Title: A multi-center, double-blinded, randomized, phase IV 6-month pilot study to compare bleeding patterns, satisfaction, and quality of life among new Copper 380A IUD users treated with naproxen sodium (440 mg twice daily) versus placebo

Short title: Copper IUD Treatment Observation Study (CITROS)

Study Protocol
Trial registration: ClinicalTrials.gov: NCT02519231
Version 9, 7/1/16

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Note: this protocol was written in accordance with SPIRIT Guidelines 2013.[1]

1.0. Summary

The Copper IUD (Cu-IUD) is the most widely used IUD in the world, and its use in the United States (US) is on the rise. The Cu-IUD is considered one of the most effective contraception methods, being as effective as permanent sterilization but having the convenience of being reversible should a woman decide to conceive.[2] The Copper 380A (TCu380A) is the only Cu-IUD available in the US; of all Cu-IUDs, the TCu380A is considered the most effective. Despite its increasing popularity in the US, studies indicate that bleeding irregularities and dysmenorrhea are common reasons for method discontinuation. Some evidence suggests that non-steroidal anti-inflammatory medications (NSAIDs) can help improve bleeding during Cu-IUD use. However, these studies did not examine NSAID use with the TCu380A specifically, nor did they evaluate readily available NSAIDs such as over-the-counter naproxen. For this reason, we propose a pilot trial in which new TCu380A users complaining of heavy or prolonged menstrual bleeding or spotting after 1 month of use are randomized to naproxen or placebo to be taken the first 7 days of menstruation for three consecutive cycles, and then observed for one cycle without treatment. The number of bleeding/spotting days will be compared using Student t-test. In addition to assessing how well naproxen reduces incidence and amount of bleeding, we will also assess the use of naproxen and TCu380A on quality of life, sexual function, method satisfaction, menstrual pain, and adverse events. By measuring these variables, we will assess both positive and negative consequences of TCu380A use, ensuring that harm does not outweigh benefits.

2.0. Background/Rationale

Intrauterine devices (IUDs) are among the most widely used reversible contraceptive methods in the world.[3] In the US, IUD use is on the rise, with more than 2 million women currently using the method.[4] The IUD is considered one of the most effective methods (>99%); it is as effective as permanent sterilization but has the convenience of reversibility should a woman decide to conceive.[2] Copper-containing IUDs (Cu-IUDs) were introduced into worldwide markets in the late 1960s and are available in a variety of types, most of which are named for their shape and amount of copper on the device. The Cu-IUD is considered non-hormonal, which is important especially for women with underlying medical conditions for which hormone-related contraceptives are contraindicated. Currently, the Copper 380A (TCu380A) is the sole Cu-IUD available in the US and is approved for use for 10 years, although effectiveness for up to 20 years has been shown.[5]

Despite its growth in popularity in the US, approximately 20% of women who have a TCu380A IUD inserted will discontinue the method within the first year of use. The most common reasons for Cu-IUD and TCu380A discontinuation are bleeding irregularities and dysmenorrhea.[5-8] TCu380A IUD users who report abnormal menstrual bleeding are 1.4 times more likely to prematurely discontinue their method than hormonal levonorgestrel IUD users.[9]

Because of the commonality of perceived heavy or prolonged menstrual bleeding among Cu-IUD users, a number of treatments have been studied. Few of these studies have included TCu380A. In a recent systematic review that evaluated 11 studies for acute treatment for Cu-IUD users with underlying heavy or prolonged menstrual bleeding, none included TCu380A.[10] Among treatments, non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely studied. Findings indicated that NSAIDs can reduce menstrual bleeding compared to baseline or placebo for a current heavy bleeding episode and may prevent heavy or prolonged menstrual bleeding.[10] The applicability to US women of findings from this systematic review is limited, however, because most NSAIDs studied were either non-FDA-approved or available by

prescription only. A study that includes an over-the-counter (OTC) NSAID medication, such as naproxen, as potential treatment for heavy or prolonged bleeding or spotting during TCu380A use could affect continuation among TCu380A users.

2.1. NSAID Treatment among Cu-IUD Users

NSAIDs are thought to help treat heavy and prolonged menstrual bleeding because they act as inhibitors of prostaglandin synthetase and decrease the endometrial prostaglandin release, thereby potentially reducing mean menstrual blood loss (MBL), even in the presence of Cu-IUDs.[11] A commonly used and readily available NSAID, such as naproxen, has never been evaluated for the treatment of heavy or prolonged menstruation during Cu-IUD use. Yet it has the potential to be a simple and accessible treatment for women who experience menstrual bleeding disturbances during TCu380A use because it currently is available over-the–counter (OTC) in the US. OTC naproxen sodium (Aleve) is often prescribed to patients between the ages of 12 and 65 for fever and minor aches. The approved dosage of Aleve is 220 mg (200 mg of naproxen and 20 mg of sodium). Patients are asked to take 220 mg (one tablet) every 8 to 12 hours.

A meta-analysis reviewed by the FDA that evaluated 8,404 patients, of which 4,138 had taken either naproxen (3,589 patients with doses 187.5-400 mg) or naproxen sodium (549 patients with doses 220-440 mg) found that OTC naproxen sodium was as safe as ibuprofen, acetaminophen, and placebo. The age of the patients ranged from 14 to 86 years. Across the 48 studies, 83% of the patients reported no adverse effects. Among the patients that withdrew for adverse effects 0.62% were in the placebo group and 0.68% were in the naproxen/naproxen sodium group. The most commonly reported adverse effects included headache (6.4% placebo, 4.8% naproxen/naproxen sodium), nausea (3.1% placebo, 3.4% naproxen/ naproxen sodium), and somnolence (1.9% placebo, 2.7% naproxen/naproxen sodium). This meta-analysis showed a low frequency of adverse events associated with OTC naproxen sodium when taken as directed.[12] Between the years 1995 and 2000, there were no reports of a fatal overdose of naproxen/naproxen sodium, as reported by the American Association of Poison Control (AAPC). According to the most recent AAPC annual report (2012), naproxen had been mentioned in 13,611 cases. Of these cases, only 11 had some major outcome due to the drug, and no deaths were reported. Safety profiles of both low-dose (220 mg) and high-dose (440 mg) naproxen sodium were not statistically significant.[13] According to the FDA review of the safety and efficacy of naproxen sodium in the two meta-analyses conducted, there was no evidence of overall dose-related increase in adverse events.[14]

A study that includes naproxen as potential treatment for heavy or prolonged bleeding or dysmenorrhea may provide useful preliminary data for a larger, adequately powered placebo-controlled comparative trial testing additional promising treatments, such as tranexamic acid. We therefore are requesting funds to conduct a double-blind, randomized controlled pilot trial in which new TCu380A users who complain of increased menstrual flow 4 to 6 weeks after insertion are randomized to OTC (440 mg) naproxen or placebo. We will follow the participants for three treatment cycles and one cycle without treatment following the treatment cycles to compare number of bleeding and/or spotting days. A recent systematic review evaluating clinical outcomes in abnormal uterine bleeding trials recommended that additional outcomes other than reduction of bleeding by the treatment should include quality of life, pain related to bleeding, sexual health, patient satisfaction, additional treatments, and adverse events.[15] By measuring these components, we assess both positive and negative consequences of TCu380A use, ensuring that harm does not outweigh benefits.

3.0. Hypothesis

TCu380A users who are randomized to the OTC (440 mg) naproxen group will have fewer bleeding and spotting days each month than users randomized to the placebo group.

4.0. Study Objectives

4.1. Primary Study Objective

- To evaluate whether treatment during menstruation with OTC naproxen reduces excess bleeding and spotting in new TCu380A users complaining of increased menstrual flow or spotting.

4.2. Secondary Study Objectives/End-Points

- To assess feasibility of recruiting, enrolling, and maintaining new TCu380A users in a randomized, placebo-controlled clinical trial.
- To describe the impact of TCu380A IUD use on satisfaction, menstruation, dysmenorrhea, sexual functioning, and quality of life (QOL) scores by treatment group.
- To describe the safety of OTC naproxen compared to placebo.

5.0. Trial Design

The CITROS pilot study is a prospective, double-blind, two-arm randomized placebo-controlled, phase IV feasibility study to be conducted at several clinics in Seattle, WA, and Chicago, IL. The primary endpoint of this study is number of bleeding/spotting days over the 3-month (84-day) treatment period. Randomization will be performed as 4-block randomization with 1:1 allocation.

6.0. Methods: Participants, Interventions, and Outcomes

6.1. Study Setting

This pilot trial will take place in two separate urban settings: the University of Washington in Seattle, WA, Stroger Hospital of Cook County in Chicago, IL. We chose these two settings to optimize the diversity in patient population and maximize our enrollment. Seattle is a large city, whose metro area makes up of approximately 600,000 residents. The average age of each resident is 36 years. The city is mostly White (70%), followed by Asian (14%) and African American (8%).[16] The University of Washington enrolls more than 43,000 students annually. The average age on campus is 24 years, and the racial mix is primarily White (48%) and Asian (23%).[17] The Hall Health, Roosevelt Women's Health Clinic, and Northgate Family Medicine Center serve both UW students and Seattle residents. Hall Health, Roosevelt Women's Health, and Northgate place approximately 300, 350, and 124 IUDs annually, respectively. It is estimated that at least 1/3 of these placements are TCu380A IUDs.

Chicago, on the other hand, is a city of almost 3 million, and the median age is approximately 33 years. Chicago city residents are largely White (45%), African American (33%), and Hispanic (29%; residents of Hispanic origin may be of any race).[18] Stroger Hospital of Cook County in Chicago serves a primarily low-income, minority population. The Family Planning Clinic at Stroger Hospital is funded with Title X government funding and serves approximately 10,000 patients annually. This clinic places approximately 20 TCu380A IUDs monthly.

6.2. Eligibility Criteria

Patients eligible for the trial must comply with all of the following at the first visit::

6.2.1. Inclusion Criteria – pre TCu380A Insertion

- Age ≥ 18 and < 49 years. We are including a wide range of ages because women of all ages request TCu380A. While we recognize that some women approaching menopause (median age = 51.4 years) may have changes in their baseline menstruation, we trust that clinicians enrolling the patients into the study will ensure that these women meet all inclusion (i.e., regular cycles) and exclusion criteria (i.e., do not have diagnosis of menorrhagia).
- Requesting to have TCu380A IUD inserted as contraceptive method.
- English or Spanish speaking.
- Regular menstrual cycles ranging 21-35 days apart (when not on hormonal contraception)
- Generally healthy.
- Willing to attend a 4- to 6-week follow-up visit and complete surveys.

6.2.2. Inclusion Criteria – Post TCu380A Insertion at 4- to 6-Week Follow-Up Visit

- Reports any change in volume and/or duration of blood loss or spotting at 4- to 6-week follow-up compared to pre TCu380A IUD insertion.
- Willing to avoid use of NSAIDs (except for study medication) for the remaining duration of the study.
- Willing to comply with the study protocol by adhering to the medication regimen.
- Has a cell phone that allows for texting.
- Willing to keep a bleeding diary.

6.2.3. Exclusion Criteria - Pre TCu380A Insertion

- Known or suspected pregnancy.
- Contraindications to NSAID use. This includes underlying heart failure, chronic renal disease, chronic liver disease, peptic ulcer disease, or history of upper gastrointestinal bleed, and allergy to NSAIDs.
- Current regular use of a NSAID.
- Unwilling to avoid use of NSAIDs (except for study medication) for the duration of the study.
- Current diagnosis of menorrhagia, metrorrhagia, symptomatic uterine fibroids, or endometrial polyps.
- Use of depot medroxyprogesterone acetate (DMPA) or levonorgestrel-releasing intrauterine device (LNG IUD) within the previous 3 months.
- Postpartum in the past 4 weeks. The average day in which non-breastfeeding postpartum women ovulate is 25 days after birth, indicating that menstrual cycles can resume after the 4^{th} postpartum week. Post medication abortion or surgical abortion does not count as post-partum- these patients are otherwise eligible for the study.
- Currently breastfeeding.
- Previous use of the TCu380A.

6.2.4. Exclusion Criteria – Post TCu380A Insertion at 4- to 6-Week Follow-Up Visit

- Lacks cell phone or has phone that does not allow texting.
- Not willing to comply with completion of bleeding diary.
- Not willing to comply with medication regimen.

6.3. Interventions

Eligible participants who meet inclusion criteria and informed consent will be asked to complete a baseline questionnaire regarding menstrual history, dysmenorrhea scale, quality of life, medical history, and demographics within 7 days of their TCu380A IUD insertion. Each woman will be asked to return for a follow-up research appointment within 4-6 weeks of their TCu380A insertion (Follow-Up Visit 1). All women will be asked to complete a brief health questionnaire to assess if the TCu380 is still in place. If a woman claims that the volume and/or duration of blood loss has changed in any way or if she mentions symptoms of spotting since TCu380A IUD insertion, she will be recruited into the randomized treatment arm of the study.

Participants will be expected to take their assigned medication as directed for 7 days starting the first day of their menstrual period for a total of three consecutive cycles (cycle defined as 28 days) following Follow-up Visit 1 (months 3, 4, and 5). We have chosen 7 consecutive days because this is consistent with current U.S. national contraceptive guidelines for NSAID treatment of unscheduled spotting or light bleeding or heavy or prolonged menstrual bleeding with Cu-IUD use.[19] Also, by limiting the number of naproxen pills, we minimize potential harm of taking excessive or prolonged doses of NSAIDs, which can lead to adverse gastrointestinal and cardiovascular side effects.

Participants will then be followed for one month after completion of the intervention (without treatment). During treatment and for the month following treatment, participants will complete a bleeding diary (described under Bleeding Diary heading below). The study team will make contact with each participant at the end of each study month to verify completion of bleeding diaries, assess the participants' perceptions of menstrual flow and for continued use of TCu380A. A second in-person follow-up visit will occur at approximately 6 months (Follow-up Visit 2) post device placement, in which participants will undergo assessment of satisfaction with TCu380A, menstruation, dysmenorrhea, quality of life, sexual functioning, and continuation.

6.3.1. Treatment

Women will take 1 capsule orally of 440 mg naproxen or placebo every 12 hours for heavy menstrual bleeding for 7 days, starting the first day of their menstrual period for 3 consecutive menstrual cycles. Women will be counseled that if they have pelvic pain, they may take regular strength OTC acetaminophen as directed on the bottle. The OTC 440 mg naproxen dose was chosen because of its accessibility to women in the US. Single-dose naproxen is dispensed as 220 mg per tablet. This study, in essence, proposes a dose equivalent to two tablets of OTC naproxen every 12 hours.

During this phase, we will track the number of people who called in or were approached by their provider, were screened, had CuT380A IUD inserted, and completed Follow-Up Visit 1. We will track the number of women who reported increase in blood loss or spotting at Follow-Up Visit 1 and were enrolled and randomized to a treatment group. During treatment and one month following treatment, we will track the number of participants completing each scheduled follow-up visit or phone call, and the number requiring interim visits.

The study drug and placebo for the clinical sites at the University of Washington will be compounded by Kelley-Ross Pharmacy in Seattle. The study drug for Stroger Hospital will be compounded by Save-Rite Pharmacy & Compounding.

6.4. Interventions: Modifications

Gastrointestinal Effects: Ingestion of naproxen has the potential to cause gastrointestinal effects, including dyspepsia, peptic ulcer disease, and bleeding. Participants who experience dyspepsia can take OTC calcium carbonate (500 mg) 15 minutes prior to ingesting their treatment capsule. Should a participant experience an acute peptic ulcer or upper intestinal bleeding, we will withdraw the participant from the study and report this as an adverse event.

Cardiovascular Effects: Naproxen, unlike other non-selective NSAIDs, does not appear to increase cardiovascular risks among otherwise healthy individuals.[20] Although other non-selective NSAIDs have been associated with increased risk of MI, stroke, heart failure, atrial fibrillation, and cardiovascular death for persons without underlying cardiovascular disease, the absolute risk is low (< 1-2 events per 1000 person-years).

Hepatic Injury: Elevations of serum transaminases are associated with NSAID use; however, liver failure is quite rare.[21] In a retrospective study of 625,000 patients, the incidence of acute liver injury was 3.7 per 100,000 NSAID users. NSAIDs that have shown a substantially greater risk of causing hepatic injury are sulindac and diclofenac, which will not be used in this study. Transaminase monitoring is thus not indicated for this study.

Allergic Reactions: Allergic reactions have been observed in rare cases, presenting as urticarial, angioedema, generalized pruritus, tachycardia or bradycardia, hypotension, cardiac arrhythmia, nausea and vomiting, or light-headedness. If allergic reaction is suspected, we will withdraw the participant from trial. We will report this as an adverse event.

6.5. Interventions: Adherence

To help ensure adherence, we will ask participants for three contacts who will generally know the whereabouts of the participant enrolled. We will use texting to document daily bleeding. Monthly bleeding diaries will be assessed. Participants will be contacted by phone or email if any bleeding diaries are missing during a given a month. The participants will be asked to approve which method(s) of contact are acceptable and, for purposes of confidentiality, if it is acceptable for the research staff to identify themselves or state the reason for the call to another party, to leave a message, or to use a code name for a message.

6.6. Interventions – Concomitant Care

Women who experience pelvic pain during TCu380A IUD use may take regular strength OTC oral acetaminophen as directed on the bottle.

6.7. Outcomes

6.7.1. Primary Outcome Measures

The primary outcome of this trial is the number of bleeding and/or spotting (B/S) days over the 3-month (84-day) treatment period, based on diary data received from the participants. Based on standard criteria, bleeding will be defined as any bleeding that requires > 1 panty liner, tampon, or pad in a day. Spotting will be defined as minimal blood loss that requires one or no use of any protection including panty liners.[22] Bleeding episodes will be defined as days of bleeding or spotting that are bounded by 2 days of no bleeding or spotting. In accordance with criteria described by Mishell et al., all bleeding in this study will be defined as unscheduled. One cycle will be defined as 28 days.

Bleeding/spotting episodes will be classified by bleeding pattern: prolonged (i.e., length of a single B/S episode 14 days or more per 84-day reference period), frequent (more than 5 B/S episodes per 84-day reference period), infrequent (i.e., less than 3 B/S episodes per 84-day

reference period) or amenorrhea (i.e., absence of B/S for at least 84 consecutive days). Subjects who report a 14-day episode and more than 5 episodes within a 84-day period will be classified as "both prolonged and frequent bleeding." Subjects who report between 3-5 bleeding/spotting episodes will be considered as having a "normal" bleeding pattern.

6.7.2. Secondary Outcomes Measures

- Compare mean number of days of bleeding and spotting for the last 28 days (post 3-month treatment period) and total study period (120 days [13 x 84-day treatments + 1 x 28 day no-treatment]) between treatment groups.
- Improvement in menstrual bleeding symptoms assessed by standardized menstrual questionnaire.
- Changes in satisfaction, sexual functioning, and QOL.
- Medication-associated side effects.

6.8. Participant Timeline

All potential participants may be pre-screened over the phone for entry criteria prior to the initial screening visit. Participants who are recruited to the study will participate in an initial screening visit. The screening visit may occur the same day as the TCu380A IUD insertion visit or within 7 days of Cu-IUD insertion.

6.8.1. Visit 0: Screening

1. Each participant will be screened to confirm study eligibility.
2. Written informed consent: A research assistant will explain the study and its associated procedures, risks, and benefits prior to conducting any study procedures. The participant will be asked to sign an informed consent form if she wishes to participate. The consent form will be written to be understandable at a 6th-grade reading level. A copy of the consent form will be given to the study participant.
3. A demographic questionnaire (Appendix B) will be obtained. Contact information will be obtained (phone and/or email). The participants will be asked to approve which method(s) of contact are acceptable and, for purposes of confidentiality, if it is acceptable for the research staff to identify themselves or state the reason for the call to another person, to leave a message, or to use a code name for a message.
4. A short medical history will be obtained. Appendix C
5. The participant will complete the Female Sexual Function Index (FSFI) questionnaire (Appendix D).[23] This is a 19-item questionnaire that assesses six separate domains: (1) desire, (2) arousal, (3) lubrication, (4) orgasm, (5) satisfaction, and (6) sexual pain factors.
7. The participant will complete the Q-LES-Q-SF quality of life questionnaire (Appendix E).[24] This questionnaire is a 16-item questionnaire that has been shown to be valid and reliable among depressed patients undergoing treatment. This questionnaire is particularly sensitive to assess change, which is important to determine before and after TCu380A use.
8. The participant will complete a menstruation and pelvic pain questionnaire. We will use a questionnaire adapted from the World Endometriosis Research Foundation (WERF EPHect Questionnaire – Standard [EPQ-S]).[25] Questions assessed include menarche, a

description of menstruation of the prior 3 months, and what a woman's period is like when not using hormones. There are 8 questions related to pelvic pain which assess pain during last period, pain control, and how the pain might affect her ability to work or attend school. (Appendix F)

6.8.2. Follow-Up Procedures

Follow-Up Visit 1 (4-6 weeks post IUD insertion)

The participant will return for a visit approximately 4 to 6 weeks (1 month) after TCU380A IUD insertion. The participant will fill out a brief health questionnaire to assess whether the Cu-IUD is still in place or if a new medical condition (newly diagnosed obesity, chlamydia or gonorrhea has been diagnosed since Cu-IUD placement).

Women who state that they have had any changes in menstrual flow or complain of spotting will be recruited into the study.

After randomization, the participant will receive:

- An instruction sheet regarding when to take the medication and with a phone number to call if she has any questions or problems (Appendix A).
- Instructions on daily texting or app usage regarding bleeding (Appendix B & C).
- Bleeding diaries to complete for 4 months. The participant will be informed that these should be completed daily in case of technical difficulties with texting.
- Assigned medication (3-month supply, or 42 capsules total), treatment or placebo, will be blinded to both provider and participant.
- Compensation will be provided to the participant for this visit.

Monthly Email or Phone Call

The participant will be contacted approximately every 28-30 days after Follow-Up Visit 1 for a total of 4 monthly emails or phone calls. The research assistant will ask questions about the following:

1. IUD.
    a. Presence of IUD.
2. Menstruation (adapted from St. Louis CHOICE project questionnaire).
    a. Study medication taken as prescribed.
    b. How she experienced her period flow (light, moderate, or heavy)
    c. Number of days of bleeding during LMP.
    d. Frequency of pain during LMP.
    e. The monthly bleeding diary will be reviewed.
3. Side Effects

Participants will be asked about headaches, abdominal cramping, nausea, vomiting or diarrhea, somnolence, and dizziness.

Follow-Up Visit 2

The participant will return for a visit approximately 5 months (Month 6) after Follow-Up Visit 1.

1) The participant will complete the Female Sexual Function Index (FSFI) questionnaire (Appendix D).
2) The participant will complete the Q-LES-Q-SF quality of life questionnaire (Appendix E).[24]
3) The participant will complete a further adapted dapted EPQ-S menstruation and pelvic pain questionnaire to collect information for the last 6 months, not historical information that was collected in Visit 0.
4) A post-study questionnaire to assess satisfaction and plans to continue using the CuT380A IUD will be obtained from the participant. (Appendix G)
5) The participant will be informed as to which type of medication she was randomized to. Any unused study medications will be returned to the research team.
6) Compensation will be provided to the participant.

Visit and contact schedule	Visit 0 Screening	Visit 1 4-6 week FU	Monthly telephone or email contact	Visit 2 6-month FU
Month	0	2	3-6	7
Day(s)	+/- 7 days of IUD insertion	28-42 (±7)	56-140 (±7)	168 (±7)
• Written informed consent	x			
• Medical history questionnaire	X	X		
• Demographic questionnaire	X			
• Female Sexual Function Index	X			X
• QOL questionnaire	X			X
• Menstruation and pelvic pain questionnaire (EPHect EPQ-S)	X			X
• Cu-IUD Satisfaction				
• Evaluation of inclusion/exclusion criteria	X	X		
• Randomization to group assignment		X		
• Dispense study drug		X		
• Train participants to respond to daily texting		X		
• Train participants to complete bleeding diaries		X		
• Obtain three contacts for each participants	X	X		
• Review daily texting of bleeding diary			X	X
• Review participant completion of diary			X	X
• Return of study drug				X
• Completion of satisfaction questionnaire		X		X
• Assessment of Paragard		X	X	X

expulsion				
• Adverse event monitoring		X	X	X

Interim Visits

1) Participants who call the study center will be interviewed by a research coordinator, and their concern will be assessed by a clinician.
2) Participants will be encouraged to come to clinic if clinically necessary.
3) Participants will be interviewed for medical issues/illnesses, issues with the TCU380A IUD (e.g., expulsions), occurrence of adverse events, use of concomitant medications, etc.
4) Clinically relevant assessments will be performed.

Early Discontinuation

1) Participants who discontinue from the study early will undergo the Follow-Up Visit 2 procedures described above.

6.8.3. Criteria for Discontinuation

- Participants may be discontinued before randomization as discussed in Section VI.b above (inclusion/exclusion criteria).
- Participants will be discontinued from the study if they become pregnant.
- Participants may withdraw from the study at any time.

6.9. Sample Size

We aim to enroll 60 women into the treatment phase of this study. Based on the study by Dietrich in which approximately 70% of women using TCu380A IUD reported "heavier" bleeding volume at 3 months, we anticipate that 86 women will need to agree to TCu380A IUD insertion[26]; approximately 24 of these women will not have any symptoms of increased blood loss or spotting at Follow-Up Visit 1 and therefore will not continue in the study . Based on the response rate of approximately 60% from a prior US-based IUD study evaluating treatments for the prevention of bleeding among new levonorgestrel users, we anticipate we will need to approach 144 women to recruit 86 women into the study, of which we anticipate 60 will experience symptoms of increased blood loss or spotting.

6.10. Recruitment

We aim to recruit 60 subjects within a 5-month period. Each site will be given a recruitment target; however, competitive enrollment will be implemented to ensure the study meets its recruitment targets. Participants will be recruited at each site using both active and passive techniques. Investigators plan to recruit directly from their clinical sites. The study coordinator will obtain names and contact information for every patient receiving a Cu-IUD at a University of Washington clinic in the last 7 days and contact them by email and phone. Flyers will be posted at clinical sites, across the site's medical centers, and at off-site clinics to attract a broader patient population and to remind clinic staff about the study. The postings and advertisements will ask interested participants to contact our research staff. This study will enroll a convenience sample, but given selection of sites for this study the final sample will be representative of TCu380A IUD users in the US.

6.10.1. Participant Incentives

Participants will be paid for the screening visit when they will complete questionnaires and enroll in the study ($25). They will be paid at Follow-Up Visit 1 ($40), as well as $1 each day for completion of bleeding data for the 3 treatment cycles plus the one non-treatment cycle (up to 4 x $28, since each cycle=28 days). They will be paid at Follow-Up Visit 2 ($45). Thus, a participant who completes the study in full will be paid $222.

7.0. Methods: Assignment of interventions

7.1. Allocation

Allocation to naproxen or placebo study group will be determined through computer block random number generator to define15 blocks of participants (each block is in 1:1 ratio for sets of 4 sequentially numbered participants) by the University of Washington Investigational Drug Service (IDS). The UW IDS will provide each clinical site their own randomization list. Because we expect enrollment to be slightly faster at the UW clinical sites, we will assign one extra block at the UW clinical site: they will be assigned 8 blocks (32 participants) and Stroger Hospital will be assigned 7 blocks (28 participants).

7.2. Blinding

Study participants, UW, Stroger Hospital research teams, and the study statistician will be blinded to intervention assignment. Treatment and placebo capsules will be compounded in Seattle, WA and distributed to the UW IDS for the UW study participants. Stroger Hospital will have their own compounding pharmacy, but the randomization list will come from UW and be provided to Stroger Hospital pharmacy, who will be responsible for dispensing medications to study participants. The Stroger Hospital site in Chicago will receive their own randomization list, which will assign each sequential participant to a study group. After the study group is assigned, the study participant will receive a pill packet indicating the same numbered study group. A study group treatment log will be maintained at each study site.

To maintain the overall quality and legitimacy of the clinical trial, code breaks should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the study participant. The Principal Investigator (PI) is to be informed by other investigators if a study participant is believed to have had an adverse event requiring un-blinding. The PI will discuss with the IRB if un-blinding may be necessary. If un-blinding is necessary, the PI will use the system for emergency un-blinding as determined by the UW IDS.

8.0. Methods: Data Collection, Management, and Analysis

8.1. Data Collection Methods

Data will be collected by each research center. Each participant will have a set of source documents (medical history, physical exam, surveys), which will be entered into an existing UW Web-based program (REDCap) that is a password-protected database managed by the UW. When a computer is available, participants will answer directly into the database, which leaves less room for transposing errors. In case of technical difficulty with computer access to the REDCap website, each clinical site will receive paper source documents. Each survey (online and paper) will be identified by the participant's study number.

8.1.1. Bleeding Diaries

Participants randomized to a treatment arm will complete both paper and electronic bleeding diaries. For the electronic bleeding diary, 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. This approach uses the same service

provider that has been previously studied by Westhoff's Columbia University group with excellent real-time response rates (>90%).[27] The digital message bleeding diary for this project will be uniquely designed by UW 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. In the daily text message, subjects are asked to classify their bleeding using the terminology recommended by Mishell et al.[22] This includes for a given 24-hour period whether the woman has experienced:

1. Bleeding: any day during which bleeding requires the use of more than one panty liner, pad, or tampon.
2. Spotting: Minimal blood loss that could be contained with one or no panty liner, pad, or tampon.
3. No bleeding.

Subjects will also be asked if they took their study medication each day for the 3 treatment months. Text responses will be 1: yes, and 2: no.

If the subject does not respond to the text or email message, a second text or email will be sent the following evening. 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. Participants are encouraged to complete paper diaries in addition to the electronic diary. If there is a discrepancy between electronic and paper diaries, we take data from the electronic diary. If there are missing data, we will take information from the paper diaries to complete the electronic diaries.

Subjects in Seattle will be given the choice , as their smart phone plan allows, to use one of two electronic methods of bleeding tracking, text messages, or the period tracking app Clue. Clue users will be able to track other side effects mentioned in the bleeding diary directly into the app. We are piloting the feasibility of using an app versus text message to collect this data.

8.2. Data Management

The University of Washington will have the overall responsibility of this project and will serve as the Data Coordinating Center. As the Data Coordinating Center, UW will create the source documents for the study and be responsible for creating and managing the web-based database for the study with feedback from Stroger Hospital. Data will be maintained in locked files in a locked room at both sites. Ideally, each site will have participants enter responses to the questionnaires directly into a UW Web-based program (REDCap). In case of technical difficulty with computer access to the REDCap website, each clinical site will receive paper source documents. Other forms collected (i.e., medical history, physical exam, interim visits) will be de-identified, with only the participant study number and entered into REDCap, a web-based, password-protected database managed by UW.

To assure the accuracy and completeness of the data, the PI and research team at UW will periodically compare data reporting forms with source documents at both sites. As part of this

study, we will also be setting up best practices for data collection and analyses for a larger, multicenter trial.

8.3. Statistical Methods

Computer Facilities: Appropriate computer facilities are readily available for data analysis. REDCap will be used for entry and preparation of data for statistical analysis. Statistical analysis will be performed using STATA 12.

- *Objective 1: To evaluate the number of days of bleeding and spotting for the treatment period of this study as reported by the participant bleeding text responses, and bleeding diaries (as a backup)*.

For the 84-day period entailing episodes of bleeding and spotting, we will perform a sensitivity analysis to compare b/s during the days they were on treatment (or eligible for treatment) and days they were not on treatment, in order to elucidate whether treatment with naproxen was effective.

We will also evaluate the number of days of bleeding and spotting according to each 28-day cycle using descriptive analysis. We will plan to show episodes of bleeding by cycle and by group using box plots. Because we anticipate skewed data, we will use the Wilcoxon rank-sum test to compare the distributions of the number of days of bleeding and spotting during the first 3 cycles of treatment (84-day reference period) between the two treatment groups. Analysis will be performed based on intention to treat, meaning all subjects who are randomized and are dispensed treatment (naproxen or placebo) will be included in the full analysis.

We will also calculate the proportion of bleeding episodes by bleeding pattern (prolonged, frequent, infrequent, or amenorrhea) by treatment group as defined in 6.7.1. Primary Outcome Measures. For each 28-day cycle, we will indicate whether each woman had any prolonged episodes and/or any frequent episodes during that cycle. To evaluate the relationship between those who have prolonged episodes and those who report frequent episodes, for each 28-day cycle, we will report a 2x2 table of counts of patients by treatment group with neither, just prolonged, just frequent, or both prolonged and frequent episodes, and compare these by Chi-Square test (or Fisher's Exact Test if any cell count is below 5 subjects). We will use a multinomial model to determine whether treatment was associated with differences in these four separate bleeding pattern categories for each 28-day cycle, and use generalized estimating equations (GEE) repeated measures model to determine whether treatment was associated with differences in these four separate bleeding pattern categories for each 84-day reference period.

Objective 2: To assess feasibility of recruiting, enrolling, and maintaining new TCu380A IUD users in a randomized, placebo-controlled clinical trial.

We will report numbers of women inquiring about the study, screened, and enrolled into the study. The status of participants at the end of the study (e.g., completed study, lost to follow-up, discontinued, reasons for discontinuation) will be reported by treatment group.

- *Objective 3: To describe the impact of TCu380A IUD use on satisfaction, menstruation, dysmenorrhea, sexual functioning, and quality of life (QOL) scores by treatment group.*
    - Satisfaction with the TCu380A IUD is measured by a 3-point Likert scale adapted from the St. Louis CHOICE project and will be compared using two sample *t* test. Open-ended questions regarding the acceptability of the study will be reported descriptively and used to inform study procedures for a future clinical trial. Satisfaction will be asked

at the end of each treatment cycle, non-treatment cycle and the follow up visit #2. We will adjust for multiple comparisons.

- Menstruation and pelvic pain will be assessed using a global score calculated from the Adapted EPQ-S.[25] Menstruation and pelvic pain will be assessed by this questionnaire at screening and after 3 consecutive months of treatment. We will compare means of menstruation and pelvic pain scores by treatment group using analysis of covariance (ANCOVA). We will adjust for baseline menstrual flow at the screening visit. We will also adjust for precision variables (significantly associated with outcome score with $p<0.05$) from the following list: age, contraceptive method type in the prior month prior to enrollment in study, baseline cycle length, baseline number of days of bleeding during menstruation, and baseline pain with period. If the outcome scores are found to be skewed, we will use Wilcoxon rank-sum test for comparisons.
- The Female Sexual Function Index (FSFI) is a 19-question survey and will be administered at screening and 6-month follow-up. Scoring is done by adding the scores of the individual items that comprise each domain and multiplying the sum of the six scores by the domain factor.[23] We will compare 6-month means adjusted for baseline using ANCOVA. If the data are found to be skewed, we will use Wilcoxon rank-sum test for comparisons.
- The Q-LES-Q-SF quality of life measure, administered at screening and the 6-month follow-up, will be compared. The scoring of the Q-LES-Q-SF involves summing only the first 14 items to yield a raw total score. The last two items are not included in the total score but are stand-alone items. The raw total score ranges from 14 to 70. The raw total score is transformed into a percentage maximum possible score using a prescribed formula.[28] We will compare 6-month means adjusted for baseline using ANCOVA. We will adjust for age and baseline depression/anxiety as reported in medical history questionnaire. If the data are found to be skewed, we will use Wilcoxon rank-sum test for comparisons.

- *Objective 4: To describe the safety of OTC naproxen compared to placebo.*
  - Participants will be asked about headaches, abdominal cramping, nausea, vomiting, diarrhea and dizziness at each monthly email or phone call and at Follow-Up Visit 2. For each reported side effect, we will compare the treatment groups using Chi-square or Fisher exact test, depending on the prevalence of each side effect.
- Subgroup analysis: We will plan to evaluate whether there is effect modification by age.

9.0. Methods: Monitoring

9.1. Disposition

We will determine the proportion of participants needed to approach, enroll, and maintain to meet goal of 30 participants per treatment group.

9.2. Safety Assessment Methods

Subjects will be informed at the start of the study that they are to report all adverse events or concerns related to the treatment.. Monitoring of data will be performed by the PI and research team at the two sites to assure that the clinical staff adheres to the protocol, that data are entered completely and accurately on the data reporting forms, that regulatory requirement for

conducting clinical research are followed, that facilities are adequate to conduct the clinical trial, and that IRB approval is obtained. They will monitor adverse events through biweekly phone meetings.

9.3. Adverse Event Management and Reporting

Each participant will be advised to contact the research site immediately if she has any significant medical problems or complaints during the course of this study. A designated study clinician will be available 24 hours a day and will evaluate all complaints and assure that appropriate health care or referral is provided for all study participants. Adverse events are defined by federal regulations (CFR, Title 21, Part 312.32) as follows:

- **"Associated with the use of the drug"** means: "There is a reasonable possibility that the experience may have been caused by the drug."
- **"Serious adverse drug experience"** (SAE) means "Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."
- **"Unexpected adverse drug experience"** means: "Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended."

All serious adverse events, including those that may appear to be unrelated to the study product, will be reported to the Institutional Review Board by the investigator (according to the local policies). If any serious adverse events or complications occur, the respective IRBs will be notified within 24 hours, and the investigators will meet with the IRBs to assess if the study can continue. No Data Safety Monitoring Board will be used for this study. The medication used for treatment (naproxen sodium) is FDA-approved and already used in a non-prescription, over-the-counter context, and side effects will be monitored on a regular basis. The principal investigators at each site will be responsible for monitoring participant safety.

Each center will maintain and track their study medications. Regular site monitoring will be done by UW to ensure that Stroger Hospital is following study procedure and to identify and rectify any problems that may be occurring. There will also be regular conference calls with the project team to discuss progress with recruitment, enrollment, retention, adverse events, etc.

We will not perform an interim analysis for safety and efficacy because of proven safety of OTC naproxen and because of the short 3-month duration of treatment.

9.4. Duration of Project

- The duration of the project is expected to be about 18 months.
- Recruitment is expected to take 5 months.
- Creation of the web-based REDCap database for data entry will occur before enrollment begins, and data entry will be ongoing throughout the study. Data entry will be completed within one month of the completion of data collection.

- All data collection will be done six month after enrollment of the last participant.

PROJECT ACTIVITIES	Oct 15-Dec 15	Feb 16-Aug 16	Mar 16-Oct 16	July 15-feb 17	Oct 16-Nov 16	Nov 16-Dec 16	Jan 17-Mar 17	Mar 17-May17 M	Jun 17-Jul 17
IRB submission, CRBB review, set up database	X	X							
• Recruitment		X	X	X					
• Screening Visit		X	X	X					
• Insertion Visit		X	X	X	X				
• Follow-up Visit #1			X	X	X	X			
• Monthly Contact			X	X	X	X	X		
• Follow-up Visit #2				X	X	X	X		
• Clean database						X	X	X	
• Analyze survey data							X	X	X
• Prepare and finalize manuscript								X	X

10.0. Ethics and Dissemination Plan

With assistance from Stroger Hospital the UW (as the Data Coordinating Center) will be responsible for preparing a summary report of the trial.

This study is a critical first step to determining whether a larger definitive study comparing treatment of heavy or prolonged menstrual bleeding with naproxen and placebo is feasible among TCu380A IUD users. Though it is a feasibility study, it will be the first head-to-head study examining naproxen for menstrual bleeding in new TCu380A IUD users. If a larger-scale study is feasible, we anticipate adding additional promising treatments (e.g., tranexamic acid) and focusing on important clinical outcomes such as unscheduled bleeding, satisfaction, and quality of life among TCu380A IUD users. We plan to present our data at a national family planning conference, as well as a conference related to primary care research. We will develop a summary paper from this feasibility study consistent with CONSORT clinical trial guidelines.

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