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Protocol

Study Title
Evaluation of the Effectiveness, Feasibility, Safety and Tolerability of the ContraMed VeraCept Intrauterine Copper Contraceptive for Long Acting Reversible Contraception

NCT Number
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Sponsor
Sebela Pharmaceuticals Development LLC

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Version 5.0 (September 19, 2017)

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Notes
This protocol is being submitted to ClinicalTrials.gov in compliance with the Final Rule for clinical trial results information reporting.

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Sandra Matsumoto	Regulatory Affairs		
Kevin Peters, PhD	Clinical Affairs		

Clinical Investigation Plan CMDOC – 0008 Version 5.0 / 13 September 2017 Attached 45 pages

DOCUMENT REVISION HISTORY

Rev.	Description	Originator	Effective Date
A	Initial Release	B. Katz	8.30.14
B	Revised per FDA feedback	B. Katz	2.17.15
C	Revised post Investigators Meeting	B. Katz	7.9.15
D	Added subject contact at the end of each 28-day cycle post the 52 Week visit.	M. Schreifels	9.19.17

CONTRAMED

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Sandra Matsumoto, PhD	Regulatory Affairs		
Kevin Peters, PhD	Clinical Affairs	[redacted]	

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Evaluation of the Effectiveness, Feasibility, Safety and Tolerability of the ContraMed VeraCept Intrauterine Copper Contraceptive for Long Acting Reversible Contraception

Protocol Number: CMDOC-0008

IND #: 119743

Version / Date: 5.0 / 19 September 2017

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By signing below, I confirm that I have read and will abide by this protocol, the signed investigator agreement and all applicable regulations.

Investigator's Name (print)	
Investigator's Signature	Date(DD/MMM/YYYY)

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REVISION HISTORY

Version	Date	Justification for Revision
1.0	01 Aug 2014	Initial version
2.0	14 Jan 2015	Revise Contact Information, format issues, version issues
3.0	17 Feb 2015	Revised in accordance with FDA recommendations
4.0	9 July 2015	Revised various sections within the protocol to reflect outcome of clinical investigators meeting.
5.0	19 September 2017	Added subject contact at the end of each 28-day cycle post the 52 Week visit. Added statistical analysis information. Separated out the post 52 week thru Year 3/Exit for more clarity. Updated the potential risks / adverse events with PhII 1-year data. Removed appendix 2, ICF template.

INVESTIGATIONAL PLAN SUMMARY

Title: Evaluation of the Effectiveness, Safety and Tolerability of the ContraMed VeraCept Intrauterine Copper Contraceptive for Long-Acting Reversible Contraception

Protocol #: CMDOC-0008
Version 5.0 / 19 September 2017

Device Name: VeraCept Intrauterine Copper Contraceptive (referred to as VeraCept or Study Device throughout this document)

Study Design: Prospective, multi-center, single-arm, open-label, Phase II clinical study

Study Purpose: To evaluate the effectiveness, device placement, safety, and tolerability of VeraCept to support commencing a Phase III Clinical Study

Study Duration: Subject enrollment will take approximately 4 months. Each subject will be followed for 12 months after device placement for the protocol endpoints, and then every 6 months thereafter for those subjects who wish to continue study device use

Enrollment: Up to 250 subjects will be consented, screened and have VeraCept placed, with a goal to have 2240 evaluable cycles at 12 months. It is planned that 225 of the 250 subjects will be within the 18-35 year age range, with a total of 2015 evaluable cycles. The remaining 25 subjects will be within the 36-40 year age range.

Investigational Site Information: This study will be conducted at up to 14 centers in the U.S

Follow-up: Physical assessment (office visit) will occur at weeks 6, 13, 26 and 52 after placement, with monthly telephone contact. For those subjects who wish to continue study device use after 12 months, follow-up office visits will occur every 6 months with contact at the end of each 28-day cycle beginning after the 52-week visit. Additional visits will be conducted if necessary for safety issues.

<u>Follow-up after early study device removal:</u>

Subjects requesting VeraCept removal to become pregnant will be followed to pregnancy or until the subject changes her mind about trying to get pregnant. All subjects in whom VeraCept is removed prior to 12 months, for any reason, will be required to use an alternative contraceptive for the first two weeks following removal. Hormonal contraceptive pills will be reimbursed by the

sponsor as a contraceptive option during this time unless the subject has a category 4 condition precluding their use.

Study Population: Pre-menopausal women ages 18 – 40, at risk for pregnancy, who are interested in using an intrauterine contraceptive for birth control will be eligible for this study. Subjects must provide written informed consent and meet the study subject selection criteria without any exclusions as outlined in the Clinical Investigation Plan (CIP).

Primary Effectiveness Outcome: The primary outcome measure is effectiveness, evaluated as the absence of pregnancy by 12 months, failure will be calculated by the Pearl Index.

Safety and Other Outcome Measures: Safety and other outcome measures include:

Study Device Placement:

- Ease of placement
- Placement success

Safety:

- Serious Adverse Events
- Adverse Events

Tolerability:

- Bleeding and spotting patterns
- Discontinuation rate and reasons for discontinuation

Subject Selection Criteria

INCLUSION CRITERIA

Subject must meet all of the following criteria to participate in this study:

1. Between 18-40 years of age at the time of study initiation;
   1.1 Enrollment will be targeted for 225 subjects aged 18-35 (for safety and effectiveness analyses) and an additional 25 subjects aged 36-40 (for safety only) (note: all subjects will be included in the analysis for device placement and tolerability);
2. Pre-menopausal, as determined by regular menstrual cycle (28 ± 5 days) for the last 3 months;
   2.1 Based on patient history, when not on hormonal contraceptives;
3. Sexually active with a male partner who has not had a vasectomy;
4. Reasonably expect to have to coitus at least once monthly during the study period.
5. Married or in a steady relationship (e.g., 3-6 months);
6. Seeking to avoid pregnancy for the next 12 months;
7. Willing to use the study device as the sole form of contraception;

8. Willing to accept a risk of pregnancy;
9. Normal PAP or ASC-US with negative high risk HPV test result within the appropriate screen timeframe, unless considered at risk;
10. Able and willing to comply with all study tests, procedures, assessment tools and follow-up; and
11. Able and willing to provide and document informed consent and Authorization for Release of Protected Health Information (PHI).

EXCLUSION CRITERIA

A subject will be excluded from participating in the study if **any** of the following conditions apply:

1. Known or suspected pregnancy; or at risk for pregnancy from unprotected intercourse earlier in current cycle
2. Subject who anticipates separation from her partner for more than 1 cycle within the next 12 months;
3. A previously inserted IUD that has not been removed by the time VeraCept is placed;
4. History of previous IUD complications*, such as perforation, expulsion, infection (pelvic inflammatory disease) or pregnancy with IUD in place.*;
5. Injection of hormonal contraceptive (e.g., Depo-Provera) within the last 10 months;
   5.1 Must have had 2 normal menstrual cycles since the last injection;
6. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during the 12 months of study participation;
7. Postpartum, prior to a minimum of 6 weeks or complete uterine involution;
8. Exclusively breastfeeding before return of menses; Lactating women will be excluded unless they have had have had two normal menstrual periods prior to enrollment.
   8.1 Must have had 2 normal spontaneous menstrual cycles since delivery
9. Unexplained abnormal uterine bleeding (suspicious for serious condition), before evaluation; Immediately post-septic abortion or puerperal sepsis;
10. Severely heavy or painful menstrual bleeding;
11. Suspected or known cervical, uterine or ovarian cancer, or unresolved clinically significant abnormal pap smear requiring evaluation or treatment.
12. Any history of gestational trophoblastic disease with or without detectable elevated ß-hCG levels, or related malignant disease;
13. Known anatomical abnormalities of the uterine cavity that may complicate IUD placement, such as:
    13.1 Submucosal uterine leiomyoma
    13.2 Asherman's syndrome
    13.3 Pedunculated polyps
    13.4 Bicornuate uterus
    13.5 Didelphus or uterine septa
14. Known anatomical abnormalities of the cervix such as severe cervical stenosis, prior trachelectomy or extensive conization that, in the opinion of the investigator would prevent cervical dilation and study device placement;
15. Current or recent (within the last 3 months) pelvic infection (cervix, endometrium, or fallopian tubes), or mucopurulent cervicitis;

16. High risk for STDs (e.g., multiple sexual partners);
17. Known or suspected AIDS;
18. Known intolerance or allergy to nickel or copper, including Wilson's Disease;
19. Currently participating or planning future participation in a research study of an investigational drug or device during the course of this investigational study;
20. Subject had VeraCept placed previously or had 2 attempts at placement;
21. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;
22. Any general health or behavioral condition that, in the opinion of the Investigator, could represent an increased risk for the subject or would render the subject less likely to provide the needed study information.

Note: If subject has a current IUD that is being removed; if subject had monthly menses, you do not need to wait any amount of time between removal of her first IUD and placement of VeraCept – however, if pain is present you should wait until pain has resolved with prior IUD before insertion of Veracept. It is however suggested the subject have a return of menses if she had amenorrhea prior to placement.

STATISTICAL METHODS

Effectiveness Outcome

The primary efficacy population will include all subjects aged 18-35 who had a study device successfully placed, provided at least 1 day of diary data, and were not pregnant before the IUD was placed.

Effectiveness will be evaluated as the absence of pregnancy during VeraCept use for up to12 months. Pregnancies judged to have occurred during study device use (determined by ultrasound and medical assessments), for which the estimated date of conception was within 7 days after study device removal or calculated date of expulsion, will be included in the per protocol analysis of pregnancies.

The Pearl Index (and 95% confidence intervals) will be calculated through 12 months for cycles in subjects aged 18-35 at the time of study device placement, excluding the following cycles (unless the subject became pregnant in the cycle):

- When back-up contraceptive or emergency contraceptive use was documented on the daily diary
- When the subject denied having any intercourse.

All pregnancies will be counted in the intent to treat analysis.

Life table analyses will be used as further assessment of pregnancies. Secondarily the Pearl index and life table analyses will be done through 3 years.

Safety and Other Outcome Measures

VeraCept ease of placement, removal and placement success will be descriptively summarized.

Safety evaluations will be based on the incidence of adverse events and serious adverse events changes from baseline in other assessments (examinations and vital signs) and by relationship to the study device or study device placement procedure. Study device tolerability will be based on changes in bleeding and spotting patterns and study discontinuation (including reasons for discontinuation).

Safety analyses will be based on the experience of all subjects who had attempted study device placement and provided any relevant data. Tolerability analyses will be based on the experience of all subjects who received a study device and provided any relevant data.

Subjects will record frequency and intensity of vaginal bleeding through a daily diary. The number of bleeding or spotting days will be summarized for each cycle. In addition, bleeding and spotting will each be summarized separately. Bleeding analyses will include all subjects who had a study device placed and have at least 1 cycle where they were not pregnant and were providing bleeding-related diary data on the days in the reference period.

In general, summaries of quantitative variables will include the sample size, mean, median, standard deviation, minimum, and maximum. For qualitative (categorical) variables the summaries will include the number and percentage of subjects in each category.

SAMPLE SIZE

No formal sample size calculations were performed for the study. It is estimated that with 225 subjects enrolled with age 18-35, a 12-month Pearl Index of 0.6 (1 observed pregnancy), and 2,015 evaluable cycles, we will observe a 95% confidence interval for the 12 month Pearl Index of (0.1, 3.3).

2,015 evaluable cycles assumes that in the overall study:

- Each subject will average10 evaluable cycles of VeraCept use
- 1% of subjects will not provide any diary data and will be excluded from the primary efficacy population
- Subjects will not have intercourse or will use backup contraception in 9.2% of cycles

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BV	Bacterial Vaginosis
C	Celsius
CBC	Complete Blood Count
CCTN	Contraceptive Clinical Trials Network
CFR	Code of Federal Regulations
cm	Centimeters
CRF	Case report forms
Cu	Copper
CVR	Contraceptive vaginal ring
d	Day
DHHS	Department of Health and Human Services
dL	Deciliter
DSMB	Data Safety Monitoring Board
EC	Emergency contraception
eCRF	Electronic case report form
EDC	Electronic data capture
ECYC	Evaluable for Cycle Control
EE	Efficacy Evaluable
EMR	Electronic medical records
ENDTX	End of treatment
EP	Evaluable for Pregnancy
F	Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Gram
GCP	Good Clinical Practices
GnRH	Gonadotropin-Releasing Hormone
hCG	Human Chorionic Gonadotropin
HD	Health Decisions
HPV	Human Papillomavirus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
kg	Kilograms
L	Liter
LTFU	Lost to follow up
MedDRA	Medical dictionary for regulatory activities
MITT	Modified Intent To Treat
mg	Milligrams
mL	Milliliter

mm	Millimeter
NDA	New Drug Application
NIH	National Institutes of Health
N/A	Not Applicable
OC	Oral Contraceptive(s)
Pap Test	Papanicolaou Test
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCCC	Statistical and Clinical Coordinating Center
SCRN	Screening
SD	Standard Deviation
SOP	Standard Operating Procedure
STD	Sexually Transmitted Diseases
TVUS	Transvaginal ultrasound
UNS	Unscheduled
US	United States
V	Visit
X	Times
WHO	World Health Organization
:	To
/	Per
%	Percent
<	Less than
>	Greater than
≤	Less than or equal to
≥	Greater than or equal to
°	Degrees
±	Plus or minus
+	Plus

1. INTRODUCTION

The VeraCept Intrauterine Copper Contraceptive is designed as a birth control device. There are over 62 million US women in their child-bearing years, ages 15 to 44. Thirty eight million (38M) use some form of contraception (62%). Thirty-one (31%) percent do not use or need contraception because they are either trying to get pregnant, are pregnant, are infertile or are not sexually active. Seven (7%) percent are at risk for unintended pregnancy since they are using no method[1].

Contraceptive options for those 38 million US women include permanent sterilization (tubal ligation or vasectomy in male partner), contraceptive implants, intrauterine devices, injections, pills, patches, vaginal rings, male and female condoms, other female barrier methods, vaginal spermicides, and behavioral methods such as coitus interruptus and fertility awareness. Of all these methods, oral contraceptives are used by 30% of sexually active women. The more effective methods, such as intrauterine contraceptives, are used by fewer than 10% of women.[2] The CHOICE Study showed that the pill failure rate is 17-20 times higher than the failure rate with intrauterine devices.[3,4]

Intrauterine devices have high initial costs, so early discontinuation rates have profound impacts on their cost-effectiveness. The early rates of user dissatisfaction due to complications or side effects may be associated with the materials used in these devices and/or their design. The Copper T380A IUD has been associated with complaints of increased bleeding, inter-menstrual bleeding and cramping pain. The LNG-IUS (Mirena®) is also associated with early complaints of irregular bleeding patterns, cramping pelvic pain and with amenorrhea. First year discontinuation rates for Copper IUDs in most studies range from 4-15%.[5,6,7]

With high unintended pregnancy rates in the U.S. (49%)[1], additional effective, safe and long-acting reversible contraceptives are needed. An intrauterine device with low-dose copper that achieves high contraceptive effectiveness, minimizes side effects and has improved mechanical advantages could offer an attractive option to women seeking effective protection against unintended pregnancy. We believe the VeraCept Intrauterine Copper Contraceptive embodies these advantages.

Pilot Study of the VeraCept Intrauterine Copper Contraceptive

A Pilot Study of the VeraCept Intrauterine Copper Contraceptive in a population of parous women enrolled at a single site demonstrated the safe use of the study device in

[1]Alan Guttmacher Institute Fact Sheets Oct 2013 (www.guttmacher.org)
[2] Jones J, Mosher WD and Daniels K, Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995, *National Health Statistics Reports*, 2012, No. 60, <http://www.cdc.gov/nchs/data/nhsr/nhsr060.pdf>, accessed August 11, 2014.
[3] Secura G, Alllsworth J, Madden T, et al. The Contraceptive CHOICE Project: reducing barriers to long-acting reversible contraception. Am J Obstet Gynecol. 2010:20130;115 e1-7.
[4] Winner, B; Peipert, JF; Zhao, Q; Buckel, C; Madden, T; Allsworth, JE; Secura, GM. (2012), "Effectiveness of Long-Acting Reversible Contraception", *New England Journal of Medicine* **366** (21): 1998–2007, doi:10.1056/NEJMoa1110855
[5] Speroff L, Darney PD. *A Clinical Guide for Contraception*. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2005
[6] The TCu380A IUD and the frameless IUD “the FlexiGard”: interim three-year data from an international multicenter trial: UNDP, UNFPA, and WHO Special Programme of Research, Development and Research Training in Human Reproduction, World Bank: IUD research group. Contraception. 1995;52:77–83. [No author listed]
[7] Hubacher D, Reyes V, Lillo S, et al. *Preventing copper intrauterine device removals due to side effects among first-time users: randomized trial to study the effect of prophylactic ibuprofen. Hum Reprod*. 2006;21: 1467–1472

approximately 463 subjects total in two phases of the study, representing approximately 6,706 combined women-months (558 women-years) of experience.

In this time period, there were no serious adverse events due to the study device or its placement. Discontinuation rate due to tolerability was low. There have been no intrauterine pregnancies over the course of the study to date, and one serious adverse event (an ectopic pregnancy) early in the Phase I portion of the study.

VeraCept was successfully placed in all enrolled subjects with no peri-procedural adverse events and without the use of anesthetics, pre-medication or mechanical dilatation. The VeraCept Intrauterine Copper Contraceptive, in this initial experience, satisfied the objectives of providing a safe, easy to place, conformable low-dose copper contraceptive that is highly tolerated.

In the Phase II Confirmation portion of the Pilot Study, the Subject Continuation Rate is 90% at 10 months, with only 2% expulsion rate and 3% discontinuation for tolerability. The remaining 5% discontinued due to other reasons (e.g. the desire to get pregnant or inability to comply with study follow-up requirements.)

Comparative Study of the VeraCept Intrauterine Copper Contraceptive

Subsequent to the Pilot Study, a 2:1 randomized, subject-blinded Comparative Study of the VeraCept Intrauterine Copper Contraceptive vs. the TCu380 IUD is being conducted in a population of parous women enrolled at a single site. The interim results to date demonstrate that VeraCept has achieved equivalent performance in terms of safety and effectiveness as compared to the predicate TCu380 IUD, i.e. no serious adverse events and no intrauterine or ectopic pregnancies in either group, while achieving clinically and statistically significant improvements in subject-related outcomes such as improved tolerability, reduced expulsions and reduced pain-at-insertion.

VeraCept was successfully placed in 99.5% of all subjects to whom the study device was randomly assigned, with no peri-procedural adverse events, and without the use of anesthetics, pre-medication or mechanical dilatation. No new or unanticipated adverse events were introduced. Statistically significant improvements (95% CI) in Subject Continuation Rate, Tolerability, Study Device Expulsion and Pain at Insertion were all demonstrated when compared to the control intrauterine device.

In this experience to date, VeraCept satisfied the objectives of providing a safe, easy to place, conformable low-dose intrauterine copper contraceptive without sacrificing safety or effectiveness. Study completion to 12 months and, subsequently, a larger multicenter study is warranted.

This Phase II Clinical Study is designed to evaluate the effectiveness, study device placement, safety, and tolerability of VeraCept to support a larger, Phase III clinical study.

2. STUDY DURATION

Subject enrollment will take approximately 4 months. Each subject will be followed for 12 months, after which subjects who choose to continue use will be followed every 6 months.

3. INVESTIGATIONAL PRODUCT DESCRIPTION

VeraCept Intrauterine Copper Contraceptive is designed for use as a birth control method. The study device consists of a Nitinol spring with copper sleeves at both the distal arms and proximal stem. The study device is shaped such that upon placement in the uterus, the Nitinol spring positions itself at the fundus, with the copper sleeved arms near the ostia of the fallopian tubes and copper sleeved stem at or near the internal os of the cervix.

Figure 1 illustrates the basic design and layout of the study device.

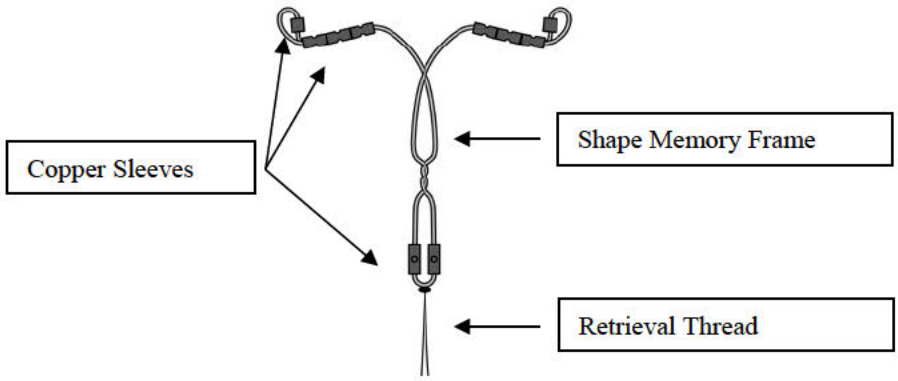

Figure 1 – Design and layout of VeraCept

The amount of copper utilized in VeraCept is 175mm^2 exposed surface area. This compares to the typical 380mm^2 of copper surface area for the standard plastic TCu 380 IUD. Because of its spring action, VeraCept can place concentrated amounts of copper in anatomically relevant positions within the uterus, designed to result in a more efficient elution profile for contraception. The study device is placed using a simple one-step introducer containing the preloaded and sterile study device. It is retrieved with a standard monofilament polypropylene retrieval thread.

Figure 2a shows the study device in its pre-loaded state (directly from the package) in the distal end of the introducer. Figure 2b shows a schematic of the study device oriented in the uterus post placement.

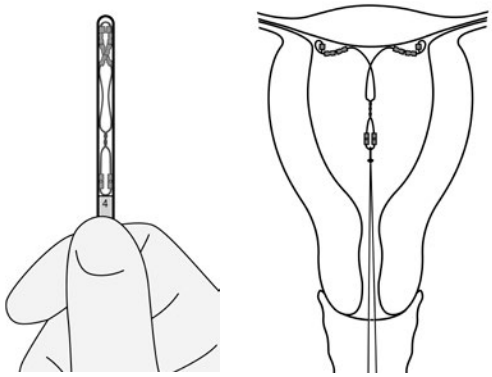

Figure 2 – (a) VeraCept in pre-loaded state (b) orientation in the uterus post placement

4. STUDY TREATMENTS

After the risks and benefits of study participation have been explained to the candidate, her questions have been answered, she has signed a written consent and PHI form, and eligibility has been established, a subject identification number will be assigned by the Study Sponsor or designee. If subject has a current IUD that is being removed; if subject had monthly menses, you do not need to wait any amount of time between removal of her first IUD and placement of VeraCept – however, if pain is present you should wait until pain has resolved with prior IUD before insertion of Veracept. It is however suggested the subject have a return of menses if she had amenorrhea prior to placement.

4.1 VeraCept Intrauterine Copper Contraceptive (Dosage and Formulation)

VeraCept contains 175mm^2 exposed copper surface area. A single VeraCept design and dosage will be used in this study. VeraCept will be supplied by ContraMed LLC. For further details, see the VeraCept Intrauterine Copper Contraceptive Investigator's Brochure.

4.2 VeraCept Supply and Administration

Each VeraCept is preloaded in the inserter and packaged as a single use sterile system. Subjects will have VeraCept placed on "Day 1" of the trial. VeraCept should be stored in its sterile sealed package until study device placement.

See the Investigator's Brochure for a more detailed VeraCept product description, and the VeraCept labelling for placement and removal instructions.

4.3 VeraCept Storage and Accountability

VeraCept should be stored at 25°C (77°F), with excursions permitted between -20 °C to +50°C (-4F to 122F) [See USP Controlled Room Temperature].

Study Device accountability, reconciliation and record maintenance are responsibilities that must be performed by the study site in accordance with all applicable regulatory requirements. Please refer to **Appendix 1,** Investigator Responsibilities for a detailed

list of Investigator Responsibilities. All unused Study Devices will be stored for inventory and collection. Shipping procedures to return unused Study Devices are detailed in the Study Reference Manual.

4.4 VeraCept Dosage Modification

All subjects will receive the same VeraCept dosage of 175mm^2 exposed copper surface area. No Study Devices will be replaced if an expulsion or removal occurs.

4.5 Concomitant Therapy

Concomitant medications are any prescription medications or over-the-counter preparations used by the subject taken from the time the subject signs the informed consent documents until Study Exit. All concomitant medications, including excluded therapies, must be documented in the Concomitant Medication eCRF.

4.6 VeraCept Retention Compliance

Subjects will be instructed on how to check for study device presence by feeling for the strings in the vagina. Subjects will not be required to routinely check for study device presence, but if a subject believes the study device may have been expelled or is no longer in place, the subject can check for the study device string if desired. If the subject does not feel the strings, feels more than the strings, or has expelled the study device, the subject should be instructed to call for an urgent study visit and refrain from having sex or use appropriate non-hormonal contraception until further evaluation is completed. For detailed instructions regarding management of missing strings, refer to the Study Reference Manual.

5. OBJECTIVES

The scientific objective of this study is to evaluate the effectiveness, study device placement, safety, and tolerability of the VeraCept Intrauterine Copper Contraceptive as birth control in parous and nulliparous women of child-bearing age.

The purpose of the study is to obtain the safety and effectiveness data necessary to support an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA) for a longer-term Phase III Pivotal Clinical Study.

5.1 Primary Outcome Measure

The primary outcome measure is effectiveness, evaluated as the absence of pregnancy by up to12 months of VeraCept use. Failure will be calculated using the Pearl Index through 12 months. All evaluable cycles prior to discontinuation or planned removal at 12 months will be included in the primary analysis of effectiveness.

5.2 Safety And Other Outcome Measures

Safety and other outcome measures include:

Study Device Placement:

- Placement success
- Ease of placement

Safety;
- Serious Adverse Events
- Adverse Events

Tolerability:
- Bleeding and spotting patterns
- Discontinuation rate

6.0 BENEFITS AND RISKS

6.1 Potential Benefits

No assurances or guarantees can be made regarding the benefits of VeraCept to the study subject. The potential benefits of VeraCept include that it is a non-hormonal contraceptive method that requires only professional placement to be effective.

6.2 Potential Risks / Adverse Reactions

The following AEs have been reported in >2% of subjects in the first year of the VeraCept Phase II study, CMDOC-0008:

- Dysmenorrhoea
- Procedural pain
- Menorrhagia
- Nasopharyngitis
- Headache
- Abdominal pain
- Upper respiratory tract infection
- Metrorrhagia
- Pelvic pain
- Bacterial vaginosis
- Urinary tract infection
- Back pain
- Vulvovaginal mycotic infection
- Uterine spasm
- Dyspareunia
- Abdominal pain lower
- Post procedural haemorrhage
- Vaginal discharge
- Nausea
- Oropharyngeal pain
- Abdominal distension
- Sinusitis
- Influenza
- Insomnia

- Pharyngitis streptococcal
- Cough
- Diarrhoea
- Migraine
- Toothache
- Vomiting
- Arthralgia
- Breast tenderness
- Dizziness
- Vaginal odour

There may also be risks that are unanticipated at this time.

6.3 Minimization of Anticipated Risks

Potential risks that may be associated with use of VeraCept have been minimized in this study by the following:

a. Establishing eligibility criteria that exclude subjects who are at higher risk for experiencing an anticipated adverse event;

b. Conducting extensive preclinical and clinical testing prior to the start of this Phase II clinical study;

c. Conducting a risk analysis and incorporating mitigations to eliminate and/or reduce risks to as low as possible in accordance with ISO 14971-Medical Devices – Application of risk analysis to medical devices

d. Selecting investigators with proper level of training and experience in placing IUDs;

e. Ensuring adequate monitoring is performed to identify any safety issues associated with the study procedure and subjects;

f. Regularly reviewing reported serious adverse events and adverse events throughout the study and taking appropriate medical measures to resolve the adverse events.

7. SELECTION AND TRAINING OF CLINICAL SITES AND INVESTIGATORS

The study will be conducted at up to 14 centers in the United States. The primary requirements of selecting an Investigator for this study are: 1) experience and adequate training in a) IUD use and b) conduct of regulated clinical studies, 2) adequate facilities and equipment, 3) adequate patient volume, 4) appropriate personnel and site research staff to support the conduct of the study, and 5) commitment to safety and adherence to the investigational plan.

Prior to acceptance of the site into this study, the Sponsor or its designee will conduct a site qualification visit. The site qualification visit will be scheduled to include time with the Principal Investigator, co-investigators, study coordinator, and other study personnel

as available. Areas of discussion include a review of personnel training, expertise, and FDA-regulated study experience, this study's specific requirements, and a review of staffing and equipment availability and appropriateness.

Prior to study implementation, the Study Monitor will ensure that study personnel:

- Have appropriate training, facilities, time, and willingness to comply fully with the study requirements.
- A central IRB will be used to review and approve the Investigational Plan wherever possible, but if it is not possible, the investigator will submit this Investigational Plan to the local IRB for appropriate review and obtain written approval for the conduct of the study prior to the initiation of any subject enrollment into this study.
- Maintain all study correspondence, this Investigational Plan, and all related and required records on file at their facility.
- Assume full responsibility for the study investigation at their individual medical practices, clinics, and medical facilities. The Study Monitor will create a written report of the pre-study site visit. Resolution of any concerns and/or completion of any appropriate study activities identified during the pre-study visit will be documented by the Study Monitor, discussed with the Sponsor and submitted to the Investigator.
- Complete any training required by the IRB regarding protection of human subjects.
- Complete training on use of the Case Report Forms (eCRFs) provided by ContraMed representative or designee.
- Review and are familiar with VeraCept Prescribing Information.
- Complete training with VeraCept, provided by a ContraMed representative or designee.

Throughout the conduct of the study, the Sponsor and/or its designees will closely monitor each site for the following:

- Compliance with the investigational plan
- Meeting enrollment commitments
- Accurate and timely submission of CRFs and additional data
- Compliance with ICH E6 Good Clinical Practice (GCP) guidelines
- Compliance with Declaration of Helsinki
- Compliance with IRB and local regulatory requirements

7.1 Laboratories

Local laboratories will be used for any lab tests performed. No central labs will be used in this study.

8. STUDY POPULATION

The study population will be pre-menopausal women, at risk for pregnancy, who are interested in using an intrauterine contraceptive for birth control. Subjects must provide written informed consent and meet the study entry criteria noted below.

8.1 Inclusion

Subject must meet all of the following criteria to participate in this study:

1. Between 18-40 years of age at the time of study initiation;
    - 1.1 Enrollment will be targeted for 225 subjects aged 18-35 (for safety and effectiveness analyses) and an additional 25 subjects aged 36-40 (for safety only); (note: all subjects will be included in the analysis for device placement and tolerability);
2. Pre-menopausal, as determined by regular menstrual cycle (28 ± 5 days) for the last 3 months;
    - 2.1 Based on patient history when not on hormonal contraceptives;
3. Sexually active with a male partner who has not had a vasectomy;
4. Reasonably expect to have to have coitus at least once monthly during the study period
5. Married or in a steady relationship (e.g., 3-6 months);
6. Seeking to avoid pregnancy for the next 12 months;
7. Willing to use the study device as the sole form of contraception;
8. Willing to accept a risk of pregnancy;
9. Normal PAP or ASC-US with negative high risk HPV test result within the appropriate screen timeframe, unless considered at risk
10. Able and willing to comply with all study tests, procedures, assessment tools and follow-up; and
11. Able and willing to provide and document informed consent and Authorization to Release Protected Health Information (PHI).

8.2 Exclusion

A subject will be excluded from participating in the study if **any** of the following conditions apply:

1. Known or suspected pregnancy; or at risk for pregnancy from unprotected intercourse earlier in current cycle
2. Subject who anticipates separation from her partner for more than 1 cycle within the next 12 months;
3. A previously inserted IUD that has not been removed by the time VeraCept is placed;
4. History of previous IUD complications*, such as perforation, expulsion, infection (pelvic inflammatory disease) or pregnancy with IUD in place.*
5. Injection of any hormonal contraceptive (e.g., Depo-Provera) within the last 10 months;
    - 5.1 Must have had 2 normal menstrual cycles since the last injection;
6. Planned use of any non-contraceptive estrogen, progesterone or testosterone any time during the 12 months of study participation;
7. Postpartum, prior to a minimum of 6 weeks or complete uterine involution;

8. Exclusively breastfeeding before return of menses; Lactating women will be excluded unless they have had at least two normal menstrual periods prior to enrollment.
   8.1 Must have had 2 normal spontaneous menstrual cycles since delivery;
9. Unexplained abnormal uterine bleeding (suspicious for serious condition), before evaluation; Immediately post-septic abortion or puerperal sepsis;
10. Severely heavy or painful menstrual bleeding;
11. Suspected or known cervical, uterine or ovarian cancer, or unresolved clinically significant abnormal pap smear requiring evaluation or treatment.
12. Any history of gestational trophoblastic disease with or without detectable elevated ß-hCG levels, or related malignant disease;
13. Known anatomical abnormalities of the uterine cavity that may complicate IUD placement, such as:
    13.1 Submucosal uterine leiomyoma
    13.2 Asherman's syndrome
    13.3 Pedunculated polyps
    13.4 Bicornuate uteru
    13.5 Didelphus or uterine septa
14. Known anatomical abnormalities of the cervix such as severe cervical stenosis, prior trachelectomy or extensive conization that, in the opinion of the investigator would prevent cervical dilation and study device placement;
15. Current or recent (within the last 3 months) pelvic infection (cervix, endometrium, or fallopian tubes), or mucopurulent cervicitis;
16. High risk for STDs (e.g., multiple sexual partners);
17. Known or suspected AIDS;
18. Known intolerance or allergy to nickel or copper, including Wilson's Disease;
19. Currently participating or planning future participation in a research study of an investigational drug or device during the course of this investigational study;
20. Subject had VeraCept placed previously or had 2 attempts at placement;
21. Known or suspected alcohol or drug abuse within 12 months prior to the screening visit;
22. Any general health or behavioral condition that, in the opinion of the Investigator, could represent an increased risk for the subject or would render the subject less likely to provide the needed study information.

Note that a subject changing from an oral contraceptive, IUD or implantable contraceptive does not need to wait before switching to VeraCept subject to the criteria above. If subject has a current IUD that is being removed; if subject had monthly menses, you do not need to wait any amount of time between removal of her first IUD and placement of VeraCept – however, if pain is present you should wait until pain has resolved with prior IUD before insertion of VeraCept. It is however suggested the subject have a return of menses if she had amenorrhea prior to placement.

9. INFORMED CONSENT

The person obtaining the informed consent shall:

- Avoid any coercion of or undue influence of the candidate to participate;
- Sustain all the candidate's legal rights;
- Provide complete, detailed description of study events, procedures, follow up and costs/reimbursements using language that is non-technical and understandable to the candidate;
- Ensure that the candidate understands risks and responsibilities;
- Provide ample time for the candidate to consider participation, answer any questions and ensure that satisfactory answers are provided;
- Include dated signatures of the candidate and of the clinical investigator (as applicable);
- Shall ensure that all relevant requirements are met for witness signatures;
- Ensure that the candidate understands the voluntary nature of participation and her ability to withdraw from the study at any time with no adverse impacts on her ability to obtain other services;
- Ensure protection of the candidate’s confidentiality; and
- Provide a copy of the Consent Form signed by the candidate and the person presenting the information for the candidate to take home.

The process that leads to informed consent will be documented.

Each investigational site must provide the Sponsor or designee with a copy of the investigational site’s IRB approval letter (or Central IRB letter) and the IRB approved informed consent form, including the Authorization For Release Of Protected Health Information (PHI) form and the Subject Bill of Rights form. The Sponsor or designee must review and approve the IRB approved informed consent form prior to any subject enrollment. The Investigator or designee must review the informed consent form, PHI form and Bill of Rights form with the candidate in her native language and explain all study risks and benefits and answer all patient questions before obtaining the candidate’s signature on the informed consent form. All subjects must provide written informed consent in accordance with local law and approved by the site’s (or Central) IRB. The PHI and Subject Bill of Rights forms must also be signed by the candidate prior to study participation.

10. ENROLLMENT

A subject is considered enrolled into the study after signing the informed consent, PHI and Bill of Rights forms and being found eligible based on her history, physical examination and screening tests. If an eligible consented patient withdraws consent before insertion for any reason this would be considered a screen failure.

11. STUDY SCHEDULE OF ASSESSMENTS
The study schedule of assessments is provided in Table 1.

Table 1. Study Schedule of Assessments

CONTRAMED	Visit 1 - Screen	Visit 2- (VeraCept Placement) Day 1	Visit 3 - Follow up Week 6 ± 2	Visit 4 – Follow up Week 13 ± 2	Visit 5 – Follow up Week 26 ± 2	Visit 6 – Follow up Week 52 ± 2 / Exit	Phone Visit (Optional) up to 52 Weeks	Monthly Phone Contact up to 52 Weeks	Long-term FU post 52-week visit (Every 6 Months 18-30 (±4wks) and 3 yrs (-3wks/+4wks) /Exit visit	End of each 28-day Cycle Contact (Post 52 Wks ± 1w)
Initiation/Subject Characteristics										
Assessment of Eligibility	X	X					X			
Distribution of information	X									
Informed consent, PHI and Bill of Rights forms	X									
Demographics and baseline characteristics	X									
Medical/surgical, gynecologic and menstrual history	X									
Safety and Effectiveness										
Vital signs and weight	X	X	X	X	X	X			X	
Height	X									
General physical exam	X	X	X	X	X	X			X	
Pelvic exam	X	X	X[1]	X[1]	X[1]	X[1]			X[1]	
Cervical cytology	X									
Cervical infection tests	X[6]									
Transvaginal ultrasound (for verifying study device position)		X	X[2]	X[2]	X[2]	X			X[2]	
Pregnancy test-urine	X	X	X	X	X	X X[4]		X	X	
Prior and interval concurrent medication	X	X	X	X	X	X		X	X	
Adverse events		X	X	X	X	X		X	X	

CONTRAMED	Visit 1 - Screen	Visit 2- (VeraCept Placement) Day 1	Visit 3 - Follow up Week 6 ± 2	Visit 4 – Follow up Week 13 ± 2	Visit 5 – Follow up Week 26 ± 2	Visit 6 – Follow up Week 52 ± 2 / Exit	Phone Visit up to 52 Weeks (Optional)	Monthly Phone Contact up to 52 Weeks	Long-term FU post 52-week visit (Every 6 Months 18-30 (±4wks) and 3 yrs (-3wks/+4wks) /Exit visit	End of each 28-day Cycle Contact (Post 52 Weeks ± 1 w)
Other										
IUD placement ease		X								
IUD placement pain		X								
IUD removal ease						X				
IUD removal pain						X				
Concomitant contraception		X	X	X	X	X	X	X	X	X
Need for contraception (intercourse)	X	X	X	X	X	X	X	X	X	X
Diary dispensing	X[3]	X	X	X	X					
Diary collected/reviewed with patient (subject)		X[3]	X	X	X	X		X		
End of study medication						X				

Note: Screening and enrollment visit *may be combined* if the patient requests and all labs and screening exams are documented as normal.

1 Pelvic exam for VeraCept string check
2 Transvaginal Ultrasound only if indicated
3 First Diary Dispensing and Collection, prior to VeraCept placement, to be used as training with the subject. This diary data is not a part of data collection or analysis. It is intended to ensure the subject understands how to complete the diary during the follow up period.
4 Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document the results.
Note: If VeraCept is removed before 52+2 weeks, Visit 6 activities should be completed for Exit Visit.
5 Screening for cervical infection tests are to be done at screening unless these tests have been previously completed within three months of the screening visit. Results must be negative.

12. STUDY PROCEDURES

12.1 Visit 1: Screening

The following evaluations must be completed prior to the study device placement procedure:

- Subject meets inclusion and exclusion criteria
- Informed Consent, PHI and Bill of Rights forms signed
- Demographics and baseline characteristics
- Medical, surgical, gynecological and menstrual history
- Vital signs (pulse, blood pressure, temperature) and weight
- Height
- General physical exam
    - General Appearance
    - Skin
    - HEENT
    - Thyroid
    - Lungs
    - Back
    - Breasts
    - Heart
    - Abdomen
    - Extremities
    - Neurological
- Pelvic exam
- Cervical cytology, if indicated or last test out of date
- Cervical infection tests (gonorrhea and Chlamydia)
- Pregnancy test
- Prior and concurrent medications

Diaries and instructions will be dispensed to the subject for completion leading up to the day of VeraCept placement. This set of diaries is intended for training purposes and will not be included in the data analysis.

12.2 Visit 2: VeraCept Placement (Day 1)

VeraCept can be placed on any day of the menstrual cycle. Subjects must have a negative urine pregnancy test just prior to VeraCept placement. Initiation of the VeraCept is consistent with standard IUD placement. Refer to the Prescribing Information for specific instructions.

If placement is unsuccessful, a second attempt may be made within one (1) week following the first attempt. If a second attempt is also unsuccessful, the subject will be discontinued early from the study. The need for cervical dilation to facilitate placement of VeraCept will be left to the discretion of the investigator and subject; however, it is recommended that placement be tried first without prior cervical dilation. Use of cervical dilation will be recorded on the case report form. The need for pain control will also be left to the discretion of the investigator and subject. Any medications given for pain control will be recorded on the Concomitant Medications case report form.

Prior to VeraCept placement, the following evaluations will be completed:

- Entry criteria confirmed
- Vital signs and weight
- Physical Exam
- Pelvic Exam
- Pregnancy test, urine
- Prior and concurrent medications
- Any adverse events.

Following VeraCept placement, evaluations will be made for:

- VeraCept placement ease
- VeraCept placement pain
- VeraCept position (evaluated by Transvaginal Ultrasound)
- Concomitant contraception
- Need for contraception if VeraCept was not properly placed

Study site staff will review the completed diaries and discuss with the subject any further training that is required and answer any questions the subject may have about how to correctly complete the diaries.

New diaries will be dispensed to the subject at this time, along with instructions for proper completion of the diaries.

12.3 Visits 3-6 (Week 6±2,13±2, 26±2 and 52±2/ Exit after VeraCept placement to week 52)

The subject will return for follow up visits at preplanned intervals following placement of the VeraCept. At these follow up visits, the subject will be evaluated for:

- Vital signs and weight
- General physical exam (same as at Screening Visit)
- Pelvic exam (string check)
- Pregnancy test, urine
- Interval and concurrent medications
- Adverse events
- Diary collection and review with subject
    - Verify sexual activity and any back-up method is documented

- Diary dispensing

Additionally, at the Week 52 / Exit visit, the following will also be performed:

- Transvaginal ultrasound to document VeraCept position
- VeraCept Removal
  - VeraCept removal ease
  - VeraCept removal pain
- Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document results.

At 52 weeks, subjects will be allowed to continue with the study device with an office follow-up visits every 6 months for a maximum of three years post study device placement).

A 2-week supply of hormonal contraceptive pills will be provided to the subject by the site as a contraceptive option for the first two weeks after VeraCept removal.

12.3.1 Monthly Phone Contact (up to 52 Weeks)

Subjects will be contacted by phone each month, after her menses, to confirm completion of the monthly diary for:

- The need for additional contraception;
- Use of concomitant contraception;
- Use of concomitant medications;
- Documentation of menstrual and intermenstrual bleeding;
- Assess if there have been any adverse events since the last contact; and
- Resolution of any prior serious adverse events or adverse events.

12.4 Long-term Follow-up post 52-week visit (Every 6 Months: Months 18-30 (±4wks) and 3 yrs (-3wks/+4wks) /Exit visit

The subject will return for follow up after their Week 52 visit, every 6 months, if they choose to continue with the study visit. During these visits, the subject will be evaluated for:

- Vital signs and weight
- General physical exam (same as at Screening Visit)
- Pelvic exam (string check)
- Transvaginal ultrasound to document VeraCept position (only if indicated)
- Pregnancy test, urine
- Interval and concurrent medications
- Adverse events
- Verify sexual activity

- Document any back-up contraception methods

Additionally, at the final visit at 3 Years / Exit visit, the following will also be performed:

- Transvaginal ultrasound to document VeraCept position
- VeraCept Removal
- Urine pregnancy test will be done 17 days after removal/study exit by the subject at home, with a follow up call by the study coordinator or PI required to document results.

A 2-week supply of hormonal contraceptive pills will be provided to the subject by the site as a contraceptive option for the first two weeks after VeraCept removal.

12.4.1 End of Each 28-day Cycle Contact (Post 52 Weeks + 1 w)

Subjects will be contacted (e.g. phone calls, e-mail or text message) at the end of each 28-day cycle, beginning after the 52-week visit. The cycle is determined from the day of VeraCept insertion:

- Verify sexual activity
- Document any back-up contraception methods

12.5 Early Discontinuation Visit

Subjects who request removal of VeraCept before 12 months will be required to use an alternative contraceptive for the first two weeks following removal. A two-week supply of Hormonal contraceptive pills will be provided by the site as a contraceptive option during this time.

If a subject requests VeraCept removal because of an adverse event, the Study Exit Visit described in Section 12.3 above should be completed and documented on the CRF at the time of VeraCept removal. The subject will be followed until resolution of the event or 30 days after removal, whichever occurs first. Subjects experiencing an on-going adverse event will continue to receive the appropriate follow-up medical care.

If a subject requests early discontinuation and VeraCept removal to become pregnant, the Study Exit Visit described in Section 12.3 above should be completed and documented on the CRF at the time of VeraCept removal. Additionally, subjects shall be followed for either; six (6) months, until they decide to no longer try to conceive or they become pregnant, whichever comes first. Outcome data regarding subject's ability to conceive, or the decision to no longer try to become pregnant will be collected via phone contact and documented on the phone contact form.

12.6 Unscheduled Visits

Unscheduled visits must be documented on a follow-up visit CRF. Medical evaluations will be conducted as indicated by the reason for the unscheduled visit.

12.7 Emergency Contraception

If the subject suspects the VeraCept has expelled, she should contact the study site. Emergency contraception may be administered, according to product labelling, if the subject suspects expulsion has occurred and an act of intercourse might be unprotected, and she does not want the risk of pregnancy. If the subject is subsequently found to have an *in situ* IUD and desires to continue in the study, the cycle during which she used EC will not be included in the analysis unless the subject conceives. If the IUD is expelled, she will be exited from the study.

13. Diaries

Subjects will be instructed to complete diaries daily. Diaries are designed to collect the following information for each day of each menstrual cycle:

- Day of cycle
- Date
- Absence or presence of menstrual or other bleeding (none, spotting, normal or heavy)
- VeraCept expulsion (yes, no, suspected)
- Usage of additional birth control methods and type of birth control used
- Presence of abnormal pain or cramping
- Other medical problems
- All medications taken that day
- Frequency of intercourse
- Liner, pad and tampon usage

14. CONCOMITANT MEDICATIONS

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken from the time the subject signs the informed consent documents until Study Exit and must be recorded appropriately on the eCRF.

15. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

During the study, the Investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed below. Subjects will also be required to record AEs on their daily diary. For the Sponsor to fulfill safety assessment obligations, the Investigator must report all SAEs to the Study Sponsor, whether or not they result from study participation, within 24 hours of learning of the event.

15.1 Definition of a Serious Adverse Event

A **serious adverse event (SAE)** is any adverse event occurring within the timelines specified in the protocol that results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at immediate risk of death);

• Inpatient hospitalization or prolongation of existing hospitalization;
• Persistent or significant disability/incapacity;
• Congenital anomaly/birth defect in the offspring of a subject who received study device; or
• Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of serious adverse events include, but are not limited to: intensive treatment in an emergency room, hospitalization for any reason, and extensive treatment at home for an adverse event. An ectopic pregnancy is considered a serious adverse event.

15.2 Definition Of An Adverse Event

An **adverse event** is any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

• Any medical condition or clinically significant laboratory abnormality with an onset date before the first date of attempted study device placement is usually considered to be pre-existing, and should not be documented in the eCRF as an AE, unless there is an increase in frequency or intensity of that AE, but should be recorded as medical history.

• Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset from the first attempt of study device placement through Study Exit should be recorded as an AE on the eCRF. All AEs must be recorded on the AE eCRF regardless of the severity or relationship to study device. It is important that Investigators also report all AEs that result in expulsion or removal of the investigational product being studied, whether serious or non-serious.

Pregnancy is an outcome, and not an adverse event in this study.

15.3 Causality: Serious Adverse Event and Adverse Event Relationship to Study Treatment

The Investigator will assess the relationship of the SAE and AE to study device placement procedure (procedure) or study device by using the following general guidelines:

Not Related: A causal relationship between the study device and the AE can be ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).

Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to procedure or study device initiation which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to first attempt of study device placement, unlikely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to first attempt of study device placement, cannot be attributed to concurrent disease or other medical devices, drugs, or chemicals, and which follows a clinically reasonable response on withdrawal.

15.3.1 Clarification of Adverse Events Related to Study Procedures

Any untoward event that occurs from the beginning of the study device placement procedure until completion of placement, or from the beginning of the removal procedure until the completion of removal, will be reported as an AE. The AE should be recorded on the AE eCRF with a causality assessment of "related to study device placement procedure." If the AE also meets the criteria for an SAE, an SAE eCRF should be completed and submitted to Sponsor.

15.4 Serious Adverse Event and Adverse Event Severity

The Investigator will assess the severity of the AE using the following general guidelines:

• **Mild:** An AE that is usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.

• **Moderate**: An AE that introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.

• **Severe**: An AE that interrupts a subject's usually daily activity and typically requires systemic drug therapy or other treatment (a severe AE may not necessarily qualify as an SAE).

• **Life-threatening**: An AE that put the subject at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

15.5 Adverse Event Outcome

The Investigator will categorize the outcome of each SAE and AE according to the definitions below:

• **Resolved:** The subject recovered from the SAE or AE.

• **Resolved with sequelae**: a condition whereby the consequences of a disease or injury include lingering effects.

• **Ongoing:** At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing SAEs and AEs are not considered resolved as a result of death and no SAE or AE stop date should be recorded for an AE that is ongoing at the time of death.

• **Fatal:** Adverse Event directly caused death. The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology. Note: Death is an *outcome* of an adverse event and not an adverse event in itself. All reports of subject death should include an adverse event term (other than "Death") for the cause of the death.

Since reporting of an SAE is required within 24 hours of discovery, Death can be reported as an initial event term and updated to the final diagnosis in a follow-up report. If an adverse event term is not provided, the Investigator will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an adverse event can be obtained from the investigative site will "Death – Unknown Cause" be used as the event term.

The Investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

In the case of abnormal labs or diagnostic tests judged to be clinically significant by the Investigator a diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE or SAE eCRF. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded on the AE or SAE eCRF. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE eCRF, preferably with baseline values and copies of laboratory reports.

15.6 Prompt Reporting of SAEs to Sponsor

The Sponsor has requirements for reporting serious adverse events to regulatory agencies for a drug under clinical investigation. The Sponsor must be notified **within 24 hours of discovery** and the Investigator determines that an adverse event meets the protocol definition of an SAE.

All SAEs occurring from the beginning of study entry through study exit require immediate reporting to the Sponsor. Investigators should not wait to receive additional information to fully document the event prior to notifying the Sponsor

but should provide as much relevant information as immediately available. Further details of the event can be provided as they become available. The procedures for reporting SAEs are as follows:

- Complete the “Serious Adverse Event Report” form;
- Submit the completed form to Sponsor;
- For fatal or life-threatening events, also submit copies of hospital case reports, autopsy reports, and other documents when requested and applicable;
- The Sponsor may request additional information from the Investigator to ensure the timely completion of accurate safety reports;
- Any fatal or life-threatening events should also be reported immediately by telephone to Sponsor;
- The SAE eCRF should be completed as thoroughly as possible and signed by the Investigator before transmittal to Sponsor. It is very important that the Investigator provides an assessment of the causal relationship between the event and the study device at the time of the initial report; and
- The Investigator, or responsible person according to local requirements, must comply with the applicable local regulatory requirements concerning the reporting of SAEs to regulatory authorities and the IRB.

15.7 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) per se are not reported as AEs. However, abnormal findings that are deemed **clinically significant** (i.e., associated with signs and/or symptoms or requiring therapeutic intervention) must be recorded as AEs if they meet the definition of an adverse event (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after study device placement or that are present at baseline and worsen following the placement of VeraCept are included as AEs (or SAEs if serious).

The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may also jeopardize the subject and may require intervention to prevent immediate consequences (e.g., a markedly high serum potassium concentration may not be accompanied by arrhythmia, yet be of a magnitude to require potassium-binding resin administration to prevent such

sequelae). Subjects should undergo repeat testing of clinically significant abnormal laboratory findings as soon as they are recognized.

15.8 Documenting Adverse Events

Any AE occurring from the beginning of the study device placement procedure through Study Exit must be documented in the subject's study records and on the AE eCRF. SAEs that occur during the study must be documented in the subject's study record, on the AE eCRF and on the SAE eCRF as appropriate.

The investigator's assessment of causality, severity and status of the adverse event must be documented. When a causality assessment is provided for a serious adverse event, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations and the results of other diagnostic procedures. The Investigator's rationale with supporting evidence is valuable when Sponsor performs a cumulative analysis of similar events.

15.9 Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs must be followed until resolution, the condition stabilizes, 30 days post study device removal, or the subject dies or is lost to follow-up (including withdrawal of consent), whichever occurs first. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals. Follow-up information should be submitted to the Sponsor in a timely many as the information is obtained.

15.10 Clarification in Reporting of Deaths

All subject deaths (regardless of relationship to study device) should be reported that occur from the beginning of study device placement through Study Exit. The information should be recorded on the Subject Death form and the SAE eCRF.

15.11 Post-Study Treatment Reporting Requirements

For all enrolled subjects, all AEs and SAEs, regardless of cause or relationship, that occur from the beginning of study device placement through Study Exit require reporting to the Sponsor. In addition, if the Investigator learns of any SAE at any time after a subject has had the study device removed, and such event seems reasonably related to study drug, the Investigator should immediately notify the Sponsor.

15.12 Study Device Malfunction

Should the study device not perform mechanically as expected, it is essential that it be returned to the study Sponsor for assessment.

16. PROTOCOL VIOLATIONS and DEVIATIONS

Except in the event of a medical emergency or where it is necessary to protect the safety, rights or welfare of the study subject, any changes to the protocol will require written approval of ContraMed LLC or designee. Violations or deviations from the Clinical Investigational Plan to protect the health and safety of the subject will be reported to the IRB and as required by local regulations. All protocol violations or deviations will be recorded on the case report forms (eCRFs). A protocol violation or deviation may be requested in advance of implementation and will be reviewed for approval by ContraMed or its designee, or a violations/deviation may be identified after the fact, by the Investigator, ContraMed, or the monitoring staff. Investigators will be asked to provide an explanation for the all violations and deviations identified. ContraMed, or designee, will be responsible for analyzing deviations and may implement corrective actions as necessary.

17. SUBJECT CONFIDENTIALITY

At all times throughout this study, all parties shall strictly observe the confidentiality of subject's health information. All data shall be secured against unauthorized access. Each subject participating in this study will have consented to allow access to her data, as described during the informed consent process and documented in the signed informed consent form. Each subject will also sign an Authorization For Release of Protected Health Information (PHI) form granting ContraMed and its designees access to her medical records, should she receive medical care from non-study sites where she gets care (e.g., emergency room, urgent care, etc.).Each subject will be assigned a unique identifier. All eCRFs will be tracked, evaluated, and stored using only this unique identifier. HIPAA guidelines and regulations will be followed.

The Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The Investigator bears responsibility for keeping this list confidential. This list will not be provided to the study Sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the eCRFs corresponds to the person who signed the consent form and the information contained in the original source documents. Such personal identifying information may include, but not limited to, the subject's name, address, date of birth, gender, race and medical record number.

In an effort to protect subject confidentiality, any source documents copied for monitoring purposes by the Sponsor or designee will be identified using the subject's assigned unique identifier and personal identifying data will be obscured.

18. PREGNANCY DETERMINATION AND FOLLOW UP

Suspected pregnancy will be confirmed with a urine pregnancy test. A positive urine test will be confirmed by a serum test. Pregnancies will be promptly

confirmed and dated by ultrasound evaluation and medical assessment as needed. Presence or absence of the study device will also be determined by ultrasound. Removal of the study device, if in place, will be performed as deemed appropriate by the study physician and upon obtaining subject consent (note: removal itself may be performed by another clinician, such as a nurse practitioner). Consideration of study device removal should include the following standard of care criteria: If the subject has an intrauterine pregnancy in the first trimester and the study device is seen to be in the uterine cavity or cervix on ultrasound, remove the study device if the retrieval threads are visible. If the retrieval threads are not accessible, the IUD should remain in the uterus until delivery (abortion or term).

Subjects will be counseled and followed through completion of pregnancy, and the clinical outcome will be recorded.

19. DATA MONITORING AND QUALITY CONTROL

19.1 Monitoring of Clinical Sites and Investigators

Periodic monitoring visits will be made at the investigational site throughout the clinical study to ensure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities remain acceptable, the investigational plan is being followed, the IRB and local authorities have been notified of approved investigational plan changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and/or its designees and the IRB, study device and study device inventory are controlled and the Investigator is carrying out all agreed upon activities. The Sponsor will reserve the right to remove either the Investigator or the investigational site from the study for noncompliance with the investigational plan or regulations. See monitoring plan for full details.

19.2 Electronic Case Report Forms (eCRF)

Electronic case report forms (eCRFs) will be used to collect all subject data during the study

The Investigator is responsible for the accuracy and completeness of all data on the eCRFs.

Sponsor personnel or designee will review completed eCRFs at regular intervals throughout the study. Information on the eCRFs will be compared to information originally recorded on source documents related to the study. Information on the eCRF must match the same information on the source documents or a data query will be issued.

The Sponsor will use the study data for statistical and tracking purposes and will treat the information as confidential.

19.3 Data Collection and Management

Qualified study staff at the investigational site will perform primary data collection. The Sponsor monitors and/or designees will perform clinical study monitoring of 100% of the subjects who pass screening evaluations and undergo VeraCept placement. This monitoring will include review of eCRF data with verification to the source documentation.

All eCRFs will be reviewed for completeness, validity, and consistency. Queries will be generated and resolved with the sites and all protocol deviations will be recorded on the eCRF.

19.4 Maintaining Records

The Sponsor and/or its designees will maintain copies of correspondence, data, shipment of study devices, adverse study device effects and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator agreements.

19.5 Record Retention

All study records and reports will remain on file for a minimum of two years (or longer if local law or clinic administration requires) after the latter of the following two dates: 2 years after a marketing application is approved, or if an application is not approved, until 2 years after shipment and delivery of the study device for investigational use is discontinued and FDA has been so notified. Study records should only be discarded upon written notification from the Sponsor. All records and reports are subject to inspection at any time.

19.6 Investigational Product Accountability

The Sponsor or designee shall ship investigational study devices only to qualified investigators. The Investigator shall maintain adequate records of the receipt and disposition of all investigational study devices. The Investigator shall return any unused devices, opened or unopened, to the Sponsor or its designees when the study has completed.

19.7 Study Closeout

Upon completion of the clinical study (when all subjects enrolled have completed the last required visit and the eCRFs and queries have been completed), the Sponsor and/or its designees will notify all investigational sites of closeout. Unused study devices, and any unused study materials will be collected and returned to the Sponsor and/or its designees.

19.8 Audits And Inspections

The Investigator will permit access to original medical records and provide all requested information in the event that the Sponsor and/or its designees or national regulatory authorities initiate any audits or inspections. In the case that it is a non-Sponsor initiated audit, the investigator must contact the Sponsor as soon as possible after notification of intent to audit.

19.9 Annual, Interim And Final Report

Annual, interim and final reports will be completed in accordance with the applicable local and federal regulations. A final report will be completed even if the study is prematurely terminated.

20. STATISTICAL METHODOLOGY AND ANALYSIS

A detailed statistical analysis plan will be finalized prior to locking the database to conduct the statistical analysis in accordance with the methods presented below.

20.1 Analysis Populations

The following analysis populations will be created:

All Enrolled: All subjects enrolled into the study.

Intent to Treat (ITT) / Safety: All enrolled subjects who underwent the study device placement procedure, regardless of whether the study device was successfully placed or not.

Evaluable for Pregnancy (EP):
Subjects must meet requirements 1 and 2 to be EP. Subjects must also meet either requirement 3 **or** requirement 4 to be EP.

1. between 18 to 35 years of age (inclusive) at enrollment
2. at least one report of pregnancy status after being enrolled
   AND
3. have at least 1 cycle of diary with intercourse and without any backup contraception or emergency contraception (EC)
   OR
4. became pregnant while VeraCept was in place.

Evaluable for Cycle Control (ECYC): all subjects Evaluable for Pregnancy with at least one cycle for which: A) a pregnancy did not occur; and B) there is bleeding related diary data.

20.2 Disposition Of Subjects

The number of subjects who are enrolled, complete scheduled study visits and who complete the study will be summarized for the All Enrolled population.

20.3 Demographic And Other Subject Characteristics

Subject demographics and pre-treatment characteristics will be summarized for the All Enrolled Population.

20.4 Extent Of Exposure

Exposure (number of subjects with VeraCept placed and number of cycles of use) to the study device will be summarized.

20.5 Pre-Trial And Concomitant Medications

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken during the

study. Pre-trial medications include any routine medications taken within 30 days of enrollment. The number and percentage of subjects using medications, as captured on the Concomitant Medication eCRF, will be tabulated according to the medication's World Health Organization Anatomical Therapeutic Drug Class and Generic Term. Pre-trial and concomitant medications will be presented separately.

20.6 Primary Outcome

The primary outcome measure is effectiveness and will be evaluated as absence of pregnancy during VeraCept use for up to 12 months. Pregnancies judged to have occurred while a study device was in place (determined by ultrasound and medical assessments) will be included in the analysis of pregnancies.

For the primary evaluation of effectiveness, the Pearl index (and 95% confidence intervals) will be calculated through 12 months for cycles in subjects aged 18-35 at the time of VeraCept placement, excluding the following (unless the subject became pregnant in the cycle):

- Cycles where back-up contraception use was documented on the daily diary
- Cycles with no intercourse.
- Cycles in which emergency contraception was used

The EP population will be used for the primary evaluation of effectiveness.

Life table analyses will be used as further assessment of pregnancies. Secondarily the Pearl index and life table analyses will be done through 3 years.

20.7 Safety And Other Outcome Measures

All safety and other outcome measures will be analyzed using the ITT/Safety Population unless noted otherwise. Confidence intervals will be provided to support interpretation of the observed safety rates.

VeraCept Characteristics
Study device ease of placement and placement success will be summarized. Cumulative study device expulsion rates will be summarized

Adverse Events
The number and percentage of subjects with each adverse event and serious adverse event will be presented in a table by MedDRA system-organ class and preferred term. Summaries will also be presented by relationship to the VeraCept placement or removal procedure and the severity of the adverse event. All adverse events will be summarized with special attention to those events that may be related to an intrauterine contraceptive, including:

- Anemia
- Back pain
- Dysmenorrhea
- Dyspareunia
- Ectopic pregnancy
- Embedment, which in some cases may require surgical removal

- Expulsion, partial or complete
- Intrauterine pregnancy
- Leukorrhea
- Medical diathermy
- Menstrual flow, prolonged / vaginal bleeding
- Menstrual spotting
- Movement of study device during MRI
- Pain and cramping
- Pelvic infection, which can lead to Fallopian tubal damage leading to ectopic pregnancy or infertility, hysterectomy, sepsis and rarely death
- Pelvic Inflammatory Disease (PID), which can lead to tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death.
- Uterine perforation, which may lead to pre-operative imaging followed by laparscopy or laparotomy to remove the IUD from the peritoneal cavity
- Septic abortion
- Uticarial allergic skin reaction
- Vaginitis
- Vasovagal reaction at the time of placement, including fainting.

VeraCept Safety-Related Removal Rates and Expulsion Rates
Cumulative VeraCept safety-related removal rates and expulsion rates at each year will be summarized.

Bleeding and Spotting Patterns
Vaginal bleeding and spotting will be recorded daily by the subject in her diary. The ECYC population will be used for the bleeding and spotting summaries. The number of bleeding or spotting days will be summarized for each cycle. In addition, bleeding and spotting will be summarized separately. Subjects who discontinue the study due to bleeding complaints prior to completing one 28-day cycle will be included in the bleeding analysis.

Other Safety Assessments

Changes in vital signs from baseline to each visit will be summarized for the physical examination and vital sign results.

20.8 Monitoring of Safety and Pregnancy

Periodic reviews of safety and pregnancy rates will be conducted by a Medical Monitor. New findings of safety concerns or pregnancies will be communicated to all study sites. A Clinical Events Committee (CEC) will be assembled to review study data if >1 pregnancy is reported.

APPENDIX 1. INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that the clinical study is conducted according to the Investigator Agreement, Clinical Investigational Plan (CIP), all conditions of national regulatory requirements, the governing IRB, and in accordance with the highest standards of medical and ICH E6 Good Clinical Practice (GCP), and the Declaration of Helsinki.

The Investigator(s) shall be responsible for the day-to-day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation. The Investigator(s) shall:

a) Have the resources to conduct the investigation properly

b) Ensure that conducting the investigation will not give rise to a conflict of interest

c) Obtain from the Sponsor the information which the Investigator(s) judges essential about the study device and be familiar with this information

d) Be well acquainted with the protocol before signing it

e) Support the monitor and/or auditor, if applicable, in their activities to verify compliance with the protocol, to perform source data verification and to correct the eCRFs where inconsistencies or missing values are identified

f) Discuss with the Sponsor management any question or modification of the protocol

g) Make sure that the protocol is followed by all responsible for the conduct of the study at his/her institution. Any deviation shall be documented and reported to the study Sponsor.

h) Make the necessary arrangements to ensure the proper conduct and completion of the investigation

i) Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject

j) Ensure that appropriate IRB approvals are obtained prior to the start of the investigation

k) Provide the communication from the IRB to the study sponsor

l) Inform the IRB about any serious adverse device effects in accordance with the IRB requirements.

m) Inform the Sponsor about any adverse events and adverse device effects in a timely manner and in accordance with the timelines laid out in this protocol

n) Endeavor to ensure an adequate recruitment of subjects

o) Ensure that the subject has adequate time and information to give informed consent

p) Ensure that informed consent authorization to release protected health information is obtained and documented prior to any study specific evaluations or procedures being performed

q) Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study

r) Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest

s) Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the investigation shall be made known to: 1) the Sponsor; 2) the subject; and 3) the subject's personal clinician (with the subject's approval), if pertinent to the safety or well-being of the subject

t) Inform the subject and/or the subject's physician (with the subject's approval) about any premature termination or suspension of the investigation with a rationale for study termination

u) Have primary responsibility for the accuracy, legibility and security of all investigational data, documents and subject records both during and after the investigation

v) Review and sign each subject's eCRFs (last page only)

w) Be responsible for the supervision and assignment of duties at his/her study center

x) Ensure that all investigational devices are accounted for (number of devices used, discarded and returned to the Sponsor)

y) Disclose to the Sponsor sufficient accurate financial information to allow the Investigator to submit complete and accurate certification or disclosure statements, and update the information during the course of the investigation and for one year following the completion of the study

z) Ensure that the Investigator discloses to the Sponsor if the Investigator has ever been associated with terminated research and the reason for such termination is provided

aa) Ensure that the Investigator discloses to the Sponsor if the Investigator has ever been barred from conducting or participating in clinical research.