Official title: Treatment of unfavorable bleeding patterns in contraceptive implant users

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Background:
The etonogestrel (ENG) subdermal contraceptive implant (ENG implant) is a highly effective method of preventing pregnancy, but it has bleeding side effects that make it unappealing for many women. Given that the ENG implant is 20 times more effective at pregnancy prevention than oral contraceptive pills, strategies to increase its acceptability will translate into improved prevention of unplanned pregnancies [1]. Many medications have been studied with progestin-only contraceptives such as the ENG implant to manage irregular bleeding. The only study to demonstrate a sustained reduction in bleeding lasting for two months was the selective estrogen receptor modulator (SERM) tamoxifen in users of the levonogestrel (LNG) contraceptive implant [2]. We conducted a small clinical trial to evaluate the effects of a 7-day course of tamoxifen in users of Nexplanon© with bothersome breakthrough bleeding, and have preliminary data that demonstrates that tamoxifen treatment reduces bleeding/spotting days during the first 30 days after use as compared to placebo [3]. This sustained post-treatment effect is novel, as prior studies of agents such as combined oral contraceptives have only demonstrated improvement in bleeding patterns while on treatment. Further study is needed to determine if our results are reproducible in a larger population, and whether the treatment response will be maintained with repeat dosing if needed.

[1] Winner B, Peipert JF, Q Z, C B, Madden TE, Allsworth JE, et al. Effectiveness of Long-Acting Reversible Contraception. New England Journal of Medicine 2012;366:1998–2007.
[2] Abdel-Aleem H, Shaaban OM, Amin AF, Abdel-Aleem AM. Tamoxifen treatment of bleeding irregularities associated with Norplant use. Contraception 2005;72:432–7.
[3] Simmons K, Edelman A, Fu Rochelle, Jensen JT. A short course of tamoxifen reduces unscheduled bleeding in etonogestrel contraceptive implant users. Obstet Gynecol 2016; 127. (*Abstract*)

Hypothesis:
1) In etonorgestrel (ENG) users with troublesome bleeding, a 7-day treatment with 10 mg tamoxifen twice daily will result in a significantly longer bleeding-free interval than placebo.
2) In etonorgestrel (ENG) users with troublesome bleeding, a 7-day treatment with 10 mg tamoxifen twice daily repeated no sooner than every 30 days if troublesome bleeding reoccurs will result in significantly fewer bleeding/spotting days and significantly longer bleeding-free intervals over the next 30 days than placebo.

Objectives:
To identify a successful treatment for troublesome bleeding and spotting in users of the ENG contraceptive subdermal implant.

Primary objective:

1. **Total number of consecutive bleeding-free days in the first 30 days from Day 1 of first treatment (TX1)**

Secondary objectives:

1. **First 90-day reference period outcomes between treatment and placebo (double blind placebo-controlled RCT):**
   a) Total number of bleeding/spotting days in the first 30 days post-Day 1 of TX1, TX2, and TX3
   b) Total number of days to bleeding cessation after Day 1 of TX1, TX2, TX3
   c) Total number of TX (1-3) taken during the first 90-day referent period
   d) Total number of bleeding free days and bleeding/spotting days over the first 90-day reference period (starting from Day 1 of TX1)
   e) Length of time (days) between each treatment.
2. **Second 90-day reference period outcomes between ongoing treatment and placebo now using active treatment (open label):**
   a) Total number of bleeding/spotting days in the first 30 days post-Day 1 of TX4, TX5, and TX6
   b) Total number of days to bleeding cessation after Day 1 of TX4, TX5, TX6
   c) Total number of TX (4-6) taken during the first 90-day referent period
   d) Total number of bleeding free days and bleeding/spotting days over the first 90-day reference period (starting from Day 1 of TX4)
   e) Length of time (days) between each treatment.
3. **Overall outcomes:**
   a) Drop out
   b) Patient satisfaction with bleeding pattern
   c) Continuation of implant or anticipation of continuation
   d) Side effects
   e) Total number of bleeding free days and bleeding/spotting days over 180 days (2 reference periods; starting from Day 1 of TX1)
   f) Stratification of primary and secondary bleeding and bleeding-free analyses by time of implant use (6mos, 1 year, 2 years, 3 years).

**Of note, maximal number of potential treatments is 3 during each 90-day reference period. However, subjects can initiate TX on the last day of the reference period. Any outcome related to TX initiated less than 30 days from end of study (Day 180 from initiation of TX1) will be curtailed at 180 days. Any subject taking study medication 7-days prior to Day 180 or Day 180 will be scheduled for an end of visit contact one week after TX completion to ensure patient safety and capture AE data.

Study design/Clinical Plan:
We are proposing a 2 phase trial for treatment of women experiencing frequent or prolonged bleeding while using the ENG contraceptive implant. The **first phase** will consist of a randomized, controlled, double blind placebo-controlled clinical trial over a 90-day reference period and the **second phase** will allow both study arms to receive open-label treatment over an additional 90-day reference period.

The primary outcome of the study will be the total number of consecutive bleeding-free days in first 30 days from Day 1 of first treatment (TX1). The study has a number of secondary outcomes (see above, study objectives) focused around the efficacy of oral tamoxifen to: 1) stop an episode of bleeding/spotting and for how long; 2) to stop recurrent episodes of bleeding/spotting with repeat dosing; and 3) to determine if total number of bleeding/spotting days are decreased over each reference period and over the entire study period (approximately 180 days from ingestion of first treatment).

In phase 1, the intervention will consist of study drug exposure (tamoxifen or placebo) twice daily for 7 days. The first dose will be taken when subjects experience at least three consecutive days of bleeding/spotting. Repeat dosing will occur no sooner than 30 days after starting TX. Participants can dose up to 3 times in each 90-day reference period. Subjects will be eligible for TX if they experience recurrent bleeding/spotting of 3 or more consecutive days. Subjects can initiate a TX on the last day of a reference period.

In phase 2, all subjects will enter an open label treatment period over the next 90 days. The intervention will consist of the same study drug exposure as Phase 1 (tamoxifen twice daily for 7 days). The first dose will be taken when subjects experience at least three consecutive days of bleeding/spotting but no sooner than 30 days after starting the last TX. Participants can dose up to 3 times in this 90 day reference period. Subjects can initiate a TX on the last day of a reference period. ; however outcomes related to bleeding patterns will be curtailed at Day 180 from initiation of TX1). Any subject taking study medication 7-days prior to Day 180 or Day 180 will be scheduled for an end of visit contact one week after TX completion to ensure patient safety and capture AE data.

The study will be conducted at Oregon Health & Science University (OHSU) in Portland, Oregon and the University of Hawaii (UH), Manoa. OHSU IRB will oversee regulatory procedures at UH.

Each subject's involvement will be approximately 180 days from Day 1 of TX1 and will require up to 8 in-person study visits (screening, enrollment plus monthly visits scheduled based on Day1 of TX1 and a close out visit), as well as a daily response to a text or email message about bleeding and use of study medication. Depending on the delay between study enrollment and Day 1 of TX1, additional phone and email contact may occur with the participant to ensure clarity of when to start study drug. The electronic diary only takes a few seconds to complete. If the participant does not respond to the diary on any given day, then they will receive a call or email from the study coordinator to check in. Additionally, if the participant reports 3 consecutive days of bleeding and does not report taking study drug, they will receive a call or email from the study coordinator.

Eligibility:

Inclusion:

- English speaking women 15-45 years of age currently using the ENG implant who have experienced frequent or prolonged bleeding while using the device:
  - To be eligible, women will need to have >7 days of continuous bleeding/spotting in the last 30 days, OR 2 or more episodes of bleeding/spotting in the last 30 days.
- Implant use for at least 1 month
- Willing to continue using the implant for at least six months from study enrollment.
- Access to a reliable cell phone and must be willing to receive and respond to a daily text or email message to assess bleeding and use of study drug

- Implant must be palpable to prove that an ENG implant is in place at time of screening and enrollment.
- Negative gonorrhea/chlamydia screening performed at screening visit

Exclusion criteria:

- Postpartum within six months
- Post-abortion within six weeks
- Currently pregnant
- Currently breast-feeding (to be eligible, must be 4-6 weeks from cessation of breastfeeding)
- Undiagnosed abnormal uterine bleeding pre-dating placement of contraceptive implant
- Bleeding dyscrasia
- Anticoagulation use
- Active cervicitis
- Allergy to tamoxifen
- History of venous thromboembolism
- Current or past breast or uterine malignancy
- Use of medication contraindicated with tamoxifen including:
    - coumadin, letrozole, bromocriptine, rifampicin, aminoglutethimide, phenobarbital
    - All contraindicated medications listed in the consent form
- Implant is due to be switched out in 4 months or less from enrollment (It is acceptable if their implant is due to be switched out in 5-6 months from enrollment as long as subject agrees to keep it in place while on study for approximately 6 months)
- Currently using oral contraceptives in addition to implant (to be eligible, needs to have a 4-6 week washout period)
- Prior pregnancy occurred while Nexplanon/Implanon was in place

Study procedures

Screening (Visit 1, V1). Estimated 1 hour
Eligibility and study consent will be signed at this visit. Baseline demographic information will be collected by interview, including menstrual history, contraception history including timing of implant placement, sexual and pregnancy history, BMI/weight, ethnicity, age, and baseline use of panty liners (as advised by Mishell et al 2007 to avoid confounding data on bleeding/spotting days). A series of questions will be asked to quantify number of bleeding and spotting days and frequency and duration of bleeding episodes over the preceding three months of implant use (or since placement, if less than three months). Current implant use will be confirmed via palpation.

Physical exam including blood pressure check, pelvic examination, urine pregnancy test, cervical cytology evaluation (if not completed within the ASCCP recommended screening interval), and testing for gonorrhea and chlamydia. A baseline assessment of satisfaction with baseline bleeding pattern will also be performed.

Once negative results from the subject's gonorrhea and chlamydia testing are demonstrated, visit 2 can be scheduled (enrollment).

Enrollment (V2), estimated 30 minutes
Randomization for part 1 of the study will occur at this visit. Pregnancy test and blood pressure will be performed. The Subject Study Drug Information Handout will be provided and explained. Study drug will be provided. At this visit if the subject happens to currently be bleeding, the

coordinator will have the woman fill out this information on a paper diary. If she has had 3 consecutive days of bleeding, then study drug can be started immediately at this visit. If she has only had 1 or 2 days, this will be noted on the paper diary and the study coordinator will explain the earliest day that she could start the study drug and instruct how to start tracking bleeding via text message.

Subjects will receive training on the use of the electronic bleeding diary procedures. This includes instruction on use of the text or email message bleeding diary.

Follow up Visits 3 to 7, estimated 30 minutes each
The third, fourth, fifth, sixth, and seventh study visits will take place approximately14-25 days after the start of study drug. Follow-up visits may need to occur outside of this range due to scheduling reasons, but every effort will be made to conduct a study visit within the 14-25 day range OR prior to the date when the next study drug bottle can be started. Follow-up visits will occur approximately every 30 days if participant does not need to take the study drug. At these visits, bleeding diary will be reviewed with study staff as well as review of medications, AEs, and health changes. Repeat STI testing only if indicated by a change in partners during the study. A short satisfaction questionnaire will be performed at study visit 3 and 5. Next dose of study drug will be provided. Unused study drug will be retuned at these visits.

End of study, Visit 8, estimated 30 minutes
The final visit will take place approximately 180 days after the first day of study drug. After this final visit, participation is complete. Blood pressure will be performed.

Visit	Details
Visit 1-Screening	• Informed consent • Review medications • Physical exam with vitals (blood pressure, pulse, weight, height) • Urine pregnancy test • Review eligibility criteria • Gonorrhea and chlamydia test • Pap (if indicated) • Baseline questionnaire
Visit 2-7 (Visit 2 – enrollment visit) (Visit 5 – transition to open-label)	• Review bleeding diary with staff • Review medications • Receive placebo or study drug and instructions • Return any unused medication • Blood pressure- Visit 2 only) • Review any health changes • Urine pregnancy test if indicated • Repeat Gonorrhea and chlamydia test if change in partner occurs during study. • Questionnaire at visit 3 and 5
Visit 8- end of study	• Review medications • Return any unused medication • Vitals (blood pressure, pulse, weight, height) • Review bleeding diary with staff • Review health changes

	• Exit questionnaire

Description of intervention/study drug

Participants will be instructed to begin use of the study medication (tamoxifen 10 mg bid x 7 days or placebo) on the third day of their next bleeding or spotting episode, and continue to take a twice daily oral dose for seven days. The day of treatment will be reference period day 1. Subjects will self-initiate subsequent study medication for additional qualifying bleeding episodes (3 days of bleeding/spotting) no sooner than 30 days after the first treatment (ref period day 30). A study coordinator will prospectively following electronic bleeding diaries at a minimum of three times weekly for each individual study subject and will prompt subjects to initiate a treatment course if they are eligible. Subjects reporting at least 3 consecutive days of current bleeding at the time of study entry/randomization will be instructed to begin the study medication immediately. In each 90-day reference period, subjects can repeat dosing up to 3 times. Subjects will receive one bottle of 14 pills at the start of the study, and then additional bottles at follow up visits. Any unused study drug will be counted and returned at each visit, and again at the conclusion of the study.

Failure to complete the texting diary will prompt a phone call from the SC. If we are unable to reach a subject by phone, email, letter, or facebook (facilitated only via private message) over a 2 week time period, their participation will be terminated. Any data obtained up to this point will be analyzed in accordance to with intention to treat.

Study procedures and data collection other than side effects and AEs will last 180 days from Day 1 of TX1. Participants who do not initiate study drug within the first 30 days of enrollment will be discontinued. Any subject taking study medication 7-days prior to Day 180 or Day 180 will be scheduled for an end of visit contact one week after TX completion to ensure patient safety and capture AE data

Compensation

Participants will be compensated up to $400 for their participation in this study. Study visit compensation breakdown is as follows:

- Visit 1- Screening: $25
- Visit 2- Enrollment: $25
- Visit 3-8: $30/each visit
- End of study bonus $70
- Diary Completion: $100

Subjects will only be compensated for the visits they complete. For example, if a subject withdraws after visit 3, they will only be compensated for those three visits ($25 + $25+$30). Participants will only receive the $70 end of study bonus if they complete all eight study visits.

Diary compensation

Diary completion is defined as responding to 2 daily text messages every day. A subject can miss up to 2 days of responses per month and still receive diary compensation for the month. If a subject misses 3 or more days of diary entry in a given month, they will not receive compensation for that month. Study coordinators will be tracking diary responses, and response

rates for the previous month will be reviewed at each visit. A $40 bonus will be given at the end of the study to subjects who have adequately completed their diaries each month. Diary compensation will be prorated per visit as follows:

- Diary @ Visit 3- $10
- Diary @ Visit 4- $10
- Diary @ Visit 5- $10
- Diary @ Visit 6- $10
- Diary @ Visit 7- $10
- Diary @ Visit-8: $10
- End of study diary bonus: $40

If a subject withdraws early from the study, they will only receive compensation for visits that they have completed

Alternative approaches:
We could use a different SERM and/or change the way we define study entry or treatment initiation. The study medication and current research methods are based on our pilot study as well as the published literature. Only tamoxifen has been studied for treatment of unscheduled bleeding in implant users. We believe its impact is due to its effect on estrogen receptor β (ERβ); newer SERMs have less selectivity for ERβ [1].

In regard to study eligibility (>7 days of bleeding/spotting or 2 episodes/30 days), we want to enroll the average woman with an "annoying" bleeding pattern and not the woman likely moving toward implant removal as this would impact our dropout rate. And finally, initiation of study medication could occur at >3 days but we believe that women significantly impacted by their bleeding patterns will want to initiate treatment as soon as possible. More stringent starting rules might adversely impact continuation in the study. We could also be more liberal in defining when to initiate treatment. For instance, recommending medication initiation when bleeding/spotting occurs the majority of days per week but not continuously (e.g. 2 days of bleeding/spotting – 1 day of no bleeding/spotting – 2 days of bleeding/spotting). This pattern of bleeding is still likely to be unpleasant for women but using an additional criterion for initiation may make correct drug initiation more complicated. In our prior study, we used 3 days of consecutive bleeding to trigger treatment initiation and that approach has also been used in prior studies.

[1] Komm BS, Mirkin S. An overview of current and emerging SERMs. J Steroid Biochem Mol Biol 2014; 143:207-22.

Sample size
Our primary outcome is the total number of consecutive bleeding-free days between tamoxifen and placebo groups following TX1 (starting from Day 1 of treatment until 30 days hence).

Based on our pilot work, a sample size of 80 women allows us to demonstrate a 15-day difference between groups [mean tamoxifen 28.8 (SD 24.5) versus placebo 13.6 (SD 19.2)]; 86% power at an alpha 0.05 = 40 women per each group. To account for drop out, we have increased the sample size by approximately 30% for a total sample size of 116. This sample size will also provide us with sufficient power to determine the difference in several of our

secondary outcomes including a difference of at least 1 treatment course used in a 90-day period and a 12-day difference in amenorrhea over a 90-day reference period.

Study drug

Tamoxifen is a nonsteroidal agent with antiestrogenic properties. Following an oral dose of 20mg, peak plasma concentration occurs about five hours after dosing. The elimination half life is 5-7 days (Package insert). Administration of 10mg tamoxifen given twice daily for three months results in average steady-state plasma concentration of 120ng/ml, which occurs after four weeks of continuous dosing. After oral administration, tamoxifen undergoes metabolism to its primary N-desmethyl tamoxifen metabolite, which has similar biologic activity to tamoxifen. It is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and is an inhibitor of P-glycoprotein. Excretion is primarily fecal (Package insert).

Tamoxifen is approved by the US Food and Drug Administration at doses of 20-40mg daily (divided dosing twice daily) and is primarily utilized for its antiestrogen properties as an adjuvant therapy to prevent recurrence of estrogen receptor (ER) positive breast carcinoma in post menopausal women following mastectomy, axillary dissection and breast irradiation. It is also approved to reduce the incidence of breast cancer in high risk women (those with a 5 year predicted risk over 1.67% according to the Gail Model. Usual dose and duration of therapy is 20-40mg daily taken for up to five years.

When tamoxifen has been used previously at a dose of 10mg twice daily for 10 days in premenopausal women as a treatment for progestin-inducted bleeding, side effects were rare and did not differ between treatment and placebo. The most common reported effect was headache, reported in up to 20% of users [1]. Our pilot study of 10mg twice daily for 7 days in premenopausal women (n = 56) as a treatment for irregular bleeding due to the contraceptive implant resulted in no serious adverse events. In addition, we also tracked evidence of ovulation in a subgroup of participants and no participant demonstrated evidence of ovulation (e.g. no evidence of tamoxifen interfering with implant effectiveness) [2].

There are reported serious adverse effects from long term tamoxifen use, but the short course of therapy in this study is unlikely to result in any of these adverse events. Risks with longer term use of tamoxifen may include endometrial changes such as hyperplasia, polyps, or malignancy, risk of venous thromboembolism, stroke or ovarian cysts. Of note, venous thrombosis events were not reported until at least two consecutive months of use. Likewise, an increased risk of endometrial cancer has only been demonstrated in postmenopausal women with use between 1 and 61 months. Increased incidence of endometrial hyperplasia and polyps have been reported only in postmenopausal women. A few reports of fibroids, endometriosis, and ovarian cysts have been observed in a small number of premenopausal women with advanced breast cancer receiving tamoxifen (Package insert).

Use of tamoxifen for this study is exempt from the requirements to submit an Investigational New Drug application to the FDA. This study is not intended to be used for support of new FDA indication for use or labeling for tamoxifen. This study is also not intended to support a significant change in advertising for tamoxifen. Lastly, this study does not use a route of administration or dosage level that is known to significantly increase the risks associated with use of tamoxifen.

[1] Abdel-Aleem H, Shaaban OM, Amin AF, Abdel-Aleem AM. Tamoxifen treatment of bleeding irregularities associated with Norplant use. Contraception 2005;72:432

[2] Simmons K, Edelman A, Fu Rochelle, Jensen JT. A short course of tamoxifen reduces unscheduled bleeding in etonogestrel contraceptive implant users. Obstet Gynecol 2016; 127. (*Abstract*). *Paper under review.*

Risks to Subjects

Human Subjects Involvement and Characteristics

Reproductive-aged (15-45 year old), healthy women currently using a contraceptive implant with no contraindications to the study medication and not at risk for or seeking pregnancy will constitute the target population for this study.

All enrollment and clinical evaluations will be performed at OHSU in Portland, Oregon. Gonorrhea and chlamydia testing and pap testing (if indicated) will be sent to the OHSU core lab for routine processing.

Sources of Materials

The sources of research material for the clinical portion of this proposal will be new specimens obtained purely for this research protocol. The study investigators and/or research assistants/nurses will perform all study procedures.

Potential Risks

One risk to taking part in this study is that the study drug may not be effective in helping to treat bleeding.

The study drug has few side effects and is considered safe by the FDA. Fewer than 20% of people experience any side effects. The most common are headache, upset stomach, or fatigue. There are risks associated with long-term use of the study drug, especially in women after menopause. These include risk of blood clots, stroke or pre-cancer in the uterus. Because participants are only using the study drug for one week at a time, these risks should not apply to the participants. Rarely women develop ovarian cysts with long-term use of the study drug. These go away when the drug is stopped.

The study drug has been used before in women using the contraceptive implant. There is a small possibility that the study drug might make the contraceptive implant less effective but our prior study demonstrated no evidence of increased ovulatory activity following study drug use. There is a small possibility that subjects could become pregnant while participating in this study. The implant does not cause harm to a developing pregnancy. However, the study drug should not be taken during pregnancy. If subjects are nursing an infant or are pregnant now, they cannot be in the study. This study drug may involve risks to an embryo, fetus, or nursing infant that are currently unknown. If pregnancy occurs during the research study, study participation would be discontinued, determination of exposure to study drug would be determined, and the PI would provide the subject with counseling and referral.

Some parts of the study may be inconvenient including the text messaging to collect data. These are regular text or email messages and will count towards text messages or data on a subject's cell phone plan. The Subject will be asked detailed questions about her bleeding and gynecologic history. Some of these questions may seem very personal or embarrassing. Women may refuse to answer any of the questions that they do not wish to answer.

Adequacy of Protection Against Risk

Recruitment and Informed Consent

Attempts to enroll a diverse study population will be made through placement of IRB approved flyers in the community, community outreach (radio and print ads) and through the availability of foreign language interpreters and research staff (see Inclusion of women and minorities). Women may also learn of the study through their routine visits in clinics or by working at OHSU. We also intend to utilize an EPIC Cohort search to identify and contact potential participants via phone, email, letter, and/or MyChart messages. We intend to use REDCap for batch emailing. We also intend to use Trialspark and Google AdWords as well as Facebook and Instagram for community outreach.

Women will be screened for eligibility and if they meet the basic criteria and agree to participate, they will undergo informed written consent. The protocols and consent will be reviewed and approved by the OHSU IRB prior to initiation of the study.

Protection Against Risk

The drug utilized in this study will be used in accordance with the FDA and at a dosage that is still considered to be safe. Women will be informed of this off-label dosing but that we have specifically chosen a dose and length of exposure time to the drug or compound with extremely low potential for significant side effects or serious risks. Women will undergo screening for any known contraindications to the study drugs chosen to trial in women.

Confidentiality of personal health information will be maintained according to HIPAA requirements for research. All subjects will receive a study number to which all subsequent data will refer. Personal identifiers will not be on questionnaires, data, abstract sheets, or in the main database. All data will be kept in locked files or a password protected computer in the Principal Investigator's (PI) office.

Data and safety monitoring of plans for clinical trials

The PI and study staffs are responsible for recording the data, and they will be verifying its accuracy throughout the process. The PI will be reviewing the data in-depth upon completion of the study. The PI will also be overseeing that the study procedures are being carried out as per the approved protocol via close supervision of study visits and procedures and through frequent communication with the study staff. The PI will also be conducting an initial assessment and periodic assessments of the study and its procedures. If any safety concerns arise, a data safety monitoring board will be convened to review the study. As this study will be performed in conjunction with the Women's Health Research Unit's (WHRU), an independent chart audit to ensure data integrity and completeness will be performed after the first 5 subjects have been enrolled and then at regular 6 months intervals.

The PI will adhere to OHSU's Institutional Review Board (IRB) policies regarding protection of human subjects and the reporting of study deviations and adverse events. In the rare case of an adverse event, she will utilize the WHRU data safety monitoring board (DSMB) to review the event and rule on a course of action. The WHRU DSMB is made up of individuals knowledgeable about women's reproductive health and therapies and will have no conflict of interest with the study or its outcomes.

Data Storage

Data for this project will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system.

Features of REDCap that protect participants' privacy and data security include:

- Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security
- Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.
- Controlled User Access: REDCap is employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes “single click” ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

Data Sharing

We intend to use “Box” to share study documents and spreadsheets between study sites.

Potential Benefits of the Proposed Research to the Subjects and Others

There are no direct benefits to study participants.

Importance of Knowledge to be Gained

This study will increase the knowledge regarding breakthrough bleeding and contraceptive implants. It may help to prolong continuation of contraceptive implant use which in turn could help women avoid unplanned pregnancies. It may go beyond the treatment of a problem, but also help in provide the potential mechanism of action and other possible interventions for this phenomenon.