Prospective Randomized Trial of Tranexamic Acid versus Levonorgestrel Intrauterine System for the Treatment of Heavy Menstrual Bleeding in Women with Uterine Fibroids

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PROSPECTIVE RANDOMIZED TRIAL OF TRANEXAMIC ACID VERSUS LEVONORGESTREL INTRAUTERINE SYSTEM FOR THE TREATMENT OF HEAVY MENSTRUAL BLEEDING IN WOMEN WITH UTERINE FIBROIDS

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Study Product: Tranexamic acid (Lysteda)
Levonorgestrel Intrauterine system (Mirena)

Protocol Number: (IRBe) 16-008671

Initial version: [11.15.2016] Version 1.0
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Revised: [04.12.2018] Version 2.1
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Revised: [07.26.2019] Version 2.3

Table of Contents

List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
LNG-IUS	Levonorgestrel-releasing intrauterine system
TXA	Tranexamic Acid
RCT	Randomized Controlled Trial
HMB	Heavy Menstrual Bleeding
UFS-QOL	Uterine Fibroid Symptom – Quality of Life
MMAS	Menorrhagia Multi-Attribute Scale
PBLAC	Pictorial Blood Loss Assessment Chart
VAS	Visual Analog Scale (for pain)
CI	Confidence Interval
LVCF	Last Value Carry Forward

Study Summary

Title	Prospective Randomized Trial of Tranexamic Acid versus Levonorgestrel Intrauterine System for the Treatment of Heavy Menstrual Bleeding in women with Uterine Fibroids
Running Title	LNG-IUS vs. Tranexamic Acid in women with uterine fibroids
Protocol Number	16-008671
Phase	IV
Methodology	Randomized controlled trial, open label
Overall Study Duration	2 years
Subject Participation Duration	9 months
Single or Multi-Site	Single-site
Objectives	Specific Aim #1: To determine the comparative effectiveness [as measured by the Menorrhagia Multi-Attribute Scale (MMAS)] and duration of use of TXA versus LNG-IUS for the treatment of HMB in women with uterine fibroids. Specific Aim #2: To determine the clinical and fibroid-related predictors of successful medical therapy of HMB in women with uterine fibroids.
Number of Subjects	160
Diagnosis and Main Inclusion Criteria	Heavy menstrual bleeding in women with uterine fibroids.
Study Product, Dose, Route, Regimen	Levonorgestrel intrauterine system (20 microgram/24 hour levonorgestrel) Tranexamic acid 1.3 grams three times per day during first 5 days of menses
Duration of Administration	Up to 5 years for the LNG-IUS and up to 1 year for tranexamic acid
Reference therapy	Compared to each other, no placebo arm

Statistical Methodology	At 3, 6, and 9 months separately, each of the continuously scaled outcomes will be compared between treatment arms based on fitting separate linear regression models and analysis of covariance (ANOCOVA) models will be fit to compare the measures between the two treatment arms after adjusting for baseline levels. Last value carry forward (LVCF) methods will be investigated to accommodate drop-outs. All analyses will be performed based on the intention to treat principle. The cumulative incidence (CI) function will be used to estimate the cumulative proportion of patients by time *t* who have intentionally discontinued treatment due to the desire or need to stop or switch treatment, after accounting for the competing risk of LNG-IUS expulsion and censoring all other participants at their date of last follow-up or end of study.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Background

Uterine fibroids and especially the heavy menstrual bleeding (HMB) they produce are a common and debilitating problem for women. Our work demonstrates 60% of women with fibroids report that symptoms affect their quality of life and impede physical activity, and 24% report that fibroid symptoms prevent them from reaching their true potential at work (1, 2). HMB, the most common symptom of uterine fibroids, affects approximately 1.4 million women per year and costs an excess $2,291 per woman annually in lost work and home management activities (3, 4). Medical therapy is the first line treatment for HMB, yet, the lack of evidence of medical efficacy in women with fibroid-related HMB leads to a high rate of surgical management and especially hysterectomy. Fibroids account for more than 40% of hysterectomies in the U.S. which have a 10-12% complication rate and may lead to the detrimental effects of early menopause, even with conservation of the ovaries (5, 6). Randomized studies of the efficacy of medical therapies for HMB typically include only women with few or small fibroids (7, 8). **The goal of this study is to determine the effectiveness of non-estrogenic medical therapy in women with a range of fibroid sizes, locations, and number.**

Two effective medical treatments for HMB have limited data in women with fibroids. The levonorgestrel intrauterine system (**LNG-IUS**) was FDA approved for the treatment of HMB in 2009 and is highly effective for decreasing menstrual bleeding, treating anemia and improving quality of life (8-10). Moreover, it can be used continuously for 5 years. Expulsion rate in women with fibroids may be as high as 12% and discontinuation rate up to 28% at 2 years based on a small sample size and no information is available about predictors of these events (8). Tranexamic acid (**TXA**) is widely used outside the U.S. and was also FDA approved for HMB in 2009; TXA reduces menstrual blood loss in 40% of women and improves quality of life (11-14). In women with fibroids, TXA has been shown to decrease HMB and cause necrosis of the fibroids, especially larger fibroids, which should augment its efficacy for women with fibroids (15).

Our preliminary data from a large insurance-claims database show that women with fibroids were more likely to continue use of LNG-IUS (62% at 6 months) than TXA (22% at 6 months) for the treatment of HMB; however, we were unable to ascertain reasons for discontinuation in either group (16). Accurately predicting which women with fibroids are optimal candidates for medical therapy is a key unanswered question of the Agency for Healthcare Research and Quality (AHRQ) evidence-based review and would have substantial impact on the clinical care for women with fibroids (17).

Thus, we propose a **randomized controlled trial (RCT)** to assess the **comparative effectiveness** of **LNG-IUS** to **TXA** for the **treatment of HMB in women with clinically-significant fibroids**. We will measure patient-reported outcomes recognized to be important to women with HMB and study the clinical factors (e.g. body mass index, age) and fibroid factors (e.g. size, location) that predict successful medical therapy.

After greater than 1 year of enrollment and randomization, we have found that we have a higher rate of drop outs in the TXA arm than expected. Nearly all participants in the TXA arm have dropped out (n=4) before 6 months participation due to various side effects. Clinically, we use this medication and do not receive the same reported side effects. Thus, we would like to evaluate the use of TXA in a population that has self-selected the use of the medication**. We will add an observational arm to the study for women who otherwise meet study criteria and select either TXA or LNG-IUS, but decline randomization.**

1.2 Investigational Agent

LNG-IUS was FDA approved for the treatment of HMB in 2009 and previously for contraception in 2000. The LNG-IUS is a T-shaped device with a polyethylene body containing a hormone reservoir, holding a total of 52 mg of levonorgestrel. LNG-IUS initially releases 20 micrograms of the progestin per day, which decreases to less than half that amount after 5 years of use. The levonorgestrel causes stromal pseudodecidualization, decreases endometrial thickness, and lowers uterine vascular density.

TXA was FDA approved for the treatment of HMB in 2009. TXA is a plasminogen-activator inhibitor that blocks fibrinolysis and reduces plasmin activity. A special formulation was designed for the treatment of HMB that reduces gastrointestinal side effects (Brand name *Lysteda*): 1300 mg taken three times per day for up to 5 days of the menstrual cycle (Lukes).

1.3 Clinical Data to Date

Several studies have shown good efficacy of both the LNG-IUS and TXA in the treatment of HMB in the presence of small uterine fibroids {Grigorieva, 2003 #1010}{Gupta, 2015 #992}{Lukes, 2010 #986}. We demonstrated in our large insurance-claims database that women with clinically significant fibroids were more likely to continue use of LNG-IUS (62% at 6 months) than TXA (22% at 6 months) for the treatment of HMB. No studies have demonstrated the reasons for discontinuation of treatment. A case report published after the start of this study shows intratumoral atherosis-like vasculopathy in a fibroid treated with tranexamic acid; no side effects were noted in this case but surgery was done due to lack of response to TXA. The side effects and reasons for discontinuation noted thus far in our study include diarrhea, abdominal cramping, lack of effect, pelvic pain and dysmenorrhea.

1.4 Dose Rationale and Risk/Benefits

Both medications are being used at the clinically acceptable dosages as indicated for the treatment of HMB. Risks of LNG-IUS related to fibroids include expulsion, perforation, or embedment of device. The risk of TXA related to fibroids is necrosis of the fibroids leading to pain.

2 Study Objectives

Primary Objective

To determine the comparative effectiveness [as measured by the Menorrhagia Multi-Attribute Scale (MMAS)] and duration of use of TXA versus LNG-IUS for the treatment of HMB in women with uterine fibroids.

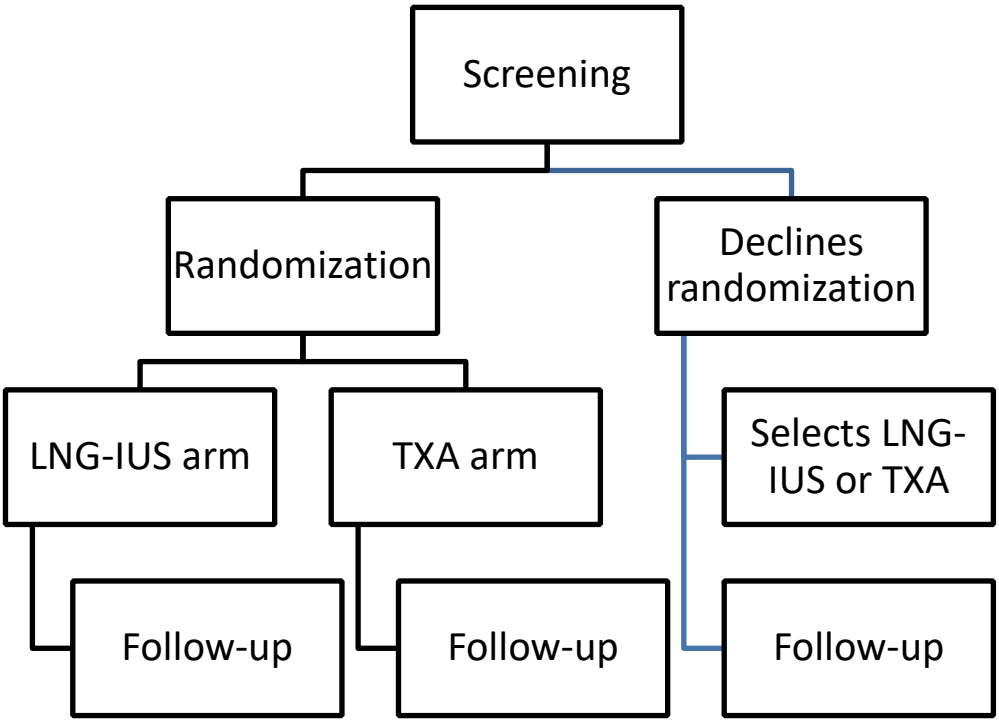
Hypothesis: A user-independent medical therapy (LNG-IUS) will result in better patient reported outcomes and longer use compared to self-administered medication (TXA)

Secondary Objective
To determine the clinical and fibroid-related predictors of successful medical therapy of HMB in women with uterine fibroids.
Hypotheses: Large fibroid size will limit the effectiveness of LNG-IUS compared with TXA; elevated BMI predicts higher success with LNG-IUS over TXA.

3 Study Design

3.1 General Design

This is a randomized controlled trial of LNG-IUS compared with TXA for the treatment of HMB in160 women with uterine fibroids. Subjects with self-reported HMB for 3 months or more that have at least one uterine fibroid >1cm in size that is either intramural or submucosal on ultrasound will be eligible for the study. Clinical evaluation for HMB needs to be completed before enrollment and participants must be eligible for either LNG-IUS or TXA.
Screening for the study will be based on baseline MMAS score with at least one domain scoring >2. Additionally, if not already performed for HMB evaluation, screening will include uterine sounding length, ultrasound documentation of number and size of fibroids, and evaluation of the uterine cavity if indicated. Once consent has been obtained, baseline laboratory studies will be completed and participants randomized to one of two arms. Placement of the LNG-IUS will be performed by study physicians in the clinic setting. Follow-up of treatment effect will continue for 9 months with monthly Pictorial Blood Loss Assessment Card (PBLAC) scores and phone calls at 3 and 6 months. A final visit for evaluation, collection of lab samples, and ultrasound examination will be conducted at 9 months.
For patients that would qualify for the study but choose not to be randomized, we will enroll them into an observation arm. We will have them complete the same questionnaires and report adverse events/side effects at baseline, 3 months, 6 months and 9 months. We will also have them obtain CBC, ferritin, and ultrasound at the end of study. Medications will be provided in the clinical setting and not provided by the study. For patients in the observation arm, the baseline serum creatinine and ultrasound will be done if clinically indicated, but are not required for enrollment.


Screening
Randomization
Declines randomization
LNG-IUS arm
TXA arm
Selects LNG-IUS or TXA
Follow-up
Follow-up
Follow-up

3.2 Primary Study Endpoints

The primary endpoints are the difference in self-reported MMAS scores at 6 months between LNG-IUS and TXA treatment and the duration of use of TXA versus LNG-IUS

3.3 Secondary Study Endpoints

The secondary endpoints are:

- Patient and fibroid characteristics that predict successful outcomes
- Differences in VAS, PBLAC, UFS-QOL and Rand SF-36 scores

3.4 Primary Safety Endpoints

Safety endpoints include:

1. The correct placement of LNG-IUS based on type of fibroids present, verified by ultrasound after placement of device.
2. Record of side effects or adverse events of each medication based on questionnaire, phone follow-up and self-report.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- Premenopausal women aged 25-50
- Seeking treatment for HMB with a completed clinical evaluation
- Image-confirmed uterine fibroids of at least 1 cm in size and either submucosal or intramural
- Monthly menses
- Completed evaluation of HMB within one year
- Able to give consent for inclusion in the study
- Understands the English language for consent and questionnaires
- Self-reported HMB 3 months or more
- Not pregnant or breast-feeding

4.2 Exclusion Criteria

- Class 0 fibroids confirmed by hysteroscopy, saline infused sonogram, or 3D ultrasound
- Uterine sounding length >14 cm
- Abnormal biopsy (pre-malignant or malignant) or incomplete clinical testing to rule out malignancy
- Venous thromboembolic history, clotting disorder, strong family history of venous thromboembolic events
- Needs hormonal contraception, including estrogen-containing medications
- Uterine size >20 weeks gestational size
- Breast, uterine or cervical malignancy
- Liver disease or liver tumor
- Pelvic inflammatory disease or infection with gonorrhea or chlamydia in last 3 months
- Hemoglobin less than 8mg/dL; for women 8-12 mg/dL recommend iron
- Serum creatinine ≥ 1.4

- Pregnant or breast-feeding

4.3 Subject Recruitment, Enrollment and Screening

For recruitment into the study, we will recruit patients from our Mayo Clinic Gynecology clinics, but we will look to our colleagues for referrals for the study. Before the start of the study, a letter will be sent to all staff providers in Gynecology (n = 69) and Family Medicine at Mayo Clinic (n = 166) and primary care providers at affiliated facilities (n= 81), including the Mayo Clinic Health System sites, for referrals to our gynecology clinics for the trial. The trial will be listed under our current studies section and at clinicaltrials.gov. The advertising brochure will be downloadable as a PDF file and flyers created for display in our medical facilities.
Self-referrals to our clinic for evaluation of the study will be allowed. We will use our Mayo Clinic Fibroids social media network (Facebook and Twitter) developed for our current fibroid studies and the assistance of our Mayo Clinic Division of Community Engagement for outreach. We have established an email address for fibroid studies that will be listed on brochures and flyers. Based on an accrual feasibility study, we project that we can recruit all of our patients from Mayo Clinic Rochester alone. We can reach out to 3 of our Mayo Clinic Health System hubs for additional referrals and outreach if needed as we are currently doing with other trials. In addition, all women seeking treatment for HMB will be advised of the study when making their appointment. They will be offered a brochure, and the option to talk with a study coordinator during their clinical visit. We estimate that we will enroll a minimum of 3 participants per week (13 months to reach target enrollment of 160 participants).
Informed consent for study enrollment will be obtained by a study coordinator in the clinic setting. The consent document and study treatments will be reviewed with the patient, and she will be allowed sufficient time to ask questions.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Participants may be withdrawn from the study at any time prior to completion of the study for the following reasons:

- Safety issues including allergic or adverse reaction to either medication
- If the participant develops clinically significant anemia from on-going HMB, she will be offered different treatment options
- Displacement of LNG-IUS will require removal and participant may opt to withdraw from study or have a new device placed
- Participant decision to withdraw from study (withdrawal of consent)
- Unable to comply with the study protocol

There are no adverse effects from stopping either treatment suddenly. We will encourage the participant to complete the study end measures (clinical laboratories, ultrasound, exam) to provide useful information to provide their primary care or gynecological provider on the management of their HMB. This data will be useful to understand the treatment effect on the fibroids, bleeding, and well-being of the participants. If withdrawn from the study and not agreeable to the additional measures, we will use only data collected to that point. We will plan our recruitment to account for 20% attrition from the study so that individual participants will not require replacement.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

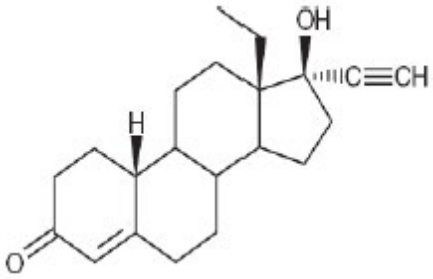
We will use the data obtained up until the person withdraws from the study, but will attempt to obtain permission for follow-up at 9 months for the subjects who have withdrawn. This endpoint will include whether the participant is still using either of the treatments, has any adverse events from treatment, had other procedures for HMB, and if there was expulsion of intrauterine device.

5 Study Drug

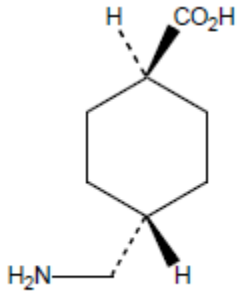
5.1 Description

Neither arm will be blinded due to the nature of the therapy.

Mirena (levonorgestrel-releasing intrauterine system) contains 52 mg of LNG, a progestin, and is intended to provide an initial release rate of approximately 20 mcg/day of LNG. Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Mirena, has a molecular weight of 312.4, a molecular formula of C21H28O2, and the following structural formula:



LYSTEDA is an antifibrinolytic drug. The chemical name is trans-4-aminomethylcyclohexanecarboxylic acid. The structural formula is:



Tranexamic acid is a white crystalline powder. It is freely soluble in water and in glacial acetic acid and is very slightly soluble in ethanol and practically insoluble in ether. The molecular formula is C 8H15N02 and the molecular weight is 157.2.
Tranexamic acid tablets are provided as white oval-shaped tablets and are not scored. Each tablet is debossed with the marking “FP650.” The active ingredient in each tablet is 650 mg tranexamic acid. The inactive ingredients contained in each tablet are: microcrystalline cellulose, colloidal

silicon dioxide, pregelatinized corn starch, povidone, hypromellose, stearic acid, and magnesium stearate.

5.2 Treatment Regimen

LNG-IUS is effective on placement and can be used up to 5 years. TXA will be dosed at 1300mg (2 tablets of 650mg) three times a day at the start of menses and used during the days that bleeding is heaviest (not to exceed 5 days per menstrual cycle).

5.3 Method for Assigning Subjects to Treatment Groups

After review of enrollment criteria, eligible participants will be randomly assigned to either LNG-IUS or TXA treatment. Using a computer generated random numbers sequence; our statistician will prepare the randomization code. Randomization will be stratified by BMI (>=30 or <30), dysmenorrhea (yes/no) and duration of HMB (<1 or >= 1 year) and will be conducted using a dynamic allocation approach based on the Pocock-Simon method.

For patients that decline randomization but meet criteria and are interested in participation, they will be followed in the treatment group that they choose (either the LNG-IUS or TXA options).

5.4 Preparation and Administration of Study Drug

Levonorgestrel intrauterine system (20microgram/24 hour levonorgestrel) will be sent from the manufacturer (Bayer Pharma AG) in sterile packaging to the clinic for insertion by physician as per clinical protocol. After pregnancy has been reliably excluded, the patient is placed in the lithotomy position and a bimanual examination is performed to assess uterine size and position. A speculum is placed in the vagina and the cervix cleaned with antiseptic solution. The uterus is sounded. The package is opened and using an aseptic technique, the sterile inserter is removed from the package. The slider is pushed forward as far as possible in the direction of the arrow to load the LNG-IUS. The inserter is carefully placed in the cervix and advanced to the uterine fundus corresponding to the sounding depth. The LNG-IUS arms are opened by pulling back the slider, the LNG-IUS positioned at the fundus, and the inserter removed. Strings should be cut to 3 cm.

Tranexamic acid will be dispensed by the Mayo Clinic Outpatient Research Pharmacy to the participant or mailed directly in 3-month supply increments. Participants will be instructed to take TXA at the initiation of each menses and use during the heaviest days of bleeding for up to 5 days. Dosage is 1.3 grams (2 pills of 650mg each) three times per day for up to 5 days.

5.5 Subject Compliance Monitoring

The study team will assess use of the medications at each follow-up phone call and visit. Subjects will be encouraged to feel for strings of the LNG-IUS to ensure uterine location. The TXA arm will be asked about the number of days they are using per menstrual cycle.

Prior and Concomitant Therapy

Concomitant therapy with NSAIDs will be allowed in both arms for treatment of dysmenorrhea or excessive bleeding. We will record NSAID use during the menstrual cycle. Estrogen-

containing medications are contradicted with TXA and thus, will not be allowed to be used during the study.

5.6 Packaging

Mirena (levonorgestrel-releasing intrauterine system), containing a total of 52 mg LNG, is available in a carton of one sterile unit NDC# 50419-423-01.
Mirena is supplied sterile. Mirena is sterilized with ethylene oxide. Do not re-sterilize. For single-use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.

LYSTEDA (tranexamic acid) tablets are provided as white oval-shaped tablets. Each tablet is debossed with the marking "FP650" and are supplied as:

Quantity	Package Type	NDC Number
30 tablets	HDPE bottle	55566-2100-2
100 tablets	HDPE bottle	55566-2100-1

The TXA will be dispensed by the Research Pharmacy to study participants during their clinic visit or by mail. The investigational product will be labeled with patient specific prescription labels and the appropriate labels affixed to the prescription bottles/package as required by state and federal regulations.

The package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use". A sample label is provided in the figure below. Note that the label is subject to change format but the information contained therein will not be changed.

Sample Label

MAYO CLINIC

RESEARCH MEDICATION
200 1ST Street SW
Rochester, MN 55905
(507) 284-2511

Today's Date: _____
Prescriber Name/Number: _____

IRB# 16-008671 **Subject #** ____ **Subject Name** _____
Study Name _____ **Kit#** _____
Medication Name/Strength Mirena (levonorgestrel-releasing intrauterine system)_
Directions (NO Abbreviations)_____

Caution-New Drug Limited By Law To Investigational Use

Sample Label

MAYO CLINIC

RESEARCH MEDICATION
200 1ST Street SW
Rochester, MN 55905
(507) 284-2511

Today's Date: _____
Prescriber Name/Number: _____

IRB# 16-008671 **Subject #** ____ **Subject Name** _____
Study Name _____ **Kit#** _____
Medication Name/Strength _ Tranexamic Acid 650mg_____
Directions (NO Abbreviations)_Two tablets three times per day for up to 5 days during the menses_____

Caution-New Drug Limited By Law To Investigational Use

5.7 Masking/Blinding of Study

Neither subjects nor researchers can be blinded to the treatment arm due to the nature of the study medications.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Mirena will be shipped by Bayer Pharmaceuticals to the Mayo Clinic Outpatient Research Pharmacy and dispensed from there. Tranexamic acid tablets will be supplied by the Mayo Clinic Outpatient Research Pharmacy.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.8.2 Storage

Mirena (levonorgestrel-releasing intrauterine system)
Store at 25°C (77°F); with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Tranexamic acid tablets
Store at room temperature 25° C (77° F); excursions permitted to 15-30° C (59-86° F). [See USP Controlled Room Temperature].

All study drugs will be dispensed from the Mayo Clinic Outpatient Research Pharmacy. The drugs will be stored in a secure location according to product storage guidelines.

5.8.3 Dispensing of Study Drug

Investigational product will be dispensed by Mayo Clinic Outpatient Research Pharmacy per standard methods.

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.8.4 Return or Destruction of Study Drug

Tranexamic acid and Mirena (levonorgestrel-releasing intrauterine system)

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and

investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

Table 1.	Enrollment	4-6 Week Visit (Levornorgestrel IUS visit)	3 mo	6 mo	9 mo[6]
Study visit	X				X
Informed Consent	X				
Phone follow-up			X	X	
Demographic and medical questionnaire	X				
Rand Short Form-36	X		X	X	X
UFS-QOL	X		X	X	X
MMAS	X		X	X	X
PBLAC (for each menses during the 9 mo.)	X		X	X	X
Visual analogue scale (VAS) for Pain	X		X	X	X
Adverse events			X	X	X
Request for relevant medical records	X				X
Medical records review	X				X
Ultrasound imaging	X[1]				X
Screening examination (uterine sounding length, estimation of uterine size by bimanual examination, and review of imaging)	X				
Phlebotomy– CBC[2], ferritin[2]	X				X
Phlebotomy– creatinine[3]	X				
Study remuneration					X
Pregnancy test (urine) – if needed	X				
History and Physical	X				X
Ultrasound to confirm placement of levonorgestrel IUS	X[4]				
Levonorgestrel IUS visit		X[5]			

[1]Will only be performed if the ultrasound is not done for clinical purposes or no pelvic imaging (Saline infused sonogram, ultrasound, MRI) has been performed for more than 1 year before enrollment
[2]Will be performed if CBC, ferritin were not done for clinical purposes in the 3 months before enrollment
[3]Patients without renal disease can have creatinine pending at the time of enrollment, but will be withdrawn if result is >=1.4. Creatinine will not be drawn for the observation cohort unless clinically indicated at the time of initiation of treatment.
[4]If enrolled in the LNG-IUS arm of the randomized cohort.
[5]Will be performed 4-6 weeks after placement of LNG-IUS for confirmation of IUS location
[6]Or at withdrawal from or termination of the study

6.1 Visit 1/ Enrollment

The screening examination will include any screening elements not already completed during clinical evaluation (uterine sounding length, estimation of uterine size by bimanual examination, and review of imaging) or completed more than 6 months prior to enrollment. At this visit, subjects

will complete the questionnaires listed in the table and have laboratory testing completed. Pregnancy test will be performed for those at risk for pregnancy. If patients are current users of hormonal treatments for uterine bleeding and wish to enroll, they can be screened for the study. If eligible for the randomized cohort, they will need to complete a 1 month washout period with no hormone use and with natural resumption of their menses before they can be randomized to treatment. If they are current users of hormonal treatments and are switched to TA or LNG-IUS (with discontinuation of other hormonal treatments), they are eligible for the observation arm without washout. If enrolled in the LNG-IUS arm, ultrasound will be performed following placement to ensure the correct position of the LNG-IUS. If the LNG-IUS is not in the optimal position, it will be removed and a new device inserted immediately.

6.2 Week 4-6 Visit (For women enrolled in the LNG-IUS arm)

For women enrolled in the LNG-IUS arm, a visit will be scheduled at 4-6 weeks after placement to check for IUS strings visible at the cervix. This will serve as confirmation of position of IUS. If strings are not visible, clinical evaluation will be performed including pelvic ultrasound and/or x-ray to confirm location of IUS or expulsion.

6.3 Visit 2 / Month 3

At month 3, subjects will complete questionnaires listed in the table and receive a phone call to screen for adverse events. LNG-IUS that are expelled may be replaced one time if patient desires to continue device and the expulsion occurred within the prior 7 days. The expulsion occurred within one week and. Patient outcome would be recorded as expulsion.

6.4 Visit 3 / Month 6

At month 6, subjects will complete questionnaires listed in the table and receive a phone call to screen for adverse events.

6.5 Visit 4 / Month 9

At month 9, subjects will return for a study visit and examination. Ultrasound will be performed for size of fibroids. Laboratory testing will be completed. Subjects will complete questionnaires listed in the table and screen for adverse events and finalize study participation. Participants assigned to the LNG-IUS arm will be carefully assessed to determine if there are any contraindications to continuing therapy. Those with cavity-distorting fibroids (Type I) will be counseled regarding removal of the LNG-IUS.

7 Statistical Plan

7.1 Sample Size Determination

Aim 1. The primary outcome variable will be the difference in MMAS score at 6 months between the treatment arms. Based on the ECCLIPSE trial, the observed effect size at 6 months for the MMAS total score was 0.58 standard deviations (8). In order for the proposed trial to

have 90% power to detect such a difference, we would need 64 patients per treatment arm. To allow for up to 20% loss to follow-up or incomplete data without the potential to carry-forward an MMAS score from an earlier assessment, we will enroll 80 patients per treatment arm. From our preliminary study of a large insurance-claims database, we found a 40% difference (62% vs. 22%) in continued use of the index medication at 6 months. Based on the sample size of 80 women per arm, we will have over 90% power to detect such a difference if it exists in the data from the proposed trial. These calculations are based on a two-sample t-test and chi-square test, respectively, assuming a type I error of 0.05 and a two-sided alternative hypothesis.

Aim 2. As described in Aim 1, we plan to enroll 80 patients in each treatment arm. Among these 160 patients, we anticipate that at least 80 patients will have intentionally discontinued treatment by the end of the study. Table 3 below summarizes the detectable hazard ratios for different factor scenarios with varying prevalence. Assuming that 50% of the study participants will have a BMI > 30 kg/m^2, this aim will have 80% power to detect an association between obesity and intentional discontinuation.

Table 2. Detectable hazard ratios with 80% power based on a two-sided logrank test with a type I error of 0.05

Prevalence of factor	Among the 160 patients in both arms (assume 80 intentionally discontinue)
20%	2.19
30%	1.98
40%	1.90
50%	1.88

7.2 Statistical Methods

Descriptive Statistics
Standard descriptive statistics will be generated for measurements at baseline, 3, 6, and 9 months, including mean, median, standard deviation (SD), and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables.

Handling of Missing Data
Last value carry forward (LVCF) methods will be investigated to accommodate drop-outs.

Primary Hypothesis: A user-independent medical therapy (LNG-IUS) will result in better patient reported outcomes and longer use compared to self-administered medication (TXA)

Statistical analysis: The distribution of each of the continuously scaled outcome measures (MMAS total score, PBLAC score, ferritin level, hemoglobin level, UFS-QOL scores, and Rand

SF-36 composite scores) will be graphically evaluated and logarithmic transformations will be applied if the distributions are skewed in order to obtain more normally distributed distributions. At 3, 6, and 9 months separately, each of the continuously scaled outcomes will be compared between treatment arms based on fitting separate linear regression models. In addition, separate analysis of covariance (ANOCOVA) models will be fit to compare the measures between the two treatment arms after adjusting for baseline levels. The cumulative incidence (CI) function will be used to estimate the cumulative proportion of patients by time t who have intentionally discontinued treatment due to the desire or need to stop or switch treatment, after accounting for the competing risk of LNG-IUS expulsion and censoring all other participants at their date of last follow-up or end of study. Likewise we will also estimate the CI of expulsion among the LNG-IUS treatment arm. The CI estimates for intentional discontinuation over the entire 9 months of follow-up will be compared between treatment arms using the methods developed by Gray (34). All analyses will be performed based on the intention to treat principle and calculated p-values will be based on two-sided hypothesis tests. P-values less than 0.05 will be considered statistically significant. Statistical analyses will be performed using the SAS version 9.4 software package and packages in R (Version 3.1.1).

Secondary Hypothesis 1: Large fibroid size will limit the effectiveness of LNG-IUS compared with TXA; elevated BMI predicts higher success with LNG-IUS over TXA.

Statistical analysis: The primary event of interest is unsuccessful medical therapy, defined as the intentional discontinuation of treatment due to the desire or need to stop or switch treatment. However, the analysis is complicated by the fact that women in the LNG-IUS have a competing cause of failure, namely expulsion. Since the covariates associated with intentional discontinuation of treatment may be different from those associated with expulsion it will be important to analyze expulsion as a competing risk (35). We will first explore the associations between the covariates of interest and the competing risks by fitting separate Fine-Gray models for each type of failure using the finegray function in the survival package in R. We will also utilize the mstate package in R to further explore these associations. We will also explore whether the factors associated with intentional discontinuation differ between the two treatment arms.

7.3 Subject Population(s) for Analysis

We will analyze all women randomized into the study, regardless of whether they received the study medications as an intention to treat analysis. In addition, we will analyze women who received at least one dose of TXA or had insertion of LNG-IUS, even if there was immediate expulsion.

8 Safety and Adverse Events

Adverse events would include perforation or embedment of the LNG-IUS. Adverse events will be recorded during the study by study coordinators or personnel and resolution of the AE reported, in particular if that required a second surgical procedure to resolve. Allergic reaction to either LNG or TXA will be collected and reported to the IRB per protocol. Worsening anemia or need for blood transfusion would be considered a safety endpoint.

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- surgical intervention for complications
- ectopic pregnancy
- Pelvic inflammatory disease
- Venous thromboembolism

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 9 months after enrollment. Events occurring after this visit will be managed clinically. For women with a contraindication to LNG-IUS (e.g. a type I fibroid), we will recommend removal of the LNG-IUS at the 9-month visit to reduce risks.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if hemoglobin were to drop below 8.0 g/dL during treatment for HMB.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse

event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

AEs that meet the criteria of serious, related to study drug, and unexpected as determined by the PI, qualify for reporting to the regulatory authorities (FDA). The Principal Investigator will assess all SAE's occurring during the study and evaluate for "unexpectedness" and relationship to study drug. The PI should complete and submit a voluntary MedWatch Report for events determined to meet the criteria as serious, study drug related and unexpected to: https://www.accessdata.fda.gov/scripts/medwatch/.

8.4 Stopping Rules

Adverse events and serious adverse events, as defined in Section 8, will be monitored by the study team for patient safety. The study team will review the adverse events and determine if there is significant difference of adverse events and SAEs between the 2 arms. Review will occur frequently and summary of findings will be documented. If there is a clinically and statistically significant difference in adverse event and SAEs, the study team will consider placing the project on hold. IRB will be notified through the IRB electronic system if the study is placed on hold. The study team will formulate an appropriate plan of action to ensure patient safety. Such a plan may include, but is not limited to, protocol modifications, immediate termination of accrual, adjustments in management of previously enrolled participants continuing to undergo study interventions.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Internal Data and Safety Monitoring Plan

We will utilize the Mayo Clinic Department of Surgery Data Safety Monitoring Board (DSMB) for oversight of the study. Adverse events (AE) will be monitored by the study team, who has primary responsibility for attribution of the AE to the study. Events that prompt the activation of the protocol-specific stopping rules will be reviewed by the study team, during which time study accrual may be halted. The team will formulate a plan of action to ensure patient safety and forward the plan to the DSMB. The DSMB will review the action plan and recommend approval or provide recommendations to the IRB. A summary of all AEs will be provided to the DSMB for review and on-going study approval.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

We will keep all of the source data including original records of clinical findings, observations, or other activities in the trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

We will use a study case report form (CRF) as the primary data collection instrument for the study. All data requested on the CRF will be recorded and all missing data explained. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, we will draw a single straight line through the incorrect entry and enter the correct data above it. All such changes will be initialed and dated. We will not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, we will print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, we will include the details to justify the correction.

Data Management

We will use the electronic database REDCap to collect and store study-related data including study case report forms. REDCap is password protected and can be used to export the data to a statistical analysis program such as SAS.

Data Processing

Data will be maintained by the small study staff from the data entry into the REDCap system through the analysis in SAS by our statisticians.

Data Security and Confidentiality

All patient information will be de-identified and kept in secure locations where only authorized study personnel can have access. All computers are password protected and secured behind institution firewall. Case report forms will be maintained, in a secure location within the institution campus.

Data Quality Assurance and Clarification Process

Data will be entered by trained personnel with randomly-selected double entry to evaluate data for errors. Validated fields of entry will ensure data ranges are appropriate. Any data queries will be adjudicated by study personnel after review of the original data form.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for the longer of the following:

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

As a service to the sponsor-investigator, this study may be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

The study will be funded through a grant from the National Institutes of Health.

12.2 Subject Stipends or Payments

Participants will be provided with $50 remuneration at the end of the study as well as parking passes for study-related visits.

13 Publication Plan

We plan on publishing the results of the study in a peer-reviewed journal in OB/GYN specialty. We will register our trial with ClinicalTrials.gov prior to recruitment and enrollment of the first patient.

14 References

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