE	Adverse event
CFR	Code of Federal Register
CRF	Case Report Form
D&C	dilatation and curettage
EA	Endometrial Ablation
ECG	electrocardiogram
eCRF	Electronic case report form
EMA	European medicines evaluation agency
FDA	Food and Drug Administration of the United States
GCP	Good clinical practices
HSG	Hysterosalpingogram
HTA	Hydro Thermablator®
ICF	Informed consent form
IEC	Independent ethics committee
IFU	Instructions for Use
IME	Important medical events
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IVRS	Interactive voice response system
LPLV	Last patient last visit
MDR	Medical device report
PAS	Post-Approval Study
PMA	Pre-market Approval
SADE	Serious adverse device effect
SAE	Serious adverse event
TVU	Transvaginal ultrasound
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
US	United States

[5] Revised per Amendment 4 and 6

1. Introduction

1.1 Endometrial Ablation

Endometrial ablation (EA) has become a well-established treatment for pre-menopausal women with menorrhagia (excessive bleeding) and an alternative to hysterectomy for some patients. Treatment for menorrhagia may include hormone therapy, endometrial curettage, endometrial ablation, and hysterectomy. Women who are opposed to hysterectomy and those for whom other treatment options were unsuccessful may consider EA rather than hysterectomy. Traditional treatments for dysfunctional uterine bleeding and menorrhagia include hormone replacement therapy, dilatation and curettage (D&C), and hysterectomy. EA and hysterectomy are offered as treatment options when medical therapy and/or D&C fail.

1.2 Risk of Pregnancy

Although women undergoing EA must be finished with childbearing, EA should not be considered a means of sterilization. Pregnancy should not be elected after an ablation because it can be dangerous for both the fetus and mother; therefore, women need to have a reliable contraceptive method if they choose to undergo EA. The Essure procedure is a hysteroscopic permanent sterilization method and a complement to various EA technologies. Women who have undergone hysteroscopic sterilization with the Essure procedure may become candidates for EA procedures should they develop menorrhagia requiring treatment in the future.[6] This study evaluates how the NovaSure EA may affect the effectiveness and safety of Essure.[7]

1.3 Essure System

The Essure procedure is a non-incisional surgical procedure that involves placing a small, flexible device called a micro-insert into each fallopian tube for the purpose of occluding the tube in order to provide permanent contraception. Besides the "space-filling" aspect of the micro-insert, the primary method of action consists of a benign tissue ingrowth that occurs after placement and occludes the fallopian tube. The Essure system consists of the micro-insert and a disposable delivery system and has undergone clinical investigation since 1996. The Essure system received Food and Drug Administration (FDA) approval in 2002 (P020014) and is commercially available in the United States, Europe (CE Mark approval received February 2001), Canada, Australia, and various Central/South American and Asian countries.

1.4 NovaSure Impedance Controlled Endometrial Ablation System

The NovaSure procedure employs radio frequency delivered via a bipolar electrode array into the uterine cavity. NovaSure received FDA approval in 2001 (P010013) for the indication of endometrial ablation in premenopausal women with menorrhagia due to benign causes for whom childbearing is complete. Though NovaSure is currently labeled and contraindicated for use in "…a patient with a thermally conductive object (e.g. metal implant) present in the

[6] Per Amendment 4
[7] Per Amendment 4

uterus or in the uterine cavity, where the object could potentially come in direct contact or close proximity to the heat generation portion of the endometrial ablation device...", clinical and commercial reports have demonstrated the safety of performing NovaSure EA with Essure micro-inserts in place (Section 1.5).

1.5 Prior Reported Clinical Studies and Commercial Data on the Compatible Use of NovaSure with Essure Micro-Inserts in Place

1.5.1 Clinical Studies

Clinical studies on the compatible use of these procedures have been evaluated in both peri- and pre-hysterectomy clinical settings. Coad, et al. conducted a feasibility study to evaluate tissue ingrowth viability along the Essure micro-inserts' length following NovaSure endometrial ablation. In accordance with Essure's Instructions for Use, the study subjects (n=6) underwent bilateral micro-insert placement greater than 90 days prior to the Essure Confirmation Test and subsequent NovaSure endometrial ablation. The study demonstrated continued Essure micro-insert tissue ingrowth viability within the distal interstitial/isthmic fallopian tube regions following NovaSure endometrial ablation. No distal thermal tissue necrosis propagation, along the micro-inserts' length, was identified outside the NovaSure ablation zone. The proximal thermally injured micro-insert ingrowth within the ablation zone should heal in conjunction with the healing timeline for the NovaSure ablation. The results support continued effectiveness of the Essure micro-inserts post-NovaSure ablation and confirm those of a prior reported peri-hysterectomy feasibility study [[1]]. Similarly, the Essure micro-inserts did not appear to affect the NovaSure endometrial ablation [[2]].

Coad, et al, reported on a feasibility study to evaluate for fallopian tube injury following sequential Essure micro-insert placement with either Hydro Thermablator (HTA) or NovaSure endometrial ablation. The Essure followed by NovaSure study subjects (n=13) underwent unilateral Essure micro-insert placement immediately followed by NovaSure ablation. The contralateral fallopian tubes served as controls. The study demonstrated that the Essure micro-inserts did not alter performance of either endometrial ablation systems. NovaSure ablations showed limited thermal tubal injury that was similar to that of the Hydro Thermablator control tubes. No serosal injury was identified. The study results support acceptable safety profiles for both HTA and NovaSure following Essure micro-insert placement [[1]],[[3]].

1.5.2 Commercial Reports

Data on the commercial and compatible use of NovaSure EA with Essure micro-inserts in place have been reported. D. Saunders conducted a retrospective case review study of 118 sequential patients who had Essure micro-insert placement followed by NovaSure endometrial ablation. The interval between the Essure placement and NovaSure procedures ranged from 2 to 108 days. All patients were informed of the Essure Instructions for Use requirements for the Essure Confirmation Test to be performed 90-days after micro-insert placement; most patients chose not to wait because of their desire for the NovaSure endometrial ablation to eliminate their excessive uterine bleeding sooner. Two patients required replacement of the micro-insert at the time of the NovaSure procedure because the micro-insert was attached to the NovaSure instrument when it was withdrawn. A second

device was placed without difficulty. At up to two years of follow up (for the earliest study participant), none of the study subjects have had a pregnancy. No complications occurred and no adverse events have required treatment or hospitalization [[4]].

Basinski, et al, conducted a retrospective review of 117 patients who had undergone Essure micro-insert placement followed by NovaSure in two in-office sessions separated by a median time of 14 days. In this study, 83/117 (71%) returned for the Essure Confirmation Test. Satisfactory placement and tubal occlusion was demonstrated in 79/83 (95%) of these patients. Amenorrhea or spotting was observed in 72/97 (74%) of patients, 22/97 (23%) reported satisfactory decrease in menstrual flow, and 3/97 (3%) patients reported failure of the ablation procedure. A total of eight adverse events was obtained on 111/117 (95%) patients that had follow up. None of the adverse events reported in the study appeared to be related to the performance of NovaSure after Essure specifically. There have been no reported pregnancies for the patients that have been relying on Essure for permanent contraception from 6 to 24 months. The study results showed that the combination of Essure followed by NovaSure did not decrease effectiveness of either procedure and no serious adverse events were attributed to the combination of the two procedures in this study [[5]].

1.5.3 Risk Analysis and Conclusions from Prior Reported Data

Clinical and commercial studies have evaluated over 250 patients who have had NovaSure EA while wearing the Essure micro-inserts. The adverse events reported in the clinical evaluations were similar to the adverse events experienced individually with each technology. All adverse events were expected, and, none of the adverse events were severe, confirming that it is safe to perform NovaSure EA on patients who are wearing the Essure micro-inserts. The most frequent adverse event that could be attributed to performing the two technologies together was the possibility of displacing or dislodging an implanted Essure micro-insert when performing NovaSure EA. The larger studies demonstrated that the Essure micro-inserts did not alter performance of NovaSure EA. The benefit of performing NovaSure EA in patients wearing the Essure micro-inserts outweighs the risk of the adverse events that are expected to occur. This clinical study will evaluate the ability of Essure micro-inserts to maintain contraception following NovaSure EA, providing further data to assess the risk-benefit ratio[8].

1.6 Regulatory and Commercial Labeling History

CE Mark approval was received in July 2008 for the addition of information to the Essure Instructions for Use (IFU) regarding the safe and effective performance of certain endometrial ablation procedures (including radio frequency ablation) in patients with Essure micro-inserts in place. United States FDA approval was received in February 2012 to add language on the safe use of the Essure System when the NovaSure procedure is performed following a successful Essure Confirmation Test (hysterosalpingogram [HSG] at three months). This post-approval study (PAS) is being conducted under FDA's "Condition of Approval" in order to evaluate the Essure System after a NovaSure procedure is performed per the approved labeling changes.

[8] Per Amendment 4

Further details can be found in the IFU, which contains comprehensive information on the study device[9].

2. Study objectives - *amended*

The objectives of this study are to:

- Evaluate the contraceptive failure rate of Essure when NovaSure is performed following a successful Essure Confirmation Test*, and
- Monitor the incidence of adverse events and/or complications associated with the performance of NovaSure in the presence of Essure micro-inserts.

*Successful Essure Confirmation Test = satisfactory bilateral micro-insert location and fallopian tube occlusion when using HSG, or satisfactory or optimal bilateral micro-insert location and retention in both tubal ostia when using transvaginal ultrasound (TVU) (i.e. the subject is able to rely on Essure for contraception). Note: all subsequent descriptions of "successful" Essure confirmation test refer to this definition.[10]

3. Investigators and other study personnel[11]

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.

Post-approval study (PAS) sites and physicians will be selected in the United States in major metropolitan areas to achieve an appropriate enrollment rate of post-approval study subjects. Sites will be selected based on physician commercial experience with both the Essure System and NovaSure EA, and site/physician utilization rates thereof.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator 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 study file.

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 investigator site 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.

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[9] Per Amendment 4
[10] Language regarding the Essure confirmation test was aligned with the IFU per Amendment 6.
[11] New section from sponsor template per Amendment 4

4. Study design

Design overview

This PAS is a prospective, multi-center, single-arm observational study to monitor and evaluate the effectiveness and safety of Essure when NovaSure is performed following a successful Essure Confirmation Test. The PAS will be conducted at up to 30 sites[12] in the United States. Each site may enroll a maximum of 35[13] subjects. A minimum of 220 female subjects will be enrolled in the study. Subjects will be followed for a total of 3 years post-NovaSure EA with evaluations to occur at the 1 week, 12 month, 24 month and 36 month follow-up time points. PAS subjects who have been identified as candidates for NovaSure EA and have had a successful Essure Confirmation Test will be considered.

At least 50% of the subjects enrolled in the study must be 45 years of age or younger.

End of study

The primary outcome will be collected after last patient - last visit (LPLV). The end of the study as a whole will be the date when the clean data base is available.

4.1 Primary variable

- Occurrence of confirmed pregnancy at 1 year and 3 years among subjects relying on Essure micro-inserts for permanent birth control when NovaSure is performed following a successful Essure Confirmation Test.

4.2 Secondary variable

- Adverse event data

5. Study population[14]

PAS sites and physicians will be selected in the United States in major metropolitan areas to achieve an appropriate enrollment rate of post-approval study subjects. Sites will be selected based on physician commercial experience with both the Essure System and NovaSure EA, and site/physician utilization rates thereof.

5.1 Eligibility

Candidates who are willing to participate in the study, meet the inclusion and exclusion criteria, and provide Informed Consent will be eligible for the study. They will then be entered onto an Informed Consent Log.

[12] Per Amendment 5
[13] Per Amendment 4
[14] Section title was formerly Recruitment Strategy for the same content, changed per Amendment 4

5.1.1 Inclusion criteria - *amended*

1. Subject is between 21-50 years of age
2. Subject is between 90-300 lbs (40-136 kg)
3. Subject has a successful Essure Confirmation Test showing bilateral satisfactory micro-insert location (when using transvaginal ultrasound [TVU]) or both bilateral satisfactory insert location and tubal occlusion (when using a modified hysterosalpingogram [HSG]) documented in her subject record[15]
4. Subject is experiencing menorrhagia due to benign causes
5. Subject is willing to use NovaSure as endometrial ablation procedure for menorrhagia
6. Subject is willing to accept the risk of pregnancy while relying on the Essure micro-inserts for prevention of pregnancy following a NovaSure ablation procedure for menorrhagia[16]
7. Subject is willing and able to give written Informed Consent prior to participation in the post-approval study, in accordance with regulatory requirements
8. Subject is willing and able to complete all follow-up visits as required by the post-approval study protocol
9. Subject is willing and able to allow their data to be shared with the post-approval study Sponsor, Institutional Review Board / Ethics Committee and the FDA

5.1.2 Exclusion criteria

1. Subject previously underwent a fallopian tube sterilization procedure (other than Essure placement)
2. Subject is pregnant or desires to become pregnant in the future
3. Subject only has one Essure micro-insert placed
4. Subject's Essure Confirmation Test was performed less than three months (up to 1 week prior to 3 months is considered acceptable) from the date of Essure placement[17]
5. Subject is currently wearing an intrauterine device or intrauterine system and is unwilling to have it removed before the NovaSure EA procedure[18]
6. Subject has undergone any intrauterine procedure in between Essure placement procedure and NovaSure EA. Endometrial biopsy or sampling if required or indicated is permitted. Intrauterine device/intrauterine system (IUD/IUS) removal is permitted. Procedures which permit direct visualization of the inserts while assessing the

[15] TVU confirmation testing criteria added per Amendment 6
[16] Per Amendment 4
[17] Per Amendment 5
[18] Per Amendment 4

endometrium to ensure that menorrhagia is due to benign causes (e.g. saline infusion sonography or diagnostic hysteroscopy) are permitted [[6]][19]

7. Subject is scheduled to undergo any other intrauterine procedures at the time of NovaSure EA (except endometrial biopsy or sampling, if required or indicated; IUD/IUS removal is permitted)[20]
8. Subject presents with any other medical complaints, conditions or symptoms unrelated to the Essure System and/or subsequent NovaSure EA including, but not limited to:
    - Gynecological co-morbidities (e.g., pelvic infection, cervicitis, undiagnosed vaginal bleeding, endometrial cancer, pre-malignant conditions of the endometrium, myomas, and polyps)
    - Reproductive tract anatomical variants and/or pathology which could make the subject unsuitable for the Essure and/or NovaSure transcervical procedures (e.g. history of previous classical cesarean section, transmural myomectomy, pathological condition that could lead to weakening of the myometrium)
    - Active genital or urinary tract infection or pelvic inflammatory disease at time of procedure
    - Any other medical condition that precludes safe participation in the study, in the opinion of investigator
9. Subject who has participated in another clinical study in the 30 days prior to signing the informed consent for the PAS

5.2 Withdrawal of subjects from study[21]

5.2.1 Withdrawal[22] - *amended*

Subjects *must* be withdrawn from the study for the following reasons:

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

Subjects may be terminated from the study by the Investigator. Reasons for termination of a subject from the study may include, but are not limited to, the following:

- Subject does not retain device (e.g. due to removal of device, expulsion, salpingectomy or other utero-tubal surgeries)

[19] Per Amendment 4 and 5
[20] Per Amendment 4
[21] New section from sponsor template per Amendment 4
[22] Withdrawal criteria adapted to suit a device meant for permanent wearing per Amendment 6.

- Death
- An adverse event (AE) preventing study participation
- Lost to follow-up and inability to contact the subject. Note that if a subject who is lost to follow-up is re-contacted, the subject will not be considered to have withdrawn from the study.

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already undergone the NovaSure procedure.

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 above) is regarded a "screening failure".

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

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

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10 (Premature termination of the study).

5.2.2 Replacement

Subjects will not be replaced if withdrawn or terminated from the study.

5.3 Subject identification[23]

After subjects have signed the informed consent form (ICF), they will be identified by a unique 5-digit subject identification number. The subject identification number which will identify the subject throughout the study is constructed as follows:

- Digit 1-2: Study center number
- Digit 3-5: Subject number, unique within any study center. Sequential number reflecting the order in which the subjects signed the ICF at the center.

6. Treatment[24]

6.1 Treatments to be administered

In this study, the NovaSure EA procedure following successful placement of a commercially available Essure device is the treatment being administered. The Essure device, with the exception of relatedness of AEs, and placement procedure are not being evaluated.

[23] New section from sponsor template per Amendment 4.
[24] New section from sponsor template (Section 6 populated with content from previous version of protocol) per Amendment 4.

6.2 Identity of study treatment

Not applicable.

6.3 Treatment assignment - *amended*

This is a non-randomized, continuous enrollment study in which all eligible subjects will be asked to enroll. To avoid selection bias, investigators will offer enrollment in the study to all eligible subjects consecutively (as they present themselves to the investigator).

A subject may not be enrolled in the study until she has a successful Essure confirmation test done that documents bilateral satisfactory device location and fallopian tube occlusion noted on HSG OR optimal or satisfactory micro-insert location noted on TVU. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion on HSG OR optimal or satisfactory micro-insert location on TVU, she may repeat the Essure Confirmation Test.[25]

6.4 Dosage and administration

Not applicable.

6.5 Blinding

Blinding will not occur in this study. Procedures for emergency unblinding are not required.

6.6 Device logistics and accountability

Not applicable.

6.7 Treatment compliance

The Essure device is intended for subjects who desire permanent contraception (female sterilization) and is not intended to be removed.

6.8 Post-study therapy

Not applicable.

6.9 Prior and concomitant therapy

Gynecological procedures and medications necessary for the subject's well-being will be allowed during the study. Any medical treatment administered for the treatment of AEs that occur during the study will be recorded in the CRF.

[25] TVU confirmation testing criteria added per Amendment 6

7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

Table 7–1 provides a tabulated overview of the study schedule of procedures.

Table 7–1: Schedule of Events

Assessments	Eligibility & Screening (-30 days)	NovaSure EA Procedure (Day 0)	One-Week Post-EA Office Visit (± 2 days)	One-, Two-, and Three-Year Post-EA Phone Call (± 28 days)
Informed Consent Signature	X			
Inclusion / Exclusion Criteria	X	X[a]		
Medical and Gynecologic History	X			
Essure Confirmation Test Results Confirmed	X			
Physical Exam and Vitals	X		X	
Pelvic Exam	X			
Urine Pregnancy Test		X[a]		
NovaSure Procedure		X		
Pregnancy Status Inquiry				X
Adverse Event Inquiry		X[b]	X	X
Extirpative Surgery Inquiry				X
Subject Interview	X	X[b]	X	X
Subject Contact Information Confirmed	X	X[b]	X	X
Study Completion / Early Termination Form				X[c]

Abbreviations: EA = endometrial ablation
a Assessment should be performed prior to NovaSure ablation
b Assessment should be performed following NovaSure ablation
c Complete the relevant form as necessary

7.1.2 Timing of assessments

7.1.2.1 Eligibility and Screening Visit (-30 days) - *amended*

As would normally occur, the subject will visit the physician seeking treatment for menorrhagia. After the subject decides to undergo the NovaSure procedure, the physician or designated site staff will:

- Inform the subject of the Essure-NovaSure PAS. Subject will not enroll in the study until she has a successful Essure confirmation test that documents bilateral satisfactory device location and fallopian tube occlusion noted on HSG OR optimal or satisfactory micro-insert location noted on TVU. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion on HSG OR optimal or satisfactory micro-insert location on TVU, she may repeat the Essure Confirmation Test.[26]
- If subject is eligible, the physician or designated site staff will administer the Informed Consent with the subject and answer any questions the subject has.
- If subject agrees to proceed with the study, subject and physician or designated site staff will each sign and date the informed consent, and, the subject will receive a signed copy.
- After having signed the Informed Consent (not before), subject will be asked all of the PAS Inclusion and Exclusion Criteria questions to verify that subject is eligible for the study. No study procedures (including asking questions) will be done without the subject having signed the Informed Consent.
- The subject will then be asked a number of demographic and medical history questions.
- Subject will then undergo a brief physical and pelvic exam.
- If subject continues to meet screening criteria, the subject should be scheduled for the NovaSure EA procedure.

In order to minimize PAS loss to follow-up, during the Site Initiation visits, the sponsor's staff, or designee(s), will instruct the PAS Investigators and their respective Study Staff to obtain the following subject information at Screening Visit: subject email addresses, both cell and home telephone numbers, and the same contact information of at least two close relatives (e.g., spouse, sister, etc) and two close acquaintances. They will also be instructed to confirm contact information at each visit/follow-up telephone call. Thus, although the actual contact will take place by telephone, each PAS site will have multiple methods of contacting the subjects to schedule a telephone contact.

7.1.2.2 NovaSure EA Procedure (Day 0)

The Investigator or designated study staff will confirm that the subject has not experienced an adverse event since the Eligibility and Screening Visit.

[26] TVU confirmation testing criteria added per Amendment 6

The NovaSure procedure will be performed in accordance with the NovaSure EA IFU and Controller Operator's Manual.

At the time of the procedure, subject's uterine cavity will be assessed to ensure that uterine cavity length is not less than 4 cm and uterine cavity width is not less than 2.5 cm (see Exclusion criteria 8; Section 5.1.2)[27]; if they are, subject is ineligible to participate in the study.

7.1.2.3 One-Week Post-NovaSure EA Office Visit (± 2 days)

One week (plus or minus two days) from the date of NovaSure EA, the subject will return to the physician's office. At that time, designated study staff will conduct the following assessments:

- Physical Exam (Vitals)
- Inquire whether or not any adverse events occurred since the NovaSure procedure
- Conduct subject interview to obtain information on subject satisfaction and comfort with wearing the Essure micro-inserts post-NovaSure EA
- Confirm subject contact information
- Discuss any additional issues subject or the Investigator may have

7.1.2.4 One-, Two- and Three-Year Post-EA Phone Call (± 28 days) - *amended*

One, two-, and three- years (± 28 days) from the date of the NovaSure EA procedure, the subject will be contacted by the physician's office to have a telephone follow-up visit. During each of these visits, designated study staff will conduct subject interview to:

- Confirm subject is not currently pregnant or has not been pregnant in the previous year
- Inquire whether or not any adverse events occurred over the past year
- Conduct subject interview to obtain information on subject satisfaction and comfort with wearing the micro-inserts post-NovaSure EA procedure
- Discuss whether or not subject has had or will have any extirpative surgery
- Confirm subject contact information
- Discuss any additional issues subject or the Investigator may have

The 3-year phone call will be the final visit in the study. If the subject reports a serious adverse event or pregnancy during the 3-year follow-up phone call, the subject will be followed by the sponsor's pharmacovigilance department until event resolution or stabilization. If a pregnancy or serious adverse event was previously reported but the event is not resolved during the 3-year phone call, the event will be followed by the sponsor's

[27] Per Amendment 4

pharmacovigilance department until resolution. Information pertaining to these events will be collected and archived in the sponsor's pharmacovigilance database.[28]

7.1.2.5 Notification of Other Relevant Events

The subject should be instructed at the beginning of the study to inform the site immediately if subject has had or is scheduled to have any surgery which may remove some or all of her reproductive organs (i.e. hysterectomy, salpingectomy or oophorectomy)[29].

The subject will also be instructed to contact the Investigator immediately if, at any time during the study, subject thinks she might be pregnant.

If a subject experiences a micro-insert expulsion or removal during or following the NovaSure procedure, subject will be followed for the duration of the adverse event, then terminated from the study.

7.2 Population characteristics[30]

7.2.1 Demographics

Demographic data collected include, but may not be limited to, date of birth (as allowed by local law), race, and ethnicity.

7.2.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected[31]:

- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.4.1.1.

7.3 Efficacy

The primary variable is occurrence of confirmed pregnancy at 1 year and 3 years among subjects relying on Essure micro-inserts for permanent birth control when NovaSure is performed following a successful Essure Confirmation Test.

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[28] Follow-up of adverse events was specified per Amendment 6.
[29] Here, a sentence was deleted per Amendment 4 (please see Section 13.2 for details).
[30] New section from sponsor template (Section 7.2 populated with content from previous version of protocol) per Amendment 4.
[31] "Not pertaining to the study indication" was deleted per Amendment 5.

7.4 Safety[32]

7.4.1 Adverse events

7.4.1.1 Definitions

7.4.1.1.1 Adverse event

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 subject or 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) product or device.

7.4.1.1.1.1 Adverse device effect (ADE) - *amended*

An AE related to the use of Essure or NovaSure, including AEs resulting from insufficient or inadequate instructions for use, deployment, implant (placement), installation or operation or any malfunction of the investigational medical device, use error or from intentional misuse of the medical device.[33]

7.4.1.1.1.2 Unanticipated adverse device effect (UADE)[34] - *amended*

A serious adverse effect is considered unanticipated if by its nature, incidence, severity or outcome it has not been identified in the IFU.

7.4.1.1.2 Serious adverse event (SAE)[35]- *amended*

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.

[32] New section headings from sponsor template (Section 7.4 populated with content from previous version of protocol) per Amendment 4
[33] NovaSure added per Amendment 6.
[34] Per Amendment 4: The definition of UADE used in protocol version 3.0 (Conceptus) is consistent with the definition of USADE in this protocol version (4.0). The definition of UADE in this protocol version (4.0) only applies to non-serious events. This is corrected in Amendment 6 in accordance with 21 CFR 812.3(s).
[35] The definition of serious adverse event (SAE) was updated per Amendment 6.

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 7.1.2)
- 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. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

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

g. Requires intervention to prevent permanent impairment of a body function /damage, to a body structure

Note: For the purposes of this protocol, ectopic pregnancy and spontaneous abortion are always considered as important events and therefore reported as SAEs.

7.4.1.1.2.1 Incident

Any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, led to, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Any event which meets all three basic reporting criteria (A-C) is considered an Incident:

A. An event has occurred, e.g.

• malfunction or deterioration in the characteristics or performance
• unanticipated adverse reaction or unanticipated side effect
• interactions with other substances or products
• degradation / destruction of the device
• inappropriate therapy
• inaccuracy in the labeling, instructions for use including omissions or deficiencies

B) The device is suspected to be a contributory cause of the incident.

C) The event led, or might have led, to one of the following outcomes:

- death of a patient, or user, or other person
- serious deterioration in state of health of a patient, user or other person

(See European Commission, Medical Devices: Guidance document MEDDEV 2.12-1)

7.4.1.1.2.2 Unanticipated serious adverse device effect (USADE) - *amended*

An unanticipated serious adverse device effect (USADE) is 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 (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. This is the same definition provided in the UADE Section 7.4.1.1.1.2. This has been corrected above in the UADE definition. However, as both terms have been used at various timepoints in this protocol, the definition is maintained here.[36]

7.4.1.1.3 Medical Device Report (MDR) Reportable Event

(1) 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

(2) An event that manufacturers or importers become aware of that reasonably suggest that one of their marketed devices:

(i) May have caused or contributed to a death or serious injury, or

(ii) 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.

(See 21 CFR 803 Medical Device reporting)

An MDR corresponds to the definition of Incident.

7.4.1.1.4 Device deficiency - *amended*

Inadequacy of Essure or Novasure related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.[33]

7.4.1.1.4.1 Device failure - *amended*

Failure of Essure or Novasure to perform or function as intended, including any deviations from the performance specifications or intended use (e.g., pregnancy when micro-insert properly located and fallopian tubes occluded; continued menorrhagia despite a completed endometrial ablation procedure). For the purposes of this study, a pregnancy that occurs in a subject told to rely on a commercially available Essure device for contraception is a device

[36] Modified per Amendment 6, see Section 7.4.1.1.1.2 UADE.

failure. For the purposes of this protocol, persistence or recurrence of heavy menstrual bleeding will be considered device failures for the Novasure device.[33]

7.4.1.1.4.2 Device malfunction - *amended*

Failure of Essure or Novasure to meet its performance specifications or otherwise perform as intended when used in accordance with the IFU (e.g., difficulties with deployment or detachment of micro-insert; device difficulties when conducting endometrial ablation).[33]

7.4.1.1.5 Important Medical Events and events of special interest - a*mended*

The Important Medical Events (IME) list is developed and published by European Medicines Evaluation Agency (EMA) (http://eudravigilance.ema.europa.eu/human/textforIME.asp). All AEs reported in this study will be reviewed against the most current IME list periodically, and any 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:

- Perforations of the uterus, cervix or fallopian tubes.[37]
- Upper genital tract infections (for example: endometritis, salpingo-oophoritis, salpingitis).
- Expulsion or migration of Essure inserts.
- Potential allergy/hypersensitivity to Essure inserts (for example: itch [pruritus], rash, hives [urticaria], facial edema, angioedema, allergy to metals).[37]

7.4.1.2 Classifications for adverse event assessment

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

7.4.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.4.1.1.

7.4.1.2.2 Severity

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

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
- Severe: or medically significant but not immediately life threatening – hospitalization or prolongation of hospitalization indicated, disabling; limiting self-care ADL.

[37] Added per Amendment 6.

7.4.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is the investigator's responsibility, and is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question of whether there was a "reasonable causal relationship" to the study treatment in question.

The following information must be entered on the CRF for all AEs and SAEs:

- Relation to the Essure device
- Relation to the NovaSure device
- Relation to the NovaSure procedure
- Relation to a pre-existing condition (additional description required)

Possible choices for causality include:

- Not related
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

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

- The temporal sequence from the Essure placement procedure: The event should occur after the procedure.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the Essure procedure and any other medical conditions the subject may have.
- Concomitant medication or procedures:
  Any drugs the subject is taking or additional procedures the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

7.4.1.2.4 Outcome

The outcome of the AE is to be documented as follows:

- Recovered without treatment
- Recovered with treatment
- Not recovered with permanent impairment
- Death
- Undetermined, describe:

7.4.1.3 Assessments and documentation of adverse events[38] - *amended*

Investigators must collect all AEs for each subject from the time of signing of the informed consent through the end of subject study participation, whether or not deemed related to the investigational device or procedure. All AE data will be recorded on the CRFs as well as documented in the subject's medical record and study source documents.[39]

All SAEs and SADEs will be followed until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Investigator must determine whether adverse event meets the definition of a serious adverse event; if so, it must be reported as required by Section 7.4.1.1.

Any SAE or incident will be reviewed and processed by the sponsor according to all applicable regulations.

Investigators must document all device failures, malfunctions and use errors, including the assessment of whether the event is considered an incident (ADE) using the Device Malfunction and Failure CRF.

Because an approved device will be used for the placement procedure, any device malfunctions will be reported to the sponsor's Product Surveillance department. Device malfunctions will not be analyzed as part of this study as the placement procedure and devices are not being evaluated.

7.4.1.4 Reporting of serious adverse events - *amended*

The definition of serious adverse events (SAEs) is given in Section 7.4.1.1. These include device deficiencies that may have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the sponsor's SAE reporting system.

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. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs and SADEs occurring during the observation period defined in Section 7.4.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the sponsor.[40] An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the sponsor's designated recipient.

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

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[38] Section was updated per Amendment 6.
[39] Per Amendment 5
[40] Sentence modified per Amendment 6.

In addition, device failures, malfunctions or incidents must be reported to Sponsor within 24 hours via fax or email.

Ectopic pregnancies and spontaneous abortions will always be considered as SAEs and reported as such to the Sponsor

Notification of the independent ethics committee (IEC)s / institutional review board (IRB)s

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

Notification of the authorities

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

Because this is a PAS, the Essure System is subject to Medical Device Reporting (MDR) regulations. The sponsor will review all serious adverse events and unanticipated adverse device effects and determine their reportability to FDA according to 21 Code of Federal Regulations 803 "*Medical Device Reporting*" Reporting MDRs to FDA is required when the sponsor becomes aware of information that reasonably suggests that a marketed device has or may have caused or contributed to a death, serious injury or long-term pain necessitating surgical intervention, or has malfunctioned, and that the device or a similar device marketed by the manufacturer would be likely cause or contribute to a death or serious injury if the malfunction were to recur. In the event information is received that the NovaSure System may have caused or may have contributed to a death or serious injury, the sponsor will notify the complaint handling function of the manufacturer of the device (Hologic, Inc.).

Sponsor's notification of the investigational site

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

If the adverse event is the result of an unanticipated adverse device effect, the investigator must report it to the sponsor within 3 working days after the investigator becomes aware of the event.[41] The investigator will send to the sponsor all pertinent paperwork (discharge summaries, office notes, etc.) within 5 working days.

Reports relating 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. The investigator must report it to the Ethics Committee / IRB within the required time frame.

[41] Wording modified per Amendment 6.

7.4.1.5 Expected adverse events

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

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

7.4.2 Device removal[42] – *new section*

Each time a removal procedure is performed, additional information will be collected about the circumstances surrounding the removal (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).

7.4.3 Pregnancies[43]

If a subject becomes pregnant at any time during the study, the pregnancy will be counted as an Essure device failure following a NovaSure ablation. Subject will also be counseled that she can no longer rely on Essure for contraception.

The Investigator must report to the Sponsor any pregnancy occurring in a study subject during the subject's participation in this study. 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 any outcome of the mother or the child should be reported. For all reports, the forms provided are to be used.

7.5 Other procedures and variables[43]

Not applicable.

7.6 Appropriateness of procedures / measurements[43]

Not applicable.

8. Statistical methods and determination of sample size

8.1 General considerations

The statistical analysis plan will be finalized and signed off before data release for analysis.[44]

Baseline NovaSure EA and follow-up data will be summarized using the appropriate statistical method. Continuous variables will be summarized using means, standard deviations, medians and ranges. Categorical data will be summarized using frequency rates (e.g., count/sample size).

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[42] Section added per Amendment 6.
[43] Per Amendment 4
[44] Per Amendment 4

8.2 Analysis sets[45]

Primary effectiveness cohort

All subjects who meet study entry criteria, sign a study-specific ICF, and undergo insertion of the NovaSure device transcervically.

Primary safety cohort

All subjects in whom a NovaSure procedure is attempted.

8.3 Variables[46]

- **Primary**: Occurrence of confirmed pregnancy at 1 year and 3 years among subjects relying on Essure micro-inserts for permanent birth control when NovaSure is performed following a successful Essure Confirmation Test.
- **Secondary**: Adverse event data

8.4 Statistical and analytical plans

8.4.1 Primary Endpoint

The primary effectiveness endpoint of this study is the 1-year and 3-year pregnancy rates. The rates will be calculated as done in prior Essure studies, as described below.

Each woman-month of follow-up represents a "Bernoulli trial" of the Essure device. A woman contributes as many women-months as her participation in the post-approval study. Upon observing f failures in w women-months, the posterior distribution of the monthly failure rate, r, is calculated as:

$$r = \text{beta}(a+f, b+w-f)$$

where a and b = 0.5, representing a non-informative prior distribution. The upper Bayesian credible interval of r is easily calculated from the inverse beta function. A 1-year failure rate can be calculated as:

$$\text{1-year rate} = 1-(1-r)^{12}$$

The 1-year rate will be calculated when all participating women have reached at least 1 year of follow-up.

As an additional related calculation, we will determine the 3-year failure as:

$$\text{3-year rate} = 1-(1-r)^{36}$$

For example, if there are 0 failures in 200 × 12 = 2,400 women-months, the posterior distribution of the monthly failure rate is beta(0.5, 0.5 + 2400). The upper Bayesian credible interval is (in Excel) betainv (.975, 0.5, 0.5 + 2400) = 0.00105. The upper 95% credible

[45] New section from sponsor template per Amendment 4
[46] New section from sponsor template; populated with text from previous version per Amendment 4

interval for the 1-year rate is 1-(1-0.00105)^{12} = 0.0125 or 1.25% [47]. This value meets the pre-determined study success threshold of 2.1%.

8.4.2 Secondary Endpoint

The secondary endpoint in the PAS is the incidence of adverse events when NovaSure EA is performed in the presence of Essure micro-inserts. There is no specific study hypothesis.

8.5 Planned interim analyses

For the first two years of the PAS, an interim PAS status report will be submitted every 6 months from the date of the pre-market approval (PMA) letter or other negotiated starting date (i.e., PAS initiation). Ongoing interim PAS status reports will be submitted annually, thereafter, until the final PAS report is written after the termination or completion of the PAS. The ongoing interim reports and final PAS report will include information related to PAS methodology and results/endpoints.

8.6 Determination of sample size

The primary objective of the PAS is to evaluate the contraceptive failure rate of Essure when NovaSure EA is performed following a successful Essure Confirmation Test and to demonstrate that the failure rate is reasonably low (see details below). Consistent with prior Essure clinical studies, a Bayesian approach will be used. The study will be considered a success if the posterior probability (PPr) that the observed failure rate at 1 year (rate1y) is <2.1% is at least 95%, i.e.:

$$PPr(rate1y < 0.021) > 0.95 *$$

* i.e., a Type 1 error rate of 5%

If the posterior probability that the 1-year rate is <0.021 exceeds 95%, we have shown with a high degree of confidence that the rate is at least as good as that which FDA has found acceptable for Adiana Permanent Contraceptive (PMA P070022).

Assumptions

The following assumptions were used to calculate the PAS sample size and power for the 1- and 3-year hypothesis:

- Participants in this PAS are women who have undergone the Essure procedure followed by a successful Essure Confirmation Test showing satisfactory micro-insert location and bilateral tubal occlusion on HSG OR optimal or satisfactory micro insert location on TVU;[48]
- Contraceptive failure rates after Essure are very low for the PAS population as demonstrated by prior clinical studies;
- For the purposes of power calculations, the one-year pregnancy rate is modeled as r=beta(0.5+a, 0.5+b), where beta(0.5,0.5) is a non-informative prior and a=0, b=600,

[47] Per Amendment 4
[48] TVU confirmation testing criteria added per Amendment 6

roughly the size of the Essure Phase II and Pivotal clinical trial relying cohorts in the Essure premarket studies;

- Multiple clinical trials are simulated with the underlying pregnancy rate of r;
- The one-sided upper Bayesian credible interval of the observed one-year failure rate amongst n=200 is calculated in 5000 simulated clinical trials using an underlying pregnancy rate of r;
- Power for the 1-year hypothesis is the probability that the Upper Confidence Limit of the 1-year rate is <2.1%, where 2.1% is the Upper Confidence Limit of the Adiana 1-year failure rate (Table 5: Contraceptive Failure Rates, Adiana Permanent Contraception Instructions For Use, AW-03216-001 Rev. 003);
- Power for the 3-year hypothesis is the probability that the Upper Confidence Limit of the 3-year rate is <2.8%, the Upper Confidence Limit of the Adiana 3-year failure rate (Table 5: Contraceptive Failure Rates, Adiana Permanent Contraception Instructions For Use, AW-03216-001 Rev. 003).

Given the assumed underlying failure rate for a successful Essure procedure followed by a confirmatory Essure Confirmation Test, a study of n=200 women has an 86% chance of showing that the Upper Confidence Limit of the 1-year failure rate will be <2.1%. The table below shows detailed results.

Expected number of failures at 1 year	Probability	2-sided upper credible interval
0	0.861	0.012
1	0.112	0.023
2	0.020	0.031
3	0.006	0.039
4	0.002	0.047
5	0.0004	0.054

9. Data handling and quality assurance [49]

9.1 Data recording

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from "only screened subjects (screening failures)"

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, data to be recorded in the CRF are demographic information (subject number, date of birth/age, sex, race and ethnicity), the

[49] All of Section 9 is a new section from sponsor template; populated according to sponsor guidelines per Amendment 4

reason for premature discontinuation and date of last visit. These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the CRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

- All information about the SAE
- All information related to the SAE such as:
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

9.2 Monitoring

In accordance with applicable regulations, Good Clinical Practices (GCP), and sponsor's 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
- 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) agree to allow the monitor direct access to all relevant documents.

9.3 Data processing

The data collection tool for this study will be via electronic CRF (eCRF). Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources.

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

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor'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.

9.5 Archiving

Essential documents shall be archived safely and securely 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 investigator site file 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.

10. Premature termination of the study [50]

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; 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
- If the study conduct (e.g. recruitment rate; drop-out 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.

[50] Section 10 is a new section from sponsor template; populated according to sponsor guidelines per Amendment 4

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 given by the sponsor for destruction.
- In case 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 5.2.1.

11. Ethical and legal aspects [51]

11.1 Ethical and legal conduct of the study

All sites will conduct the study according to the same protocol and will obtain approval from an Institutional Review Board (IRB) or Ethics Committee (EC) before study commencement. Additionally, all sites will be monitored in accordance with Good Clinical Practices (GCP), US medical device regulations, the Informed Consent provisions of the Declaration of Helsinki, and ISO 14155: Clinical investigation of medical devices for human subjects – Good clinical practice. The study will be registered in accordance with worldwide regulatory requirements.

11.2 Subject information and consent

Women who have the mental capacity to read, understand, sign and date the Informed Consent Form will be eligible for the study. All subjects should have a signed informed consent and all completed case report forms kept under the subject's designated number in the Study Binder.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

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

[51] Section 11 is a new section from sponsor template; populated according to sponsor guidelines and text from previous version of protocol per Amendment 4

11.4 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.

11.5 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.

12. Reference list[52]

[1]. Coad JE, Garza-Leal J, Castillo-Saenz L, et al. Essure permanent birth control followed by global endometrial ablation: an in vivo peri-hysterectomy study. J Minim Invasive Gynecol. 2010;17(suppl):S39-S40.

[2]. Coad JE, Garza-Leal J, Hernandez-Leon I, et al. Essure contraception followed by NovaSure endometrial ablation: preservation of viable tissue in-growth after ablation. J Minim Invasive Gynecol. 2011 Jul-Aug;18(4):445-448.

[3]. Garza-Leal J, Hernandez-Leon I, et al. Essure transcervical sterilization combined with NovaSure endometrial ablation: a peri-hysterectomy safety study. J Minim Invasive Gynecol. 2008;15:44S.

[4]. Saunders D. Essure and endometrial ablation: clinical studies and case reviews of Essure with 118 NovaSure procedures. OBG Management. 2010;22(3 suppl):S1-S8.

[5]. Basinski CM, Price P, Burkhart J, Johnson J. Safety and effectiveness of NovaSure endometrial ablation after placement of Essure micro-inserts. J Gynecol Surg. 2012;28(2):83-88.

[6]. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 81, May 2007. Obstet Gynecol. 2007;109(5):1233-48.[53]

[52] Section 12 is a new section from sponsor template; populated according to sponsor guidelines per Amendment 4

[53] Added per Amendment 5

13. Protocol amendments

13.1 Amendments 1 through 3

The original protocol was called Version 0 and was dated 22 DEC 2011. The protocol was subsequently amended as detailed in the table below before the acquisition of Conceptus, Inc by Bayer HealthCare, LLC.

Version Number	Description of Change	Effective Date
Version 0	Draft for FDA concurrence	December 22, 2011
Version 1	Modification of draft protocol addressing issues outlined in FDA e-mail dated January 24, 2012	February 3, 2012
Version 2	Updated section F.2 Simulation Results, Table 1, as requested in FDA e-mail dated February 15, 2012	February 15, 2012
Version 3	Revised protocol to allow subject enrollment only after subject has undergone the Essure procedure and Essure Confirmation Test. Added an inclusion criteria for subject age range from 21-50 and study requirement for enrollment of at least 50% of subjects in the age range ≤ 45. Added Abbreviations table, Risk Analysis summary, Adverse Event definitions, and Investigator Responsibilities section. Modified protocol organization and individual sections layout to facilitate use by study sites. Made other minor revisions to provide clarity and ease-of-use.	December 19, 2012

13.2 Amendment 4

Amendment 4 was approved by the FDA on 12 DEC 2014.

13.2.1 Overview of changes

Amendment 4 was initiated to incorporate changes to the safety reporting procedures and change of Sponsor responsibilities following the acquisition of Conceptus, Inc. by Bayer HealthCare, LLC. In addition, administrative changes were made, including the change of the Sponsor's medical expert as well as minor editorial changes and abbreviations were added. A few minor editorial/typographical errors were corrected for clarification.

Revision of protocol and CRFs was needed as a result of change in sponsor from Conceptus, Inc. to Bayer HealthCare.

(1) The text from Version 3 of the protocol was transferred to the Bayer protocol template, which resulted in:

a) shifting the sequence of sections in order to conform with the Bayer protocol template,

b) modification of section headers as the Bayer protocol template is not specific to medical device studies,

c) population of protocol sections that previously did not exist in Version 3 with standard language from the Bayer protocol template which reflects Bayer standard practices.

(2) The safety reporting process was transferred from Conceptus to Bayer, so language in the protocol was modified to reflect this change.

(3) Adverse events were previously categorized by the investigator and Sponsor (Conceptus) in terms of relatedness and severity to the Essure device; the current Sponsor (Bayer) will only categorize SAEs/SADEs in terms of expectedness, seriousness, and causal relationship to the Essure device which is Bayer's usual practice. Investigator responsibilities for categorizing AEs are unchanged.

(4) The exclusion criteria were modified so that potential subjects with IUD/IUS in place would be excluded only if they were unwilling to have the IUD/IUS removed prior to NovaSure EA. Also, subjects are permitted to have endometrial sampling (to ensure benign causes for menorrhagia) or IUD/IUS removal prior to the time of NovaSure EA.

(5) Appendix E was added to show general study timelines.

(6) Minor edits to clarify language from the previous protocol version.

13.2.2 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. Specific changes to the text are described by section below.

Title page and synopsis

The title page in the Bayer template was added and the sponsor's medically responsible party was added. A synopsis section was added to summarize the main points of the protocol.

1. Introduction

The majority of the content of the introduction is unchanged. It was transferred to the new protocol template. The specific text changes are shown below.

1.2. Risk of Pregnancy

Old text:

Although women undergoing EA must be finished with childbearing, EA should not be considered a means of sterilization. Pregnancy should not be elected after an ablation because it can be dangerous for both the fetus and mother; therefore, women need to have a reliable contraceptive method if they choose to undergo EA. The Essure procedure is a hysteroscopic permanent sterilization method and a complement to various EA technologies. ~~Contrariwise,~~ ~~w~~omen who have undergone hysteroscopic sterilization with the Essure procedure may

become candidates for EA procedures ~~in the future~~ should they develop menorrhagia requiring treatment.

New text:

Although women undergoing EA must be finished with childbearing, EA should not be considered a means of sterilization. Pregnancy should not be elected after an ablation because it can be dangerous for both the fetus and mother; therefore, women need to have a reliable contraceptive method if they choose to undergo EA. The Essure procedure is a hysteroscopic permanent sterilization method and a complement to various EA technologies. Women who have undergone hysteroscopic sterilization with the Essure procedure may become candidates for EA procedures should they develop menorrhagia requiring treatment in the future. This study evaluates how the NovaSure EA may affect the effectiveness and safety of Essure.

1.5.3 Risk Analysis and Conclusions from Prior Reported Data

Old text:

Clinical and commercial studies have evaluated over 250 patients who have had NovaSure EA while wearing the Essure micro-inserts. The adverse events reported in the clinical evaluations were similar to the adverse events experienced individually with each technology. All adverse events were expected, and, none of the adverse events were severe, confirming that it is safe to perform NovaSure EA on patients who are wearing the Essure micro-inserts. The most frequent adverse event that could be attributed to performing the two technologies together was the possibility of displacing or dislodging an implanted Essure micro-insert when performing NovaSure EA. The larger studies demonstrated that the Essure micro-inserts did not alter performance of NovaSure EA. The benefit of performing NovaSure EA in patients wearing the Essure micro-inserts outweighs the risk of the adverse events that are expected to occur. ~~The~~ clinical study ~~that is the subject of this protocol~~ will evaluate the ability of Essure micro-inserts to maintain contraception following NovaSure EA, providing further data to assess the risk-benefit ratio.

New text:

Clinical and commercial studies have evaluated over 250 patients who have had NovaSure EA while wearing the Essure micro-inserts. The adverse events reported in the clinical evaluations were similar to the adverse events experienced individually with each technology. All adverse events were expected, and, none of the adverse events were severe, confirming that it is safe to perform NovaSure EA on patients who are wearing the Essure micro-inserts. The most frequent adverse event that could be attributed to performing the two technologies together was the possibility of displacing or dislodging an implanted Essure micro-insert when performing NovaSure EA. The larger studies demonstrated that the Essure micro-inserts did not alter performance of NovaSure EA. The benefit of performing NovaSure EA in patients wearing the Essure micro-inserts outweighs the risk of the adverse events that are expected to occur. This clinical study will evaluate the ability of Essure micro-inserts to maintain contraception following NovaSure EA, providing further data to assess the risk-benefit ratio.

1.6. Regulatory and Commercial Labelling History

New text:

Further details can be found in the IFU, which contains comprehensive information on the study device.

2. Objectives

The objectives were not changed but they appear in a different location in the format of this amended protocol.

3. Investigators and other study personnel

The content of this section is primarily from the Bayer template but also has language taken verbatim from the previous version of the protocol.

4. Study design

Old text:

Design overview

This PAS is a prospective, multi-center, single-arm observational study to monitor and evaluate the effectiveness and safety of Essure when NovaSure is performed following a successful Essure Confirmation Test. The PAS will be conducted at up to 15 sites in the United States. Each site may enroll a maximum of ~~30~~ subjects. A minimum of 220 female subjects will be enrolled in the study. Subjects will be followed for a total of 3 years post NovaSure EA with evaluations to occur at the 1 week, 12 month, 24 month and 36 month follow-up time points. PAS subjects who have been identified as candidates for NovaSure EA and have had a successful Essure Confirmation Test will be considered.

New text:

Design overview

This PAS is a prospective, multi-center, single-arm observational study to monitor and evaluate the effectiveness and safety of Essure when NovaSure is performed following a successful Essure Confirmation Test. The PAS will be conducted at up to 15 sites in the United States. Each site may enroll a maximum of 35 subjects. A minimum of 220 female subjects will be enrolled in the study. Subjects will be followed for a total of 3 years post-NovaSure EA with evaluations to occur at the 1 week, 12 month, 24 month and 36 month follow-up time points. PAS subjects who have been identified as candidates for NovaSure EA and have had a successful Essure Confirmation Test will be considered.

5. Study population (section title was Recruitment Strategy in prior version)

5.1.1 Inclusion criteria

Old text:

6. Subject is willing to accept the risk of pregnancy while relying on the Essure micro-inserts for prevention of pregnancy

New text:

6. Subject is willing to accept the risk of pregnancy while relying on the Essure micro-inserts for prevention of pregnancy following a NovaSure ablation procedure for menorrhagia

5.1.2. Exclusion criteria

Old text:

5. Subject is currently wearing an intrauterine device

6. Subject has undergone any other intrauterine procedures in between Essure placement procedure and NovaSure EA.
7. Subject is scheduled to undergo any other intrauterine procedures at the time of NovaSure EA.

New text:

5. Subject is currently wearing an intrauterine device or intrauterine system and is unwilling to have it removed before the NovaSure EA procedure
6. Subject has undergone any other intrauterine procedures (except endometrial biopsy or sampling, if required or indicated; IUD/IUS removal is permitted) in between Essure placement procedure and NovaSure EA.
7. Subject is scheduled to undergo any other intrauterine procedures at the time of NovaSure EA (except endometrial biopsy or sampling, if required or indicated; IUD/IUS removal is permitted).

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

New text:

Subjects must be withdrawn from the study for the following reasons:

- 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.

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

Subjects may be withdrawn from the study for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

Subjects may be terminated from the study by the Investigator. Reasons for termination of a subject from the study may include, but are not limited to, the following:

- Subject does not retain device (e.g. due to removal of device, expulsion, salpingectomy or other utero-tubal surgeries)
- Death
- An AE preventing study participation
- Lost to follow-up and inability to contact the subject. Note that if a subject who is lost to follow-up is recontacted, the subject will not be considered to have withdrawn from the study.

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already undergone the NovaSure procedure.

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 above) is regarded a "screening failure".

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

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

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10 (Premature termination of the study).

5.2.2 Replacement

Subjects will not be replaced if withdrawn or terminated from the study.

5.3. Subject identification

After subjects have signed the informed consent form (ICF), they will be identified by a unique 5-digit subject identification number. The subject identification number which will identify the subject throughout the study is constructed as follows:

- Digit 1-2: Study center number
- Digit 3-5: Subject number, unique within any study center. Sequential number reflecting the order in which the subjects signed the ICF at the center.

Section 6 did not exist in the previous version by name and is now populated with the appropriate text from the previous version of the protocol.

6. Treatment

6.1 Treatments to be administered

In this study, the NovaSure EA procedure following successful placement of a commercially available Essure device is the treatment being administered. The Essure device, with the exception of relatedness of AEs, and placement procedure are not being evaluated.

6.2 Identity of study treatment

Not applicable.

6.3 Treatment assignment

This is a non-randomized, continuous enrollment study in which all eligible subjects will be asked to enroll. To avoid selection bias, Investigators will offer enrollment in the study to all eligible subjects consecutively (as they present themselves to the Investigator).

A subject may not be enrolled in the study until she has an Essure confirmation test done that documents bilateral satisfactory device location and fallopian tube occlusion. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion, she may repeat the Essure Confirmation Test.

6.4 Dosage and administration

Not applicable.

6.5 Blinding

Blinding will not occur in this study. Procedures and Follow-up for emergency unblinding are not required.

6.6 Device logistics and accountability

Not applicable.

6.7 Treatment compliance

The Essure device is intended for subjects who desire permanent contraception (female sterilization) and is not intended to be removed.

6.8 Post-study therapy

Not applicable.

6.9 Prior and concomitant therapy

Gynecological procedures and medications necessary for the subject's well-being will be allowed during the study. Any medical treatment administered for the treatment of AEs that occur during the study will be recorded in the CRF.

7.1.2.2. NovaSure EA Procedure (Day 0)

Old text:

The Investigator or designated study staff will confirm that the subject has not experienced an adverse event since the Eligibility and Screening Visit.

The NovaSure procedure will be performed in accordance with the NovaSure EA IFU and Controller Operator's Manual.

At the time of the procedure, subject's uterine cavity will be assessed to ensure that uterine cavity length is not less than 4 cm and uterine cavity width is not less than 2.5 cm; if they are, subject is ineligible to participate in the study.

New text:

The Investigator or designated study staff will confirm that the subject has not experienced an adverse event since the Eligibility and Screening Visit.

The NovaSure procedure will be performed in accordance with the NovaSure EA IFU and Controller Operator's Manual.

At the time of the procedure, subject's uterine cavity will be assessed to ensure that uterine cavity length is not less than 4 cm and uterine cavity width is not less than 2.5 cm (see Exclusion criteria 8; Section 5.1.2); if they are, subject is ineligible to participate in the study.

7.1.2.5 Notification of Other Relevant Events

Old text:

The subject should be instructed at the beginning of the study to inform the site immediately if subject has had or is scheduled to have any surgery which may remove some or all of her reproductive organs (i.e. hysterectomy, salpingectomy or oophorectomy). ~~The site should call Conceptus immediately to make arrangements to have extirpated tubes containing the micro-inserts shipped to Conceptus which will in turn, send them out for histological evaluation~~.

The subject will also be instructed to contact the Investigator immediately if, at any time during the study, subject thinks she might be pregnant.

If a subject experiences a micro-insert expulsion or removal during or following the NovaSure procedure, subject will be followed for the duration of the adverse event, then terminated from the study.

New text:

The subject should be instructed at the beginning of the study to inform the site immediately if subject has had or is scheduled to have any surgery which may remove some or all of her reproductive organs (i.e. hysterectomy, salpingectomy or oophorectomy).

The subject will also be instructed to contact the Investigator immediately if, at any time during the study, subject thinks she might be pregnant.

If a subject experiences a micro-insert expulsion or removal during or following the NovaSure procedure, subject will be followed for the duration of the adverse event, then terminated from the study.

Section 7.2 did not exist in the previous version by name and is now populated with the appropriate text from the previous version of the protocol.

7.2 Population characteristics

7.2.1 Demographics

Demographic data collected include, but may not be limited to, date of birth (as allowed by local law), race, and ethnicity.

7.2.2 Medical history

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

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.5.1.1.

Section 7.4 did not exist in the previous version by name and is now populated according to sponsor template requirements.

7.4. Safety

Old text:

~~**J. Safety**~~

~~**J.1 Adverse Events**~~

~~**J.1.1** Adverse event information will be collected from the time the subject signs the informed consent through the time the patient terminates from or completes the study. Subjects who experience an adverse event will be followed until the resolution of the adverse event or stabilization of the patients health (in the case of long-term event), regardless of a scheduled or unscheduled termination. An event will be considered resolved when the subject health returns to its baseline state.~~

~~**J.1.2** Adverse events will be recorded on the CRFs by the Investigator or study staff. Event, date of onset, severity, duration, and relationship to device or procedure will be recorded on the appropriate CRF.~~

- ~~Investigator must determine whether adverse event meets the definition of a serious adverse event; if so, it must be reported as required by Section J.3.~~
- ~~Investigator must determine whether adverse event is an unanticipated adverse device effect; if so, it must be reported as required by Section J.4.~~

~~**J.1.3** Conceptus will ensure independent review and adjudication of the reported adverse events by an external third-party physician for procedure or device relatedness.~~

~~J.2 Definitions~~

~~Adverse Event - An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and including events related to the procedure(s) involved.~~

~~Relatedness~~

~~Not Related – The adverse event is clearly not related to the intervention~~

~~Possible – The adverse event may be related to the intervention~~

~~Probable – The adverse event is likely related to the intervention~~

~~Definite – The adverse event is clearly related to the intervention~~

~~Serious adverse event is an event that:~~

- ~~Led to death,~~
- ~~Led to serious deterioration in the health of the subject, that either resulted in~~
  - ~~A life-threatening illness or injury, or~~
  - ~~A permanent impairment of a body structure or a body function, or~~
  - ~~In-patient or prolonged hospitalization, or~~
  - ~~Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or~~
- ~~Led to fetal distress, fetal death or a congenital abnormality or birth defect~~

~~Planned hospitalization for a pre-existing condition, or a procedure required by the PAS protocol, without serious deterioration in health, is not considered a serious adverse event.~~

Severity

Mild - asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate - minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Severe or medically significant but not immediately life-threatening - hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

~~Life-threatening consequences - urgent intervention indicated.~~

~~Death related to AE.~~

~~Unanticipated adverse device effect means 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 (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.~~

~~J.3 Serious Adverse Events Reporting Requirements~~

~~J.3.1~~ ~~If the adverse event is a serious adverse event (including device or procedure-related adverse events/effects and deaths), the Investigator must report it immediately (within 24 hours) by telephone to Conceptus at 650.962.4055. The Investigator will send to Conceptus all pertinent paperwork (discharge summaries, office notes, etc.) within 5 working days. Reports relating to the subject's subsequent medical course must be submitted to Conceptus until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.~~

~~The Investigator must also report all required adverse events to the relevant IRB / Ethics Committee in accordance with IRB / Ethics Committee requirements.~~

~~J.4 Unanticipated Adverse Device Effect Reporting Requirements~~

~~J.4.1~~ ~~If the adverse event is also an unanticipated adverse device effect,~~

~~J.4.2~~ ~~The Investigator must report it to Conceptus within 3 working days after the Investigator becomes aware of the event.~~

- ~~The Investigator will send to Conceptus all pertinent paperwork (discharge summaries, office notes, etc.) within 5 working days.~~
- ~~Reports relating to the subject's subsequent medical course must be submitted to Conceptus until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.~~
- ~~The Investigator must report it to the Ethics Committee / IRB within the required time frame.~~

~~J.5 MDR Reportable Events~~

~~Because this is a PAS, the Essure System is subject to Medical Device Reporting (MDR) regulations. Conceptus' product surveillance department will review all serious adverse events and unanticipated adverse device effects and determine their reportability to FDA according to 21 Code of Federal Regulations 803 "Medical Device Reporting." Reporting MDRs to FDA is required when the manufacturer (Conceptus, Inc.) becomes aware of information that reasonably suggests that a marketed device has or may have caused or~~

~~contributed to a death, serious injury or long-term pain necessitating surgical intervention, or has malfunctioned, and that the device or a similar device marketed by the manufacturer would be likely cause or contribute to a death or serious injury if the malfunction were to recur. In the event information is received that the NovaSure System may have caused or may have contributed to a death or serious injury, Conceptus' product surveillance department will notify the complaint handling function of the manufacturer of the device (Hologic, Inc.).~~

~~**J.6 Device Failures and Malfunctions**~~

~~All device failures and malfunctions should be reported to Conceptus on the appropriate CRF. These will be reported in the PAS results. Essure System devices that fail or malfunction should be returned to Conceptus for analysis after appropriate decontamination per Study Site guidelines.~~

~~**J.6.1 Device Failure**~~

~~For this protocol, device failure will be defined as the failure of a device to perform as intended even though the device was successfully used according to the labeling.~~ (E.g. pregnancy when micro-insert properly located and fallopian tubes occluded; continued menorrhagia despite a completed endometrial ablation procedure)

~~**J.6.2 Device Malfunction**~~

~~For this protocol, a device malfunction will be defined as the failure of a device to meet its performance specifications or to function as intended when used according to the labeling.~~ (E.g. Difficulties with deployment or detachment of micro-insert; device difficulties when conducting endometrial ablation)

~~Contact Conceptus Product Surveillance~~

~~In order to return devices, contact Conceptus' Product Surveillance department at~~ PPD ~~option 5.~~

New text:

7.4.1.1. Definitions

7.4.1.1.1 Adverse event

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 subject or 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) product or device.

7.4.1.1.1.1 Adverse device effect (ADE)

An AE related to the use of Essure, including AEs resulting from insufficient or inadequate instructions for use, deployment, implant (placement), installation or operation or any malfunction of the investigational medical device, use error or from intentional misuse of the medical device.

7.4.1.1.1.2 Unanticipated adverse device effect (UADE)

An AE is considered unanticipated if, by its nature, incidence, severity, or outcome it has not been identified in the IFU.

(Added as footnote 24): The definition of UADE used in protocol version 3.0 (Conceptus) is consistent with the definition of USADE in this protocol version (4.0). The definition of UADE in this protocol version (4.0) only applies to non-serious events.

7.4.1.1.2 Serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence but is not related to a medical device that, meets any of the following criteria:

1. Led to death
2. Led to a serious deterioration in the health of the subject that:
    - resulted in a life-threatening illness or injury
    - resulted in a permanent impairment of a body structure or body function
    - required hospitalization or prolongation of existing hospitalization
    - resulted in a medical or surgical intervention to prevent permanent impairment to body structure or function

Note: For the purposes of this protocol, ectopic pregnancy and spontaneous abortion are always considered as important events and therefore reported as SAEs.

7.4.1.1.2.1 Incident

Any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, led to, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Any event which meets all three basic reporting criteria (A-C) is considered an Incident:

B. An event has occurred, e.g.

• malfunction or deterioration in the characteristics or performance

• unanticipated adverse reaction or unanticipated side effect

• interactions with other substances or products

• degradation / destruction of the device

• inappropriate therapy

• inaccuracy in the labeling, instructions for use including omissions or deficiencies

B) The device is suspected to be a contributory cause of the incident.

C) The event led, or might have led, to one of the following outcomes:

- death of a patient, or user, or other person

- serious deterioration in state of health of a patient, user or other person

(See European Commission, Medical Devices: Guidance document MEDDEV 2.12-1)

7.4.1.1.2.2 Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect (USADE) is 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 (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.4.1.1.3 Medical Device Report (MDR) Reportable Event

(1) 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

(2) An event that manufacturers or importers become aware of that reasonably suggest that one of their marketed devices:

(i) May have caused or contributed to a death or serious injury, or

(ii) 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.

(See 21 CFR 803 Medical Device reporting)

An MDR corresponds to the definition of Incident.

7.4.1.1.4 Device deficiency

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

7.4.1.1.4.1 Device failure

Failure of Essure to perform or function as intended, including any deviations from the performance specifications or intended use (e.g., pregnancy when micro-insert properly located and fallopian tubes occluded; continued menorrhagia despite a completed endometrial ablation procedure). For the purposes of this study, a pregnancy that occurs in a subject told to rely on a commercially available Essure device for contraception is a device failure.

7.4.1.1.4.2 Device malfunction

Failure of Essure to meet its performance specifications or otherwise perform as intended when used in accordance with the IFU (e.g., difficulties with deployment or detachment of micro-insert; device difficulties when conducting endometrial ablation).

7.4.1.1.5 Important Medical Events and events of special interest

The Important Medical Events (IME) list is developed and published by European Medicines Evaluation Agency (EMA) (http://eudravigilance.ema.europa.eu/human/textforIME.asp). All AEs reported in this study will be reviewed against the most current IME list periodically, and any 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:

- Upper genital tract infections (for example: endometritis, salpingo-oophoritis, salpingitis).
- Expulsion or migration of Essure inserts.

7.4.1.2. Classifications for adverse event assessment

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

7.4.1.2.1. Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.4.1.1.

7.4.1.2.2. Severity

The severity of an AE is classified according to the following categories:[54]

7.4.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is the investigator's responsibility, and is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question of whether there was a "reasonable causal relationship" to the study treatment in question.

The following information must be entered on the CRF for all AEs and SAEs:

- Relation to the Essure device
- Relation to the NovaSure device
- Relation to the NovaSure procedure
- Relation to a pre-existing condition (additional description required)

Possible choices for causality include:

- Not related
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

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

[54] (existing definitions of severity were maintained in this section, only the introductory sentence is new)

- The temporal sequence from the Essure placement procedure: The event should occur after the procedure.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the Essure procedure and any other medical conditions the subject may have.
- Concomitant medication or procedures:
  Any drugs the subject is taking or additional procedures the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

7.4.1.2.4. Outcome

The outcome of the AE is to be documented as follows:

- Recovered without treatment
- Recovered with treatment
- Not recovered with permanent impairment
- Death
- Undetermined, describe:

7.4.1.3. Assessments and documentation of adverse events

Investigators must collect all AEs for each subject from the time of signing of the informed consent through the end of subject study participation, whether or not deemed related to the investigational device or procedure. All AE data will be recorded on the CRFs as well as documented in the subject's medical record.

All SAEs and SADEs will be followed until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Investigator must determine whether adverse event meets the definition of a serious adverse event; if so, it must be reported as required by Section 7.4.1.1.

Any SAE or incident will be reviewed and processed by the sponsor according to all applicable regulations.

Investigators must document all device failures, malfunctions and use errors, including the assessment of whether the event is considered an incident (ADE) using the Device Malfunction and Failure CRF.

Investigator must determine whether adverse event is an unanticipated adverse device effect; if so, it must be reported as required by Section 7.4.1.1.

Because an approved device will be used for the placement procedure, any device malfunctions will be reported to the sponsor's Product Surveillance department. Device malfunctions will not be analyzed as part of this study as the placement procedure and device are not being evaluated.

7.4.1.4. Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.4.1.1. These include device deficiencies that may have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the sponsor's SAE reporting system.

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. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs and incidents (ADEs) occurring during the observation period defined in Section 7.4.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the sponsor. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the sponsor's designated recipient.

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

In addition, device failures, malfunctions or incidents must be reported to Sponsor within 24 hours via fax or email.

Ectopic pregnancies and spontaneous abortions will always be considered as SAEs and reported as such to the Sponsor

Notification of the independent ethics committee (IEC)s / institutional review board (IRB)s

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

Notification of the authorities

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

Because this is a PAS, the Essure System is subject to Medical Device Reporting (MDR) regulations. The sponsor will review all serious adverse events and unanticipated adverse device effects and determine their reportability to FDA according to 21 Code of Federal Regulations 803 "*Medical Device Reporting*" Reporting MDRs to FDA is required when the sponsor becomes aware of information that reasonably suggests that a marketed device has or may have caused or contributed to a death, serious injury or long-term pain necessitating surgical intervention, or has malfunctioned, and that the device or a similar device marketed by the manufacturer would be likely cause or contribute to a death or serious injury if the malfunction were to recur. In the event information is received that the NovaSure System

may have caused or may have contributed to a death or serious injury, the sponsor will notify the complaint handling function of the manufacturer of the device (Hologic, Inc.).

Sponsor's notification of the investigational site

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

If the adverse event is also an unanticipated adverse device effect, the investigator must report it to the sponsor within 3 working days after the investigator becomes aware of the event. The investigator will send to the sponsor all pertinent paperwork (discharge summaries, office notes, etc.) within 5 working days.

Reports relating 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. The investigator must report it to the Ethics Committee / IRB within the required time frame.

7.4.1.5. Expected adverse events

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

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

7.4.2 Pregnancies

Section 7.4.2 did not exist in the previous version by name and is now populated according to sponsor template requirements.

New text:

If a subject becomes pregnant at any time during the study, the pregnancy will be counted as an Essure device failure following a NovaSure ablation. Subject will also be counseled that she can no longer rely on Essure for contraception.

Sections 7.5 and 7.6 did not exist in the previous version by name and are now populated according to sponsor template requirements.

7.5 Other procedures and variables

Not applicable.

7.6 Appropriateness of procedures / measurements

Not applicable.

8.1. General considerations

Old text:

Baseline NovaSure EA and follow-up data will be summarized using the appropriate statistical method. Continuous variables will be summarized using means, standard deviations, medians and ranges. Categorical data will be summarized using frequency rates (e.g., count/sample size).

New text:

The statistical analysis plan will be finalized and signed off before data release for analysis.

Baseline NovaSure EA and follow-up data will be summarized using the appropriate statistical method. Continuous variables will be summarized using means, standard deviations, medians and ranges. Categorical data will be summarized using frequency rates (e.g., count/sample size).

Sections 8.2 and 8.3 did not exist in the previous version by name and are now populated according to sponsor template requirements.

8.2 Analysis sets

Primary effectiveness cohort

All subjects who meet study entry criteria, sign a study-specific ICF, and undergo insertion of the NovaSure device transcervically.

Primary safety cohort

All subjects in whom a NovaSure procedure is attempted.

8.3 Variables

- Primary: Occurrence of confirmed pregnancy at 1 year and 3 years among subjects relying on Essure micro-inserts for permanent birth control when NovaSure is performed following a successful Essure Confirmation Test.
- Secondary: Adverse event data

8.4.1 Primary variable

Old text:

For example, if there are 0 failures in 200 × 12 = 2,400 women-months, the posterior distribution of the monthly failure rate is beta (0.5, 0.5 + 2400). The upper Bayesian credible interval is (in Excel) betainv (.975, 0.5, 0.5 + 2400) = 0.00105. The upper 95% credible interval for the 1-year rate is $1-(1-0.00105)^{12} = 0.012$ or 1.2%. This value meets the pre-determined study success threshold of 2.1%.

New text:

For example, if there are 0 failures in 200 × 12 = 2,400 women-months, the posterior distribution of the monthly failure rate is beta(0.5, 0.5 + 2400). The upper Bayesian credible interval is (in Excel) betainv (.975, 0.5, 0.5 + 2400) = 0.00105. The upper 95% credible interval for the 1-year rate is $1-(1-0.00105)^{12} = 0.0125$ or 1.25%. This value meets the pre-determined study success threshold of 2.1%.

8.5. Planned interim analyses

Old text:

~~Based upon Conceptus data on the average monthly rate of Essure micro-insert placement and estimates of NovaSure procedures by physicians throughout the United States, it is believed that each PAS Investigator/site will perform about 1 procedure per month. As such, Conceptus expects this PAS to maintain the following timeline:~~

~~Expected date of study initiation~~	~~October 2012~~
~~Expected rate per month of PAS sites with IRB approval~~	~~2~~
~~Expected date of initiation of patient enrollment~~	~~November 2012~~
~~Expected rate per month per site of subjects enrolled~~	~~1~~
~~Expected date for subject enrollment completion~~	~~March 2014~~
~~Expected date of final subject follow-up~~	~~April 2017~~
~~Expected date complete final PAS report~~	~~June 2017~~

New text and new Table:

For the first two years of the PAS, an interim PAS status report will be submitted every 6 months from the date of the pre-market approval (PMA) letter or other negotiated starting date (i.e., PAS initiation). Ongoing interim PAS status reports will be submitted annually, thereafter, until the final PAS report is written after the termination or completion of the PAS. The ongoing interim reports and final PAS report will include information related to PAS methodology and results/endpoints.

(The table was moved to Section 14 (Appendices – Appendix E) with changes in wording and dates.)

9. Data management and quality assurance

Old text:

~~J.9A.1 Site Data Monitoring and Quality Control~~

~~Each PAS study site must be experienced with both the Essure and NovaSure procedures and have appropriate equipment and facilities to conduct the study. In addition, a prospective PAS site will be evaluated to ensure that it has an adequate patient base and can provide sufficient staff and documentation support to conduct the PAS properly. A site qualification / site initiation visit will be conducted with each study site in order to orient the prospective Investigator and study staff to the PAS and protocol, applicable regulations and requirements,~~

~~and expectations of the PAS, including the numbers and time frame for patient enrollment, patient selection, Informed Consent, required clinical data and record keeping, etc.~~

~~PAS site monitoring will be performed by Conceptus personnel or their designees. Each site will be routinely remotely/centrally/on-site monitored to ensure that the PAS is conducted in full compliance with all applicable regulations, and with the PAS protocol. Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation for a specified period. If corrective actions are not subsequently undertaken, the PAS site will be asked to withdraw.~~

~~A designated site monitor will maintain personal contact with the Investigator and staff throughout the PAS by phone, mail, and on-site visits. The site monitor will compile and file an observation report at each visit. Monitoring will ensure continued PAS protocol compliance, adequate patient enrollment and accurate data reporting.~~

~~At the close of the PAS, the site monitor will perform a final on-site close-out visit. The purpose of this visit is to collect all outstanding PAS data documents, ensure that the Investigator's files are accurate and complete, ensure completion and submission of IRB / Ethics Committee final report, review record retention requirements with the Investigator, and ensure that all applicable requirements are met for the PAS. The observations and actions made at this visit will be documented as a final report. One year following the close-out visit, the Investigator must provide a financial disclosure form to Conceptus.~~

New text:

9.1 Data recording

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from “only screened subjects (screening failures)”

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, data to be recorded in the CRF are demographic information (subject number, date of birth/age, sex, race and ethnicity), the reason for premature discontinuation and date of last visit. These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the CRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

- All information about the SAE
- All information related to the SAE such as:
    - Concomitant medication
    - Medical history
    - Other information needed for SAE complementary page

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's 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
- 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.

9.3 Data processing

The data collection tool for this study will be via electronic CRF (eCRF). Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources.

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

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor'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.

9.5 Archiving

Essential documents shall be archived safely and securely 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 investigator site file 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.

Section 10 did not exist in the previous version by name and is now populated according to sponsor template requirements.

New text:

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; 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
- If the study conduct (e.g. recruitment rate; drop-out 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 given by the sponsor for destruction.
- In case 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 5.2.1.

Section 11 did not exist in the previous version by name and is now populated according to sponsor template requirements.

New text:

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

All sites will conduct the study according to the same protocol and will obtain approval from an Institutional Review Board (IRB) or Ethics Committee (EC) before study commencement. Additionally, all sites will be monitored in accordance with Good Clinical Practices (GCP), US medical device regulations, the Informed Consent provisions of the Declaration of Helsinki, and ISO 14155: Clinical investigation of medical devices for human subjects – Good clinical practice. The study will be registered in accordance with worldwide regulatory requirements.

11.2 Subject information and consent

Women who have the mental capacity to read, understand, sign and date the Informed Consent Form will be eligible for the study. All subjects should have a signed informed consent and all completed case report forms kept under the subject's designated number in the Study Binder.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

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

11.4 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.

11.5 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.

Section 12 (Reference List) was added per the sponsor template requirements.

13.3 Amendment 5

13.3.1 Overview of changes

Amendment 5 was initiated to address recruitment challenges by revising eligibility criteria (see Modifications 1 and 2 below) and increase the number of sites (see Modification 3) that can participate in the study. In addition, other changes were made that were deemed important for the conduct of the study (see Modification 4).

13.3.1.1 Modification 1: revision of exclusion criterion #4

For Essure confirmation test, the allowed time window was extended (up to 1 week prior to 3 months from the date of placement).

Rationale for change: the study team received feedback from sites that they had potential subjects who had undergone Essure Confirmation Testing at just under 3 months from the date of Essure insert placement. Allowing a window of up to 1 week prior to the 3 months post-placement for the confirmation test may allow additional subjects to be enrolled and is not expected to have an effect on the success of the confirmation test.

Sections affected by this modification:

- Section 5.1.2 Exclusion criteria

13.3.1.2 Modification 2: revision of exclusion criterion #6

The wording related to procedures done between Essure placement and NovaSure EA was modified to allow procedures, as long as they permit direct visualization of the inserts (for example, direct hysteroscopic visualization or ultrasound guidance are permitted) while assessing that menorrhagia is due to benign cause.

Rationale for change: While the protocol allows for endometrial biopsy or sampling to assess the endometrium prior to ablation, feedback from investigators indicated that standard medical practice for their site included evaluation of the uterine cavity and endometrium with saline infusion sonography or diagnostic hysteroscopy [[6]].

Sections affected by this modification:

- Section 5.1.2 Exclusion criteria
- Section 12 Reference list

13.3.1.3 Modification 3: number of sites increase

The number of sites was increased from 15 to 30.

Rationale for the change: An increase in the number of sites is expected to increase subject recruitment.

Sections affected by this modification:

- Section 4 Study design
- Section 14 Appendices

13.3.1.4 Modification 4: minor clarifications

A. "Not pertaining to the study indication" as one of the criteria for medical history was deleted.

Rationale for the changes:

"Not pertaining to the study indication" was included previously in Protocol Amendment 4 as this text was part of the sponsor's protocol template. "Not pertaining to study indication" was meant to specify the diagnosis that is being studied in the trial. For this trial, all subjects are required to have menorrhagia due to benign causes to enroll. Therefore, it would be redundant to include in the medical history "menorrhagia" for all study subjects, as it's understood that all subjects in the trial have menorrhagia in order to participate. The diagnosis of menorrhagia due to benign causes is covered by the inclusion criteria.

Since the submission of Protocol Amendment 4, feedback has been received by the sponsor that the statement "not pertaining to the study indication" was confusing and seemed contradictory with "considered relevant to the study" Therefore, for this protocol amendment, "not pertaining to study indication" was deleted to avoid confusion with "considered relevant to the study."

Sections affected by this modification:

- Section 7.2.2 Medical history

B. It was clarified that AEs should be recorded in the subjects' source documents in addition to the subjects' medical records.

- Section 7.4.1.3 Assessments and documentation of adverse events

13.3.2 Changes to the protocol text

13.3.2.1 Section 4 Study design

This section was changed as a result of Modification 3.

Old text:

The PAS will be conducted at up to ~~15~~ sites in the United States.

New text:

The PAS will be conducted at up to 30 sites in the United States.

13.3.2.2 Section 5.1.2 Exclusion criteria

This section was changed as a result of Modifications 1 and 2.

Old text:

4. Subject's Essure Confirmation Test was performed less than three months from the date of Essure placement

New text:

4. Subject's Essure Confirmation Test was performed less than three months (up to 1 week prior to 3 months is considered acceptable) from the date of Essure placement

Old text:

6. Subject has undergone any ~~blind (for example without direct hysteroscopic visualization or ultrasound guidance)~~ intrauterine ~~procedures (except~~ Endometrial biopsy or sampling~~,~~ if required or indicated~~;~~ IUD/IUS removal is permitted~~) in between Essure placement procedure and NovaSure EA~~

New text:

6. Subject has undergone any intrauterine procedure in between Essure placement procedure and NovaSure EA. Endometrial biopsy or sampling if required or indicated is permitted. IUD/IUS removal is permitted. Procedures which permit direct visualization of the inserts while assessing the endometrium to ensure that menorrhagia is due to benign causes (e.g. saline infusion sonography or diagnostic hysteroscopy) are permitted [6]

13.3.2.3 Section 7.2.2 Medical history

This section was changed as a result of Modification 4.

Deleted text:

- ~~Not pertaining to the study indication~~

13.3.2.4 Section 7.4.1.3 Assessments and documentation of adverse events

This section was changed as a result of Modification 4.

Old text:

All AE data will be recorded on the CRFs as well as documented in the subject's medical record.

New text:

All AE data will be recorded on the CRFs as well as documented in the subject's medical record and study source documents.

13.3.2.5 Section 12 Reference list

This section was changed as a result of Modification 2.

Added text:

[6] ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 81, May 2007. Obstet Gynecol. 2007;109(5):1233-48.

13.3.2.6 Section 14 Appendices

This section was changed as a result of Modification 3.

Old text/timelines:

Revised/projected study milestones based on enrollment rates:

Study start date – First subject enrolled	November 2012
Expected subject enrollment at 12 sites (subjects/month/site)	~~0.5~~
Expected subject enrollment rate per year	~~80~~
Expected subject enrollment completion date	~~OCT 2015~~
Expected final subject follow-up date	~~NOV 2018~~
Expected completion of final post-approval study report	~~MAY 2019~~

New text/timelines:

Revised/projected study milestones based on enrollment rates:

Study start date – First subject enrolled	NOV 2012
Expected subject enrollment at 12 sites (subjects/month/site)	0.4
Expected subject enrollment rate per year	43 based on 9 current sites able to enroll
Expected subject enrollment completion date	DEC 2017
Expected final subject follow-up date	JAN 2021
Expected completion of final post-approval study report	JUL 2021

13.4 Amendment 6

13.4.1 Overview of changes

13.4.1.1 Modification 1: addition of the TVU as an approved method for Essure Confirmation Test

Rationale for change: In June 2015, TVU/HSG confirmation testing was approved for inclusion in the US IFU.

Sections affected by this modification:

- Synopsis
- Section 5.1.1 Inclusion criteria
- Section 6.3 Treatment assignment
- Section 7.1.2.1 Eligibility and Screening Visit (-30 days)
- Section 8.6 Determination of sample size

13.4.1.2 Modification 2: definition of a successful Essure Confirmation test was clarified

Rationale for change: Language in the protocol was aligned with language in the IFU and the definition of a successful ECT was clarified.

Sections affected by this modification:

- Section 2 Study objectives

13.4.1.3 Modification 3: modification of the Bayer template language regarding withdrawal criteria

Rationale for change: Since compliance with wearing the device is not an issue as it is permanent, this language is being removed.

Sections affected by this modification:

- Section 5.2.1 Withdrawal

13.4.1.4 Modification 4: information regarding the follow-up of adverse events was specified

Rationale for change: As subjects are consented for data collection until the 3-year telephone contact, according to ICH-GCP no further study data can be collected beyond this point. However, serious adverse events and pregnancies are followed to resolution by Bayer's pharmacovigilance department. The follow-up of non-serious AEs after 3 years is done according to the investigator's medical judgment and local standard of care.

Sections affected by this modification:

- Section 7.1.2.4 One-, Two- and Three-Year Post-EA Phone Call (± 28 days)

13.4.1.5 Modification 5: NovaSure device was included in the definition of the adverse device effect, device deficiency, failure and malfunction

Rationale for change: Since NovaSure is a medical device that will be used during the study, adverse device effects related to the use of NovaSure as well as NovaSure device deficiency, failure and malfunction are possible.

Sections affected by this modification:

- Section 7.4.1.1.1.1 Adverse device effect (ADE)
- Section 7.4.1.1.4 Device deficiency
- Section 7.4.1.1.4.1 Device failure
- Section 7.4.1.1.4.2 Device malfunction

13.4.1.6 Modification 6: definition of the unanticipated adverse device effect was modified for consistency

Rationale for change: This is the definition for unanticipated adverse device effect that is listed in the code of Federal Register (CFR).

Sections affected by this modification:

- Section 7.4.1.1.1.2 Unanticipated adverse device effect (UADE)

13.4.1.7 Modification 7: the definition of serious adverse event (SAE) was revised

Rationale for change: Clarification of SAE definition and to align with Bayer internal language for SAE definition.

Sections affected by this modification:

- Section 7.4.1.1.2 Serious adverse event (SAE)

13.4.1.8 Modification 8: definition of USADE was clarified

Rationale for change: Since the protocol defines UADE and USADE separately but in the CFR the term UADE in fact refers to serious adverse events, a statement was added in the protocol to avoid confusion.

Sections affected by this modification:

- Section 7.4.1.1.2.2 Unanticipated serious adverse device effect (USADE)

13.4.1.9 Modification 9: perforations and potential allergy/hypersensitivity to Essure inserts were added to the Important Medical Events and events of special interest

Rationale for change: To collect information on perforations of the uterus, cervix or fallopian tubes and to help identify any study subjects who develop potential allergy or hypersensitivity to Essure inserts.

Sections affected by this modification:

- Section 7.4.1.1.5 Important Medical Events and events of special interest

13.4.1.10 Modification 10: instructions for the Investigator to assess whether an AE is an unanticipated adverse device effect were removed

Rationale for change: Change was made in order to align with Bayer safety reporting processes. Following the change in sponsor of this study from Conceptus to Bayer, this

question is no longer required to be answered by the investigator as this is an internal sponsor assessment.

Sections affected by this modification:

- Section 7.4.1.3 Assessments and documentation of adverse events

13.4.1.11 Modification 11: addition of a new section regarding device removal

Rationale for change: Addition of a device removal CRF to obtain more robust information regarding device removals.

Sections affected by this modification:

- Section 7.4.2 Device removal

13.4.1.12 Modification 12: minor edits and clarifications

Rationale for change: Minor edits and clarifications that were not previously identified in protocol Amendment 5.

Sections affected by this modification:

- Title page
- Section 7.4.1.4 Reporting of serious adverse events
- Section 14 Appendices

13.4.2 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. Specific changes to the text are described by section below.

13.4.2.1 Title page

Section revised per modification 12.

Old text:

Bayer HealthCare, LLC
~~1011 McCarthy Boulevard~~
~~Milpitas, CA 95035~~
USA

New text:

Bayer HealthCare, LLC
100 Bayer Boulevard
Whippany, NJ 07981
USA

13.4.2.2 Synopsis

Section revised per modification 1.

Old text:

Diagnosis and main criteria for inclusion	[…] • Subject has a successful Essure Confirmation Test ~~with~~ satisfactory micro-insert location ~~and fallopian tube occlusion in both tubal ostia~~ documented in her subject record. […]

New text:

Diagnosis and main criteria for inclusion	[…] • Subject has a successful Essure Confirmation Test showing bilateral satisfactory micro-insert location (when using transvaginal ultrasound [TVU]) or both bilateral satisfactory location and tubal occlusion (when using a modified hysterosalpingogram [HSG]) documented in her subject record. […]

13.4.2.3 Section 2 Study objectives

Section revised per modification 2.

Old text:

The objectives of this study are to:

- Evaluate the contraceptive failure rate of Essure when NovaSure is performed following a successful Essure Confirmation Test, and

[…]

New text:

The objectives of this study are to:

- Evaluate the contraceptive failure rate of Essure when NovaSure is performed following a successful Essure Confirmation Test*, and

[…]

* Successful Essure Confirmation Test = satisfactory bilateral micro-insert location and fallopian tube occlusion when using HSG, or satisfactory or optimal bilateral micro-insert location and retention in both tubal ostia when using transvaginal ultrasound (TVU) (i.e. the subject is able to rely on Essure for contraception). Note: all subsequent descriptions of "successful" Essure confirmation test refer to this definition.

13.4.2.4 Section 5.1.1 Inclusion criteria

Section revised per modification 1.

Old text:

[…]

3. Subject has a successful Essure Confirmation Test ~~with~~ satisfactory micro-insert location ~~and fallopian tube occlusion in both tubal ostia~~ documented in her subject record

[…]

New text:

[…]

3. Subject has a successful Essure Confirmation Test showing bilateral satisfactory micro-insert location (when using transvaginal ultrasound [TVU]) or both bilateral satisfactory insert location and tubal occlusion (when using a modified hysterosalpingogram [HSG]) documented in her subject record

[…]

13.4.2.5 Section 5.2.1 Withdrawal

Section revised per modification 3.

Old text:

[…]

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

~~Subjects *may* be withdrawn from the study for the following reasons:~~

- ~~At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).~~

Subjects may be terminated from the study by the Investigator. Reasons for termination of a subject from the study may include, but are not limited to, the following:

[…]

New text:

[…]

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

Subjects may be terminated from the study by the Investigator. Reasons for termination of a subject from the study may include, but are not limited to, the following:

[…]

13.4.2.6 Section 6.3 Treatment assignment

Section revised per modification 1.

Old text:

[…]

A subject may not be enrolled in the study until she has ~~a~~an Essure confirmation test done that documents bilateral satisfactory device location and fallopian tube occlusion. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion, she may repeat the Essure Confirmation Test.

New text:

[…]

A subject may not be enrolled in the study until she has a successful Essure confirmation test done that documents bilateral satisfactory device location and fallopian tube occlusion noted on HSG OR optimal or satisfactory micro-insert location noted on TVU. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion on HSG OR optimal or satisfactory micro-insert location on TVU, she may repeat the Essure Confirmation Test.

13.4.2.7 Section 7.1.2.1 Eligibility and Screening Visit (-30 days)

Section revised per modification 1.

Old text:

[…]

- Inform the subject of the Essure-NovaSure PAS. Subject will not enroll in the study until she has ~~a~~an Essure confirmation test that documents bilateral satisfactory device location and fallopian tube occlusion. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion, she may repeat the Essure Confirmation Test.

[…]

New text:

[…]

- Inform the subject of the Essure-NovaSure PAS. Subject will not enroll in the study until she has a successful Essure confirmation test that documents bilateral satisfactory device location and fallopian tube occlusion noted on HSG OR optimal or satisfactory micro-insert location noted on TVU. If subject has had Essure placement but she does not have an Essure Confirmation Test that documents bilateral satisfactory device location and fallopian tube occlusion on HSG OR optimal or satisfactory micro-insert location on TVU, she may repeat the Essure Confirmation Test.

[…]

13.4.2.8 Section 7.1.2.4 One-, Two- and Three-Year Post-EA Phone Call (± 28 days)

Section revised per modification 4.

Old text:

[…]

The 3-year phone call will be the final visit in the study. If the subject reports a~~n~~ adverse event or pregnancy during the 3-year follow-up phone call, the subject will be followed until event resolution. If a pregnancy or adverse event was previously reported but event is not resolved during the 3-year phone call, event will be followed until resolution. ~~If no adverse events or pregnancies are reported, the Study Completion or Early Termination CRF will be completed after the 3-year phone call.~~

New text:

[…]

The 3-year phone call will be the final visit in the study. If the subject reports a serious adverse event or pregnancy during the 3-year follow-up phone call, the subject will be followed by the sponsor's pharmacovigilance department until event resolution or stabilization. If a pregnancy or serious adverse event was previously reported but the event is not resolved during the 3-year phone call, the event will be followed by the sponsor's pharmacovigilance department until resolution. Information pertaining to these events will be collected and archived in the sponsor's pharmacovigilance database.

13.4.2.9 Section 7.4.1.1.1.1 Adverse device effect (ADE)

Section revised per modification 5.

Old text:

An AE related to the use of Essure, including AEs resulting from insufficient or inadequate instructions for use, deployment, implant (placement), installation or operation or any malfunction of the investigational medical device, use error or from intentional misuse of the medical device.

New text:

An AE related to the use of Essure or NovaSure, including AEs resulting from insufficient or inadequate instructions for use, deployment, implant (placement), installation or operation or any malfunction of the investigational medical device, use error or from intentional misuse of the medical device.

13.4.2.10 Section 7.4.1.1.1.2 Unanticipated adverse device effect (UADE)

Section revised per modification 6.

Old text:

A~~n AE~~ is considered unanticipated if by its nature, incidence, severity or outcome it has not been identified in the IFU.

New text:

A serious adverse effect is considered unanticipated if by its nature, incidence, severity or outcome it has not been identified in the IFU.

13.4.2.11 Section 7.4.1.1.2 Serious adverse event (SAE)

Section revised per modification 7.

Old text:

An SAE is classified as any untoward medical occurrence ~~but is not related to a medical device that, meets any of the following criteria:~~

1. ~~Led to death~~
2. ~~Led to a serious deterioration in the health of the subject that:~~
    - ~~resulted in a life-threatening illness or injury~~
    - ~~resulted in a permanent impairment of a body structure or body function~~
    - ~~required hospitalization or prolongation of existing hospitalization~~
    - ~~resulted in a medical or surgical intervention to prevent permanent impairment to body structure or function~~

Note: For the purposes of this protocol, ectopic pregnancy and spontaneous abortion are always considered as important events and therefore reported as SAEs.

New text:

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 7.1.2)
- 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. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

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

g. Requires intervention to prevent permanent impairment of a body function /damage, to a body structure

Note: For the purposes of this protocol, ectopic pregnancy and spontaneous abortion are always considered as important events and therefore reported as SAEs.

13.4.2.12 Section 7.4.1.1.2.2 Unanticipated serious adverse device effect (USADE)

Section revised per modification 8.

Old text:

An unanticipated serious adverse device effect (USADE) is 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 (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

New text:

An unanticipated serious adverse device effect (USADE) is 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 (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. This is the same definition provided in the UADE Section 7.4.1.1.1.2. This has been corrected above in the UADE definition. However, as both terms have been used at various timepoints in this protocol, the definition is maintained here.

13.4.2.13 Section 7.4.1.1.4 Device deficiency

Section revised per modification 5.

Old text:

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

New text:

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

13.4.2.14 Section 7.4.1.1.4.1 Device failure

Section revised per modification 5.

Old text:

Failure of Essure to perform or function as intended, including any deviations from the performance specifications or intended use (e.g., pregnancy when micro-insert properly located and fallopian tubes occluded; continued menorrhagia despite a completed endometrial ablation procedure). For the purposes of this study, a pregnancy that occurs in a subject told to rely on a commercially available Essure device for contraception is a device failure.

New text:

Failure of Essure or Novasure to perform or function as intended, including any deviations from the performance specifications or intended use (e.g., pregnancy when micro-insert properly located and fallopian tubes occluded; continued menorrhagia despite a completed endometrial ablation procedure). For the purposes of this study, a pregnancy that occurs in a subject told to rely on a commercially available Essure device for contraception is a device failure. For the purposes of this protocol, persistence or recurrence of heavy menstrual bleeding will be considered device failures for the Novasure device.

13.4.2.15 Section 7.4.1.1.4.2 Device malfunction

Section revised per modification 5.

Old text:

Failure of Essure to meet its performance specifications or otherwise perform as intended when used in accordance with the IFU (e.g., difficulties with deployment or detachment of micro-insert; device difficulties when conducting endometrial ablation).

New text:

Failure of Essure or Novasure to meet its performance specifications or otherwise perform as intended when used in accordance with the IFU (e.g., difficulties with deployment or detachment of micro-insert; device difficulties when conducting endometrial ablation).

13.4.2.16 Section 7.4.1.1.5 Important Medical Events and events of special interest

Section revised per modification 9.

Old text:

[…]

- Upper genital tract infections (for example: endometritis, salpingo-oophoritis, salpingitis).
- Expulsion or migration of Essure inserts.

New text:

[…]

- Perforations of the uterus, cervix or fallopian tubes.
- Upper genital tract infections (for example: endometritis, salpingo-oophoritis, salpingitis).
- Expulsion or migration of Essure inserts.
- Potential allergy/hypersensitivity to Essure inserts (for example: itch [pruritus], rash, hives [urticaria], facial edema, angioedema, allergy to metals).

13.4.2.17 Section 7.4.1.3 Assessments and documentation of adverse events

Section revised per modification 10.

Old text:

[…]

Investigators must document all device failures, malfunctions and use errors, including the assessment of whether the event is considered an incident (ADE) using the Device Malfunction and Failure CRF.

~~Investigator must determine whether adverse event is an unanticipated adverse device effect; if so, it must be reported as required by Section 7.4.1.1.~~

Because an approved device will be used for the placement procedure, any device malfunctions will be reported to the sponsor's Product Surveillance department. Device malfunctions will not be analyzed as part of this study as the placement procedure and device are not being evaluated.

New text:

[…]

Investigators must document all device failures, malfunctions and use errors, including the assessment of whether the event is considered an incident (ADE) using the Device Malfunction and Failure CRF.

Because an approved device will be used for the placement procedure, any device malfunctions will be reported to the sponsor's Product Surveillance department. Device malfunctions will not be analyzed as part of this study as the placement procedure and devices are not being evaluated.

13.4.2.18 Section 7.4.1.4 Reporting of serious adverse events

Section revised per modification 12.

Old text:

Investigator's notification of the sponsor

[…]

All SAEs and ~~incidents (~~ADEs~~)~~ occurring during the observation period defined in Section 7.4.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the sponsor. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the sponsor's designated recipient.

[…]

Sponsor's notification of the investigational site

[…]

If the adverse event is ~~also~~ an unanticipated adverse device effect, the investigator must report it to the sponsor within 3 working days after the investigator becomes aware of the event. The investigator will send to the sponsor all pertinent paperwork (discharge summaries, office notes, etc.) within 5 working days.

[…]

New text:

Investigator's notification of the sponsor

[…]

All SAEs and SADEs occurring during the observation period defined in Section 7.4.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the sponsor. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the sponsor's designated recipient.

[…]

Sponsor's notification of the investigational site

[…]

If the adverse event is the result of an unanticipated adverse device effect, the investigator must report it to the sponsor within 3 working days after the investigator becomes aware of the event. The investigator will send to the sponsor all pertinent paperwork (discharge summaries, office notes, etc.) within 5 working days.

[…]

13.4.2.19 Section 7.4.2 Device removal

Section added per modification 11.

Old text:

Not applicable

Added text:

Each time a removal procedure is performed, additional information will be collected about the circumstances surrounding the removal (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).

Note that the Section numbering inside the Section 7.4 has changed due to this modification.

13.4.2.20 Section 8.6 Determination of sample size

Section revised per modification 1.

Old text:

[…]

Assumptions

The following assumptions were used to calculate the PAS sample size and power for the 1- and 3-year hypothesis:

- Participants in this PAS are women who have undergone the Essure procedure followed by a successful Essure Confirmation Test showing satisfactory micro-insert location and bilateral tubal occlusion;

[…]

New text:

[…]

Assumptions

The following assumptions were used to calculate the PAS sample size and power for the 1- and 3-year hypothesis:

- Participants in this PAS are women who have undergone the Essure procedure followed by a successful Essure Confirmation Test showing satisfactory micro-insert location and bilateral tubal occlusion on HSG OR optimal or satisfactory micro insert location on TVU;

[…]

13.4.2.21 Section 14 Appendices

Section revised per modification 12.

Old text:

~~Appendices A-D were to be distributed to all sites with the protocol and were not attached to this amendment to reduce redundancy.~~

~~Appendix E:~~ Detailed Study Timelines

Revised/projected study milestones based on enrollment rates:

[…]

New text:

All appendices from prior protocol amendments (Essure IFU, NovaSure Instructions for Use and Controlled Operator's Manual, Case Report Form and the Informed Consent) have been distributed to the sites with previous protocol versions and are therefore not attached here to avoid redundancy.

15. Detailed Study Timelines

Revised/projected study milestones based on enrollment rates:

[…]

14. Appendices - *amended*

All appendices from prior protocol amendments (Essure IFU, NovaSure Instructions for Use and Controlled Operator's Manual, Case Report Form and the Informed Consent) have been distributed to the sites with previous protocol versions and are therefore not attached here to avoid redundancy.[55]

15. Detailed Study Timelines

Revised/projected study milestones based on enrollment rates:

Study start date – First subject enrolled	NOV 2012
Expected subject enrollment at 12 sites (subjects/month/site)	0.4
Expected subject enrollment rate per year	43 based on 9 current sites able to enroll
Expected subject enrollment completion date	DEC 2017
Expected final subject follow-up date	JAN 2021
Expected completion of final post-approval study report	JUL 2021

[55] Text modified per Amendment 6.