Official Title:
Tamoxifen to reduce unscheduled bleeding in new users of the Levonorgestrel-releasing intrauterine system (LNG-IUS)

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Project summary

The 52 mg levonorgestrel-releasing intrauterine system (LNG-IUS, trade name “Mirena” or “Liletta”) is a highly effective method of preventing pregnancy, but its use is often associated with early “nuisance bleeding” which may lead to discontinuation. Given that the LNG-IUS 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 LNG-IUS 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 levonorgestrel (LNG) contraceptive implant (2). The proposed research project will be the first to test the effectiveness of tamoxifen to improve bleeding patterns in users of the LNG-IUS.

This is a randomized, controlled, double blind clinical trial enrolling new users of the LNG-IUS to try to improve frequent or prolonged bleeding after insertion. Participants are randomized to receive tamoxifen 10mg or placebo twice daily for seven days starting 21 days after IUS insertion. All participants will maintain daily bleeding diaries via text or email message and on paper for a total of 51 days, including three weeks of baseline data and 30 days of data following initiation of treatment. The primary anticipated outcome is that women who receive tamoxifen will have a reduction in bleeding/spotting days compared to placebo in the 30 days after starting study drug.

1. DESCRIPTION OF THE PROJECT

1.1 Rationale and objectives of the study

1.1.1 *Rationale*

The 52 mg levonorgestrel-releasing intrauterine system (LNG-IUS) is a highly effective method of reversible contraception with a failure rate within the first year of less than 1% (3). Like other progestin-only methods, the LNG-IUS is associated with bleeding pattern changes ranging from amenorrhea, infrequent and irregular bleeding, to frequent or prolonged bleeding. Bleeding irregularities apart from amenorrhea are most pronounced in the first six months of use. Between 11-26.3% of women experience frequent or prolonged bleeding during LNG-IUS use (4–8). Discontinuation of the LNG-IUS within the first year ranges from 7-30% of users, with the majority of women citing bleeding pattern changes as one of their primary motivations for discontinuation (4–7,9). Patients with excessive bleeding or spotting were 2.7 or 1.8 times more likely to discontinue LNG-IUS, respectively (7). Preventing frequent or prolonged bleeding in LNG-IUS users should decrease discontinuation. Given that long-acting, reversible contraceptives (LARCs) including the LNG-IUS are 20 times more effective at pregnancy prevention than oral contraceptive pills, strategies to increase their acceptability will translate into prevention of unplanned pregnancies (1).

Many prior studies have examined strategies to manage irregular bleeding resulting from progestin-only contraceptives. Mechanisms for irregular bleeding are multifactorial and poorly understood, but may involve changes in vascular growth, vascular fragility, estrogen withdrawal, and disruption in repair mechanisms within the endometrium (10–16). These theories have inspired studies of non-steroidal anti-inflammatory medications, antibiotics, and estradiol preparations to stabilize endometrium and reduce bleeding, but no single approach has shown a consistent benefit (2,15,17,18). The most commonly prescribed medication for persistent bleeding is combined oral contraceptive pills, but these have shown conflicting success in decreasing bleeding, may cause side effects, and are not a therapeutic option for women with contraindications to estrogen (15). Selective progesterone receptor modulators (SPRMs) including mifepristone have shown some promise in reducing bleeding, possibly due to induction of an atrophic endometrium or promotion of tissue repair mechanisms (12,19–21). In humans, single doses of at least 50mg of mifepristone or similar SPRMs consistently reduced either the duration of bleeding episodes, total number of bleeding days, or percentage of bleeding days in users of progestin-only pills (11), depo medroxyprogesterone acetate (DMPA) (22), LNG-IUS (23), and LNG implant (24,25).

Few studies have investigated medications to prevent or treat frequent or prolonged bleeding early in LNG-IUS use. Therapies tested have included selective progesterone receptor modulators, non-steroidal anti-inflammatory drugs, and estrogen patches (16,23,26,27). As mentioned above, mifepristone administered in doses of 100mg monthly starting at LNG-IUS insertion and repeated monthly for three months showed a significant reduction in duration but not frequency of intermenstrual bleeding/spotting in one small, non-randomized, open-label trial (23). Tranexamic acid and mefenamic acid both failed to significantly alleviate breakthrough bleeding in the first 90 days after LNG-IUS insertion when participants were randomized to take them versus placebo when experiencing a bleeding or spotting episode (27). In another randomized controlled prevention trial, Naproxen 500mg twice daily for five days every 4 weeks over 12 weeks after insertion did show a 10% reduction in bleeding/spotting days compared to placebo (RR 0.9, 95% CI 0.84-0.97) whereas estradiol patch use was associated with increased bleeding/spotting days compared to placebo (RR 1.25, 95% CI 1.17-1.34) (26).

In another randomized controlled trial, Warner et al investigated use of a different selective progesterone receptor modulator, CBD-2914, for prevention of unscheduled vaginal bleeding in the first 4 months after LNG-IUS insertion (16). Participants were randomized to

placebo or CBD-2914 50mg for three consecutive days over 4 week intervals administered starting on day 21, day 49, and day 77 after LNG-IUS insertion. Over the first 21 days of use, women reported bleeding/spotting on 70.6% of days (placebo) and 64.7% of days (CBD-2914). In the first 28 days after the first treatment, the percentage of bleeding/spotting days in the treatment arm was an average of 10.6% less than placebo (mean difference of 3 days, p=0.011). However, this effect was attenuated after the second treatment, and bleeding/spotting actually increased in the treatment arm compared to the placebo arm after the third treatment (38.2% days with bleeding/spotting vs 28.7%, 6 day increase, p = 0.022), suggesting that CBD-2914 offered only an early, short term benefit (16).

One study examined the selective estrogen receptor modulator (SERM) tamoxifen to reduce bleeding days in users of a LNG contraceptive implant who complained of vaginal bleeding irregularities (2). Women were randomized to receive 10mg of tamoxifen or placebo twice daily for 10 days and were followed for 90 days. Women taking tamoxifen had significantly fewer days of bleeding and spotting than placebo over the first two months after dosing (6.24 vs 12.29 days in month one, p=0.0003; 6.78 v 11.87 days in month two, p=0.0008). The effect waned by the third month. This is the only treatment for progestin-induced bleeding which has shown a sustained bleeding reduction that lasted beyond the treatment period (18). Bleeding stopped within 7 days of starting the medication for 82% of tamoxifen users (compared to 56% of placebo, p=0.005). Women reported a higher level of satisfaction with tamoxifen compared to placebo, there were fewer discontinuations due to bleeding over the course of the study (2 vs 9), and side effects were minimal.

Exogenous progestins such as LNG cause decidualization of the endometrium with proliferation of fragile and thin walled vessels, which may be responsible for unscheduled bleeding (13,14). Tamoxifen is a mixed agonist-antagonist to estrogen and competitively inhibits estrogen binding at the estrogen receptor. Whether its effect is agonistic or antagonistic depends on the promotors present in each cell type (28,29). In the endometrium, tamoxifen acts as an antagonist to estrogen receptor beta cells, which may contribute to downregulation of endometrial angiogenesis, leading to decreased breakthrough bleeding (21,28,30). Given the impressive ability of tamoxifen to stop an episode of bleeding and to reduce total bleeding days in users of the LNG implant, it is promising that tamoxifen may have a similar ability to reduce irregular bleeding in users of the LNG-IUS. Developing tamoxifen for this new indication would be a benefit to women and clinicians managing this common contraceptive side effect.

This project will address whether administration of a short course (seven days) of tamoxifen can reduce early bleeding/spotting days in users of the LNG-IUS. Similar to the Warner study, study medication will be administered for 7 days starting 21 days after insertion of LNG-IUS, and bleeding outcomes will be assessed for 30 days after treatment.

1.1.2 *Objectives and hypotheses*

Hypothesis: Users of the LNG-IUS who receive tamoxifen 21 days after insertion of their device will have a reduction in bleeding/spotting days over the next 30 days compared to placebo.

Primary objective: To determine whether tamoxifen taken preventively in users of the LNG-IUS can reduce the total number of bleeding/spotting days by 40% over 30 days compared to placebo.

Secondary objectives: To determine whether tamoxifen:

1. Leads to a longer duration of bleeding-free days after dosing than placebo
2. Improves satisfaction with the LNG-IUS
    a. Visual analog scale; anchors 0 = not at all satisfied, 100mm = very satisfied
        i. With bleeding pattern

ii. With LNG-IUS overall as a method of contraception

3. Improves continuation of the LNG-IUS
    a. Track discontinuation of the device during the study
4. Causes side effects
    a. Track self-reported adverse events (AEs) and severe adverse events (SAEs)

1.2 Previous similar studies

Tamoxifen has never been studied as an adjunctive therapy to the LNG-IUS. Similar prior studies using other medications were addressed in the rationale section (1.1.1).

1.3 Design and methodology

1.3.1 *Research design and general methodological approach*

This is a randomized, controlled, double blind clinical trial of 42 women initiating the LNG-IUS. The study will assess the efficacy of oral tamoxifen to decrease bleeding days when taken prophylactically at a dose of 10mg twice daily for seven days starting on day 21 after insertion. The study will be conducted at Oregon Health & Science University (OHSU) in Portland, Oregon. Each subject's involvement will last 51 days and will require a total of up to two study visits in addition to the insertion visit, as well as a daily response to a text or email message about bleeding and use of study medication. Study procedures will be initiated following approval of the protocol by the institutional review board at OHSU. We anticipate that it will take six months to complete enrollment and a total of 15 months to complete all study procedures and analysis.

1.3.2 *Number of subjects and statistical power*

Our study is powered to detect a clinically significant 40% reduction in bleeding/spotting days over 30 days. No studies to date have examined the effect of tamoxifen on bleeding patterns in LNG-IUS users. The study on CBD-2914 and the LNG-IUS reported mean bleeding/spotting days for 30-day intervals after IUS insertion. Between days 22-51 (analogous to our 30-day follow up period), placebo users had a mean of 18 days of bleeding/spotting with a standard deviation of 7 days (16). Our sample size was calculated to be able to detect a 40% difference in bleeding days (+/- 7 days out of 30) with tamoxifen compared to placebo at 80% power and α=0.05 (Aim 1). We propose to enroll 42 women, 21 women in each group (experimental and placebo) to account for a 20% dropout rate (17).

1.3.3 *Criteria for the selection of subjects*

Subjects: This study will prospectively enroll English and Spanish speaking women 15-45 years of age seeking initiation of LNG-IUS for contraceptive purposes at the OHSU OB/GYNS clinics. They must have access to a reliable cell phone and must be willing to receive and respond to a daily text or email message to assess bleeding.

Exclusion criteria: Postpartum within six months, pregnant, breast-feeding, LNG-IUS prescribed to treat abnormal uterine bleeding, switching from DMPA, IUS removal and replacement, undiagnosed abnormal uterine bleeding pre-dating placement of IUS, 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 (coumadin, letrozole, bromocriptine, rifampicin, aminoglutethimide, phenobarbital).

Additional exclusions prior to randomization: noncompliance with electronic bleeding diary; clinical evidence of IUD complication (e.g. heavy bleeding suspicious for expulsion (complete or partial); unusual pelvic pain; fever and clinical exam suggesting endometritis.

No vulnerable populations will be specifically recruited or included in this study. Subjects between the ages of 15-18 years of age may be enrolled in this study, but will not be considered a vulnerable population or children since research procedures involve providing birth control information and services.

1.3.4 ***Subject recruitment and allocation***

We plan to recruit patients seeking LNG-IUS insertion through targeted recruitment at the OHSU OB/GYN clinics. The decision to initiate IUS use will be made by the patient prior to enrollment in the study. Women who are scheduled for LNG-IUS insertion in the OHSU Center for Women's Health will be screened by chart review and contacted by phone within three days before their visit. On this phone call, study staff will describe the study using standardized text and assess interest in participation.

We will also advertise on the OHSU website or with Craig's List, as other OHSU Women's Health Research Unit (WHRU) projects are advertised, targeting ads to women who are planning to initiate the LNG-IUS. Women who call the WHRU will be screened for inclusion/exclusion criteria and directed to an appropriate OHSU clinic for LNG-IUS insertion and study enrollment, if desired. These recruitment documents will refer to tamoxifen as "drug" or "medication," and not list the study drug by name (as was done in a previous study using the same drug - OHSU IRB#10228). We found in the last tamoxifen study that potential subjects were being misinformed by internet searches about the study drug prior to their visits, and that allowing subjects to learn about the drug directly from study staff avoided this misinformation and improved recruitment. A through discussion about the study drug, tamoxifen, will take place at the initial visit before enrolling women into the study to avoid any misinformation from the internet.

At the time of their clinic visit for IUS insertion, those women previously indicating interest and those we were not able to reach in advance will be approached by study staff with information about the study. The decision to obtain the LNG-IUS and the insertion process will be completed with the patient's medical provider independent of the study. Those women who are eligible based on inclusion/exclusion criteria and who are willing to participate will complete the informed consent and enrollment process as described in section 1.3.6.

Women who enroll in the study will track bleeding and spotting starting on the day after LNG-IUS insertion via response to daily automated text messages. Those who are compliant with text message diaries over the first 14 days (responding 12 or more days, approximately 90% response rate) will be invited by phone to return for study visit 1 (occurring between 14-21 days after IUS insertion). On this scheduling phone call, post-insertion exclusions will be reviewed. Eligible women scheduled for study visit 1 will be randomized by the OHSU research pharmacy on the day prior to their scheduled visit. We anticipate that ensuring compliance with preliminary data collection will help minimize loss to follow up or missing data after randomization. The baseline bleeding data may be used as a covariate in final analysis.

The OHSU research pharmacy will randomize subjects to tamoxifen or placebo through a computer-generated algorithm using a block size of six. Treatment allocation will be double-blinded and study investigators will not have access to the randomization scheme or treatment assignments. The research pharmacy will maintain allocation concealment until completion of the study. Study drug (oral tamoxifen 10mg) will be purchased and routed through the OHSU research pharmacy, and identical placebo will be compounded by the research pharmacy. At

study visit 1, each subject will receive a total of seven days of medication to take home (14 pills). They will be instructed to start this medication on day 21 after insertion of their LNG-IUS.

Women with inadequate responses to the text message diary (less than 12 of 14 days) during the 14-day observation period will be contacted by phone to confirm discontinuation from the study, and they will stop receiving automated text messages.

1.3.5 ***Description of the drug to be studied***

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. 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 (31). 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 (31).

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 (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 (31).

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. As the dosage used in this study will be 10mg twice daily for seven days, it is anticipated that associated side effects will be rare and mild as previously reported when tamoxifen was used for a similar purpose for a 10 day course (2). In trials that have shown a non-statistically significant increased risk of pulmonary embolism and stroke in patients taking tamoxifen, >85% of these events have occurred in women 50 years of age or older who will not be included in this study (31). More severe side effects as noted above are typically not seen until higher dosages for longer periods of time than will be administered in this study.

1.3.6 ***Admission procedure***

Consistent with usual clinical practice, 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 (if indicated based on Centers for Disease Control and Prevention screening algorithms) will be performed at the insertion visit by the primary medical provider. Patients will have access to these results which will be in their primary medical records. Bedside ultrasound may be performed to ensure correct fundal placement of the IUS per provider preference, but this is not routine care and will not be required. Patients will be instructed on how to palpate their IUS strings.

After the medical visit is complete, interested and eligible participants will meet with study staff to complete the informed consent process. Consenting of Spanish-speaking patients will be performed with use of an in-person or phone Spanish interpreter to ensure informed consent. Study forms translated into Spanish will be available. Baseline demographic information will be collected by brief interview, including menstrual history, contraception history, sexual and pregnancy history, BMI/weight, ethnicity, age, and baseline use of panty liners (as advised by Mishell et al to avoid confounding data on bleeding/spotting days) (32). Subjects will receive training on the use of the bleeding diary procedures including the text message/email and paper diaries. Estimated time to complete study procedures during the clinic visit is 20 minutes. For patients who express interest in participating in the study but are unsure of their desire to enroll immediately, there will be the option of returning to the clinic within three days of IUS insertion to complete the enrollment study procedures as described above. Prospective bleeding data will be collected starting on the day of enrollment. Women who enroll after their insertion visit will verbally provide data for bleeding or spotting that occurred after insertion and prior to enrollment.

Between IUS insertion and study visit 1 (occurring 14-21 days after insertion), baseline bleeding with the LNG-IUS will be prospectively collected using bleeding diaries. This data will be used later as a covariate in analysis. A co-investigator (ob/gyn physician) will call each subject after at least 12 days of bleeding data collection to review exclusion criteria and to schedule study visit 1 if appropriate, as described in section 1.3.4. Subjects reporting concerns with their IUS will be referred to their primary provider or scheduled for a triage visit in family planning clinic to be examined by a physician as clinically indicated.

At study visit 1, bleeding diaries will be reviewed, and VAS scales (0-100mm) will be completed to obtain baseline assessment of bleeding satisfaction with the LNG-IUS. Each subject will receive one bottle of their assigned medication. Participants will be instructed to begin use of the study medication on day 21 after the insertion of their LNG-IUS and continue to take a twice daily oral dose of 10 mg for seven days. Estimated time to complete this visit is 15 minutes. Participants will receive a single text message or email reminder on the day they are due to start study medication. There will not be any specimens collected at this visit and there will be no results to share with subjects.

1.3.7 *Follow-up procedure*

Bleeding diaries

The primary outcome variable of this study is the total number of bleeding/spotting days over 30 days, but other bleeding outcomes including duration of bleeding-free episodes and frequency of bleeding episodes will be assessed as secondary outcomes. In order to collect bleeding data, all subjects will be asked to complete both paper and electronic bleeding diaries. For the electronic bleeding diary, after initial enrollment, participants will start receiving a daily text or email message from a study-affiliated messaging service (developed with Mir3, San Diego, CA) prompting a response about their bleeding for the day. Subjects can indicate at enrollment whether they want to receive the message via text or email. This approach using the

same service provider has been previously used by our group and others with excellent real-time response rates (>90%) (33). The text message/email bleeding diary for this project was uniquely designed by OHSU and Mir3 to fit the needs of this study. Subject ID numbers and their cell phone numbers or email addresses are entered into the system to allow subjects to receive messages and send responses to the study database. The company adheres to a strict privacy policy for phone numbers in the system, which is detailed in section 1.3.10. In the daily text or email message, subjects are asked to classify their bleeding using the terminology recommended by Mishell et al (32). This includes for a given 24-hour period whether the woman has experienced:

1. Bleeding – any day during which bleeding requires the use of protection with a tampon, pad or panty liner.
2. Spotting – Minimal blood loss that does not require the use of any protection including panty liners (Use of precautionary liners does not qualify as spotting).
3. No bleeding

A second message will be sent one minute after the first to inquire whether subjects took the study medication that day. If the subject does not respond to the text or email messages, a second set of texts or emails (2) will be sent the following morning. The subject has only these two chances to report their bleeding information for that day, and otherwise must use the paper diary. Responses to the messaging system will be compiled in a secured web database by Mir3, which can be accessed by research staff for data retrieval and entry onto research computers. Paper diaries will also be provided for use in case of technical difficulty in receiving or responding to text or email messages. Subjects are encouraged to complete paper diaries in addition to the electronic diary.

Follow up visits

Thirty days after initiating study drug, participants will receive an email with a link to a final study online survey via REDCap (attached). This survey will include questions assessing side effects, adverse events, and bleeding and IUS satisfaction. The satisfaction questions will utilize an electronic 100-mm visual analog scale. This study survey should take approximately 5-10 minutes to complete. Subjects not returning the survey within 7 days will be contacted by phone, text or email (based on stated contact preferences) and reminded to reply.

Compensation

Subjects will be compensated $10 at enrollment and $30 at the first study visit, which totals $40. Additionally, subjects will be provided with compensation for completing the electronic bleeding diaries after use of study drug. Subjects will receive an additional $1 each day that they respond to the electronic messages (up to 30 days total) and $20 for completing the final survey. This is a total of up to $50 that they can earn from completing the diaries and completing the study. The total compensation per subject is a maximum of $90. Compensation will be loaded onto a debit card, which participants will receive at the enrolment visit.

1.3.8 *Risks and Benefits to Participants*

Risks and discomforts

Risks to subjects include experiencing side effects from tamoxifen. The most common side effects reported with long term use are hot flushes (33%), bone pain (6%), gastrointestinal distress (5%), or fatigue (4%) (31). Risks of endometrial pathology including endometrial hyperplasia have been associated with long-term use of tamoxifen, but not with short-term use (31). Other risks of long-term use include increased risk of blood clots and stroke. Among women who developed pulmonary emboli, diagnosis occurred at a mean of 27 months from onset of tamoxifen treatment, with earliest event reported at 2 months of treatment (31). Women

using tamoxifen may be at increased risk for developing ovarian cysts with long-term use, but these resolve after discontinuation of use. Given that participants will only be using tamoxifen for one week in this study, an increase in severe adverse events is not anticipated. In short term use, the most common side effect reported was headache in up to 20% of women

Women with a contraindication to tamoxifen use will be excluded from this study. This includes pregnant women given concern for teratogenicity. It is not known if tamoxifen is excreted in breast milk, but it has been shown to inhibit lactation. It has also been shown to cause reproductive tract lesions in exposed neonatal rodents (31), thus lactating women will also be excluded. Women regularly taking medications that interact with tamoxifen will also be excluded as described in section 1.3.3.

Other risks to participants include time spent participating in study without guarantee of benefit. It is estimated that daily time spent on participation will be no more than five minutes per day, in addition to the 15-minute study visit and the 5-10 minutes for the completion survey. Despite little time required for participation, this may be seen as an inconvenience to subjects.

There is a small risk of breach of confidentiality with potential risk disclosure of sensitive information including menstrual, sexual, and obstetric histories. Information discussed may be seen by participants as embarrassing or very personal. They will have a right to refuse disclosure of any questions they do not wish to discuss.

Benefits:

Participants may or may not personally benefit from being in this study. There is a possibility the study drug will improve participants' bleeding patterns and satisfaction with their LNG-IUS.

1.3.9 *Criteria for discontinuation*

Patients have the right to withdraw from the trial at any time on their own request for any reason; the reason for withdrawal will be recorded in detail. Subjects wishing to discontinue their LNG-IUS while enrolled in the study will terminate their participation with the study as of IUS removal. These subjects will be asked to complete the final online study survey prior to IUS removal to review bleeding profiles and satisfaction questions. No further data will be obtained from the patient once withdrawal occurs. Any data obtained up to this point will be analyzed in accordance with intention to treat.

We will have close contact with participants through the daily electronic bleeding diary. Failure to respond to the bleeding diary for three consecutive days will prompt a phone call from the study coordinator to inquire about technological difficulties versus disinterest in the study. If we are unable to reach a subject by phone, email or letter over two weeks, their participation will be terminated. Likewise, subjects declining to return for the study visit or complete the final survey will be discontinued from the study. Any data obtained up to this point will be analyzed in accordance with intention to treat.

If a subject becomes pregnant while participating in the study, her participation will be discontinued. She will be asked to come in for a study visit with the investigator. Her study medication will be unblinded and she will receive counseling from the investigator on how to seek medical care.

1.3.10 *Data management and confidentiality*

Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN). The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network WHRU drive in a limited access folder. Electronic data will be maintained on the secured WHRU OHSU computer server utilizing only subject IDs without personal identifying information, or in a web-accessible REDCap database housed on an OHSU secure server. No patient names will be included with any study data records or during statistical analysis. Paper files will be stored in locked filing cabinets in restricted WHRU offices at OHSU.

Subject phone numbers, email addresses and study ID numbers will be entered into the OHSU/Mir3 message system solely for the purpose of sending and receiving bleeding diary text or email messages. No additional identifying information will be entered into this system. Mir3 works with some of the largest banks, healthcare institutions, universities and government institutions and follows a strict privacy policy to ensure that each customer's data, including phone numbers, are kept private and encrypted. Any data transmitted via the Mir3 system is encrypted according to advanced standards. No subject information will be retained by Mir3 after each subject completes the project.

Once subjects begin responding to messages, study coordinators will access their bleeding diary responses through a secure, encrypted and password protected Mir3 database. Coordinators will transfer responses into a second database on the secured OHSU WHRU computers to allow for statistical analysis. The study staff member entering the data for each study subject will be recorded; however the PI is responsible for the accuracy of data entered. Records of responses on the Mir3 system are destroyed after 90 days, but will be maintained in the secure OHSU database for data analysis.

Study procedures including screening phone calls, consenting, history collection, review of bleeding diaries and study medication use, and administering study medication will be performed by the study co-investigators or other study faculty. A co-investigator (Cohen) will randomly sit in on study visits twice per month to ensure procedures are being conducted per the approved protocol. She will also review bleeding diary information and study medication use once per month.

Bleeding diaries and satisfaction data will be tallied and entered into STATA by the co-investigators at the conclusion of the study. Once the data has been entered into STATA, descriptive statistics will be used to check to outliers. In addition, random data entry checks will be performed to further verify correct entry of the data.

The investigators and study staff are responsible for recording the data, and they will be verifying its accuracy throughout the process. The Principal Investigator, will be reviewing the data in-depth periodically throughout 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 the study visit and procedures and through frequent communication with the other investigators and staff. Anytime that an AE, SAE, UP or protocol deviation is reported by an investigator or study staff, the PI will review and assess the data, and proceed as per OHSU reporting policy. Otherwise, the PI entity will be reviewing the records periodically throughout the study. All adverse events will be assessed and reportable UPs will be submitted to the IRB, if judged related to the study protocol. All data will be stored within the REDCap database at the completion of the study for future analysis and stored in the WHRU Repository. There will be no specimens collected that require handling or storage.

All telephone screenings and website submission forms will be stored in a locked office at OHSU, with access limited to study staff. For subjects electing to enroll in the study, this

information will become a part of their protected research record. For subjects choosing not to enroll or who screen fail, all PHI will be stored confidentially with the research study information in a locked cabinet and archived with other study-specific documents at the close of the trial. All potential participants that contact the department for research studies will be added to a password-protected log listing their contact information, only accesible through OHSU password-protected computers by study staff. Phone screens (including for individuals who choose not to participate or are ineligible) and the log containing potential participants' information are saved to ensure that our department has a record of contact with the participant and to monitor our recruitment outreach efforts. Confidentiality of personal health information will be maintained according to HIPAA requirements for research and all data will be kept in locked files or in a password-protected document on a password protected computer. Once the study is complete and all data analysis and publication has been completed, the study information is stored indefinitely in a secure manner that follows OHSU Standard Institutional practices and all FDA and HIPAA guidelines.

1.3.11 *Data analysis*

Data will be extracted and entered into STATA on a password-protected computer. Analysis will be performed with the blinded data. P value of 0.05 defines statistical significance. Randomization will be assessed and if there is imbalance found between treatment and placebo groups, regression analyses will be completed to accommodate these differences.

Primary objectives: The primary measurement for this study will be the mean number of bleeding or spotting (b/s) days experienced by participants in the treatment group compared to placebo group over 30 days after treatment initiation. We will record baseline data on b/s days in the 21-day run-in period to confirm that the randomization was successful in allotting women with equivalent baseline b/s days to each group. Each day, subjects will indicate via numeric coded text or email message response whether they had spotting, bleeding, or none. From these diaries, counts of total bleeding/spotting days will be obtained. Other secondary bleeding outcomes will be examined including number of bleeding/spotting episodes, the number of prolonged bleeding episodes (>8 days), and the longest bleeding-free interval. Comparisons between groups will be made using an independent sample two sided t-test. Data will be analyzed in an intention-to-treat fashion. If data are very skewed, non-parametric methods will be used to compare groups.

Secondary objectives:

1. Satisfaction and side effects

At the study visit and in the final survey, subjects will answer questions regarding their satisfaction with the IUS and their bleeding patterns, acceptability of bleeding, as well as side effects and adverse events. Satisfaction responses will be quantified using a visual analog scale between 0-100mm. Discontinuation from the study and discontinuation of the IUS during the study will be monitored as markers of dissatisfaction. Comparison of means between tamoxifen and placebo groups will be made using two sided t-tests, and side effects will be reported descriptively.

1.3.12 *Study limitations*

Medication dosing: The only prior published study to evaluate tamoxifen for this indication utilized 20mg daily (split dosing) for 10 days. However, the differences in bleeding patterns were detected within 3-7 days of starting medication; 82% of tamoxifen users stopped bleeding

within 7 days, compared to 56% of placebo (p=0.005). A shorter medication course is easier for patients and would be preferred if the clinical effect was the same, and a completed study at OHSU utilized a seven-day course. Therefore, we are also studying a seven-day course of tamoxifen, administered 10mg twice daily.

Study follow up: In prior similar studies, subjects recorded prospective daily bleeding diaries for 90 days following enrollment and receive multiple doses of study medication. This study will only follow patients prospectively for 30 days following one drug administration. It was felt that extending the duration of subject involvement to three months would be prohibitive for recruitment and for completion of the study within the desired time frame. Subsequent studies can expand on the results of this initial study if tamoxifen is found to be beneficial.

1.3.13 *Duration of project*

We anticipate that it will require approximately 6 months to complete enrollment, and hope to begin enrollment in May, 2016. We aim to complete enrollment by October, 2016, with the last subject finishing her study period by November, 2016. Data analysis and write-up will continue through late 2017. Total duration of the project is anticipated to be approximately 15 months.

1.4 Project management

This project requires collaboration between the investigators, study personnel, and Mir3 for bleeding diaries. The study will remain the responsibility of the PI, Dr. Jeffrey Jensen, and the co-investigators, Drs. Megan Cohen, Katharine Simmons and Alison Edelman. Assistance with statistical analysis will be provided by Dr. Jeong Lim in the department of Ob/Gyn at OHSU.

1.5 Links with other projects

This study is not linked to other projects.

1.6 Main problems anticipated

Recruitment: The family planning clinic at OHSU provides insertion of approximately 3-5 LNG-IUS devices per week. Additional insertions occur in the resident and generalist clinics. By targeting eligible women at clinic visits and by minimizing follow up procedures, we anticipate that recruitment will be feasible to complete within six months.

Retention: The short duration of the study and minimal follow up procedures should maximize retention. Similar prior studies in the LNG-IUS had low dropout rates, all with <20% loss to follow up (16,26,27). The proposed project is shorter duration (51 days total), which should decrease dropout even further. Nevertheless, our sample size was designed to account for a 20% dropout rate due to this risk of poor retention in women experiencing ongoing bleeding. Details on how we will manage loss to follow up are included in section 1.3.7.

Bleeding diaries: The text or email message bleeding diary through Mir3 has been utilized in similar studies with excellent response rates. However, a portion of participants in older studies had difficult receiving or responding to text messages due to incompatible cell phone technology. Subjects who have difficulty receiving or responding to daily text messages can opt to receive identical email study survey messages instead and will have a paper diary to use as backup, which will utilize the exact same question and response categories.

Any unanticipated problems will be addressed by the PI and study co-investigators, with changes to the protocol as needed. Unanticipated problems could include medication side

effects or pregnancy in a study subject. Any pregnancy occurring during the study will be considered a serious adverse event and will prompt review of the study protocol and possible study discontinuation of the study.

1.7 Expected outcomes of the study and dissemination of findings

We anticipate that tamoxifen taken preventively will reduce the total number of bleeding days by at least 40%. We anticipate that subjects using tamoxifen to manage bleeding will report higher satisfaction with their bleeding profiles and with the LNG-IUS, and that more women receiving tamoxifen will report their bleeding as acceptable. Overall, improvements in bleeding patterns will translate into better overall acceptability of this highly effective LARC, which should improve continuation and uptake. Increasing the uptake and continuation of LARCs such as the LNG-IUS will lead to a reduction in unplanned pregnancies, which is a major public health concern (1,9).

The results of this study will be submitted for publication in a journal specific to obstetrics and gynecology, and will be presented to the national family planning professional community at the annual Family Planning Fellowship meeting.

1.8 References

1. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of Long-Acting Reversible Contraception. N Engl J Med. 2012 May 24;366(21):1998–2007.

2. Abdel-Aleem H, Shaaban OM, Amin AF, Abdel-Aleem AM. Tamoxifen treatment of bleeding irregularities associated with Norplant use. Contraception. 2005 Dec;72(6):432–7.

3. Hatcher RA, Trussell J, Nelson AL, Cates W. Contraceptive technology. 20t ed. [New York, N.Y.]: Ardent Media; 2011.

4. Cox M, Tripp J, Blacksell S. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 5-year report. J Fam Plan Reprod Health Care Fac Fam Plan Reprod Health Care R Coll Obstet Gynaecol. 2002 Apr;28(2):73–7.

5. Grunloh DS, Casner T, Secura GM, Peipert JF, Madden T. Characteristics associated with discontinuation of long-acting reversible contraception within the first 6 months of use. Obstet Gynecol. 2013 Dec;122(6):1214–21.

6. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. Contraception. 2002 Feb;65(2):129–32.

7. Backman T, Huhtala S, Blom T, Luoto R, Rauramo I, Koskenvuo M. Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nation-wide study of 17,360 users. BJOG Int J Obstet Gynaecol. 2000 Mar;107(3):335–9.

8. Suvisaari J, Lähteenmäki P. Detailed analysis of menstrual bleeding patterns after postmenstrual and postabortal insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. Contraception. 1996 Oct;54(4):201–8.

9. Peipert JF, Zhao Q, Allsworth JE, Petrosky E, Madden T, Eisenberg D, et al. Continuation and satisfaction of reversible contraception. Obstet Gynecol. 2011 May;117(5):1105–13.

10. Chegini N, Rhoton-Vlasak A, Williams RS. Expression of matrix metalloproteinase-26 and tissue inhibitor of matrix metalloproteinase-3 and -4 in endometrium throughout the normal menstrual cycle and alteration in users of levonorgestrel implants who experience irregular uterine bleeding. Fertil Steril. 2003 Sep;80(3):564–70.

11. Gemzell-Danielsson K, van Heusden AM, Killick SR, Croxatto HB, Bouchard P, Cameron S, et al. Improving cycle control in progestogen-only contraceptive pill users by intermittent treatment with a new anti-progestogen. Hum Reprod Oxf Engl. 2002 Oct;17(10):2588–93.

12. Glasier AF, Wang H, Davie JE, Kelly RW, Critchley HOD. Administration of an antiprogesterone up-regulates estrogen receptors in the endometrium of women using Norplant: a pilot study. Fertil Steril. 2002 Feb;77(2):366–72.

13. Guttinger A, Critchley HOD. Endometrial effects of intrauterine levonorgestrel. Contraception. 2007 Jun;75(6):S93–8.

14. Hickey M, Fraser IS. Surface vascularization and endometrial appearance in women with menorrhagia or using levonorgestrel contraceptive implants. Implications for the mechanisms of breakthrough bleeding. Hum Reprod Oxf Engl. 2002 Sep;17(9):2428–34.

15. Mansour D, Bahamondes L, Critchley H, Darney P, Fraser IS. The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users. Contraception. 2011 Mar;83(3):202–10.

16. Warner P, Guttinger A, Glasier AF, Lee RJ, Nickerson S, Brenner RM, et al. Randomized placebo-controlled trial of CDB-2914 in new users of a levonorgestrel-releasing intrauterine system shows only short-lived amelioration of unscheduled bleeding. Hum Reprod. 2010 Feb 1;25(2):345–53.

17. Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen LA, Findlay JK, et al. A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. Hum Reprod Oxf Engl. 2009 Aug;24(8):1852–61.

18. Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gaffield ML, Gülmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev. 2013;10:CD003449.

19. Morison NB, Kaitu'u-Lino TJ, Fraser IS, Salamonsen LA. Stimulation of epithelial repair is a likely mechanism for the action of mifepristone in reducing duration of bleeding in users of progestogen-only contraceptives. Reprod Camb Engl. 2008 Aug;136(2):267–74.

20. Grow DR, Reece MT, Hsiu JG, Adams L, Newcomb PM, Williams RF, et al. Chronic antiprogestin therapy produces a stable atrophic endometrium with decreased fibroblast growth factor: a 1-year primate study on contraception and amenorrhea. Fertil Steril. 1998 May;69(5):936–43.

21. Grow DR, Reece MT. The role of selective oestrogen receptor modulators in the treatment of endometrial bleeding in women using long-acting progestin contraception. Hum Reprod Oxf Engl. 2000 Aug;15 Suppl 3:30–8.

22. Jain JK, Nicosia AF, Nucatola DL, Lu JJ, Kuo J, Felix JC. Mifepristone for the prevention of breakthrough bleeding in new starters of depo-medroxyprogesterone acetate. Steroids. 2003 Nov;68(10-13):1115–9.

23. Lal S, Kriplani A, Kulshrestha V, Sharma M, Agarwal N. Efficacy of mifepristone in reducing intermenstrual vaginal bleeding in users of the levonorgestrel intrauterine system. Int J Gynecol Obstet. 2010 May;109(2):128–30.

24. Cheng L, Zhu H, Wang A, Ren F, Chen J, Glasier A. Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel. Hum Reprod Oxf Engl. 2000 Sep;15(9):1969–72.

25. Massai MR, Pavez M, Fuentealba B, Croxatto HB, d'Arcangues C. Effect of intermittent treatment with mifepristone on bleeding patterns in Norplant implant users. Contraception. 2004 Jul;70(1):47–54.

26. Madden T, Proehl S, Allsworth JE, Secura GM, Peipert JF. Naproxen or estradiol for bleeding and spotting with the levonorgestrel intrauterine system: a randomized controlled trial. Am J Obstet Gynecol. 2012 Feb;206(2):129.e1–129.e8.

27. Sørdal T, Inki P, Draeby J, O'Flynn M, Schmelter T. Management of Initial Bleeding or Spotting After Levonorgestrel-Releasing Intrauterine System Placement: A Randomized Controlled Trial. Obstet Gynecol. 2013 May;121(5):934–41.

28. Barkhem T, Carlsson B, Nilsson Y, Enmark E, Gustafsson J, Nilsson S. Differential response of estrogen receptor alpha and estrogen receptor beta to partial estrogen agonists/antagonists. Mol Pharmacol. 1998 Jul;54(1):105–12.

29. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. 1439 p.

30. Critchley HO, Brenner RM, Henderson TA, Williams K, Nayak NR, Slayden OD, et al. Estrogen receptor beta, but not estrogen receptor alpha, is present in the vascular endothelium of the human and nonhuman primate endometrium. J Clin Endocrinol Metab. 2001 Mar;86(3):1370–8.

31. United States Food and Drug Administration. Nolvadex (tamoxifen citrate) package insert. 2004 p. 1–38.

32. Mishell DR, Guillebaud J, Westhoff C, Nelson AL, Kaunitz AM, Trussell J, et al. Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. Contraception. 2007 Jan;75(1):11–5.

33. Nippita S, Oviedo JD, Velasco MG, Westhoff CL, Davis AR, Castaño PM. A randomized controlled trial of daily text messages versus monthly paper diaries to collect bleeding data after intrauterine device insertion. Contraception. 2015 Dec;92(6):578–84.

2. ETHICAL CONSIDERATIONS

The study will be reviewed by the OHSU Institutional Review Board.

2.1 Informed decision-making and confidentiality

See attached lay language summary and consent form for patients who are choosing to enroll in this study. The statement of privacy from Mir3 is also attached.

3. BUDGET

3.1 Line-Item Budget

Please see separate form

3.1 Budget Justification

A. Personnel

Investigators:

Jeffrey Jensen, MD MPH, principal investigator
Megan Cohen, MD MPH, co-investigator, study oversight, final data analysis
Katharine Simmons, MD MPH, co-investigator, study oversight, final data analysis
Alison Edelman, MD MPH, co-investigator
Jeong Lim, PhD, biostatistician
Marci Messerle Forbes, RN, Women's Health Research Unit
Andrea O'Donnell, RN, Women's Health Research Unit
Additional family planning faculty/fellows and residents to assist with study procedures if needed: Alyssa Colwill, Jackie Lamme, Eva Patil, Leo Han, Maureen Baldwin, Maria Rodriguez, Lisa Bayer, Paula Bednarek, Sylvia Moses, Teresa Worstell, Emily Griffin, Vanessa Lee, Thomas Brennan, Emily Schloff, Amie Leaverton, Amy Caldwell, Annessa Kernberg, Hernan Freitas

Research coordinators:

This study will not utilize research coordinators. Family planning fellows and faculty as well as the PIs will perform all study procedures.

B. Equipment

Text message bleeding diary

Use of an electronic bleeding diary improves real time response rates for documentation of bleeding and use of study medication. The company Mir3 (San Diego, CA) has a customizable program for sending automated text or email messages to a specific group of people. Purchasing this program will allow us to send uniform, scheduled messages to all participants and to record real-time responses from subjects regarding bleeding and study medication use.

C. Materials and supplies

Pharmacy: Required initiation fee, compounding fee, monthly maintenance fee, and dispensing fee.
Study medication: Purchased through the OHSU research pharmacy
IRB review: No cost
Project outreach/educational expenses: None
Investigative tools: None
Laboratory specimens: None.

D. Participant Costs

Subjects will be compensated $10 at enrollment and $30 for visit 1, for a total of $40 per subject for in-person study visit completion. Parking will be available at no cost at OHSU. Subjects can earn up to an additional $30 for completion of daily electronic bleeding diaries and $20 for completion of the final visit survey. The total possible compensation per subject is $90.

E. Travel

No travel is required as part of the study.

F. Other costs

Copying/printing: Printing costs for fliers for the study. Copying costs to generate the data forms for each trial participant's data collection file, as well as paper bleeding diaries.
Consultant services: None
Contractual costs: None

4. APPENDICIES

Appendix A: Consent and authorization form
Appendix B: Text of bleeding diary and study medication text and email messages

Bleeding diary guide

(to be reviewed at the first visit, and given to each subject to take home)

Every day that you are in the study, you should receive two messages at about 8pm. The first message will ask about your bleeding. You should respond with the number that corresponds to your bleeding for that day.
You can choose:

1. Bleeding – any day when your bleeding requires the use of protection with a tampon, pad or panty liner. It can be light or heavy.
2. Spotting – Minimal bleeding that does not require the use of any protection. For example, spotting just on toilet paper.
3. No bleeding - If you wear a pantyliner "just in case," but don't have bleeding, choose this response.

The second message will ask if you took the study drug on that day.
You can choose:

1. Yes
2. No

When you fill out the paper diary, please use this same code.

Text of the text messages sent each day by Mir3:

Over the past 24 hours, have you experienced:

1. Bleeding
2. Spotting
3. No bleeding or spotting

Did you take the study drug today?

1. Yes
2. No

Text of the email messages sent each day by Mir3:

Email subject line: Bleeding survey issued at (date) 8:00 PM

Over the past 24 hours, have you experienced:

You may respond by doing one of the following:

- Call +18666098026 and use Telephony ID 628329179
- Select one of the responses below by clicking on the desired Response text.
- Reply to this email with the corresponding number to your response on the top line within the body of the email, e.g., 1 for indicating that you wish to use response option 1.

Option# Response:

1. Bleeding
2. Spotting
3. No bleeding or spotting

Appendix B: Bleeding diary text

Email subject line Study medication survey issued at (date) 8:02 PM

Did you take the study drug today?

You may respond by doing one of the following:

- Call +18666098026 and use Telephony ID 628329179
- Select one of the responses below by clicking on the desired Response text.
- Reply to this email with the corresponding number to your response on the top line within the body of the email, e.g., 1 for indicating that you wish to use response option 1.

Option# *Response*:

1. Yes
2. No