**Buccal Misoprostol Prior to Myomectomy for Reduction of Intraoperative Blood Loss: A Randomized Placebo-Controlled Trial (NCT02209545)**

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**Study Drug/Study Device:**
Active: Buccal Misoprostol (Cytotec) 400mcg
Placebo: Buccal Pyridoxine (Vitamin B6) 100mg

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**TABLE OF CONTENTS**

**LIST OF ABBREVIATIONS**

EBL- Estimated Blood Loss
Hgb- Hemoglobin
Hct - Hematocrit

**STUDY SUMMARY**

| | |
|---|---|
| Title | Buccal misoprostol prior to either an abdominal and laparoscopic myomectomy for reduction of intraoperative blood loss: a randomized placebo-controlled trial |
| Short Title | Buccal misoprostol prior to either an abdominal and laparoscopic myomectomy |
| Protocol Number | STU00091259 |
| Phase | IV |
| Methodology | Randomized double-blinded placebo-controlled parallel group trial |
| Study Duration | 12 months |
| Study Center(s) | Prentice Women's Hospital, Northwestern Memorial Hospital |
| Objectives | Examine efficacy of buccal misoprostol at reduction in intraoperative blood loss at time of either an abdominal and laparoscopic myomectomy |
| Number of Subjects | 70 |
| Diagnosis and Main Inclusion Criteria | Symptomatic uterine fibroids, desire to retain uterus |
| Study Product(s), Dose, Route, Regimen | Misoprostol 400mcg buccally |
| Duration of administration | 1 hour pre-procedure – At least 4 hours post-procedure |
| Reference therapy | Placebo (100mg Vitamin B6 tablets) |
| Statistical Methodology | Power calculation indicates 35 patients per arm will detect 1 standard deviation difference with 90% power. Fisher's exact test to be used for categorical variables and T test to be used for continuous variables with $P < .05$. |

## 1.0 BACKGROUND AND RATIONALE

### 1.1 Disease Background

Leiomyomata are the most common tumors of the uterus. Though the majority of women with fibroids are asymptomatic, a significant portion suffer symptoms including abnormal bleeding, pain, pressure and abdominal distention (1). Submucosal and large intramural fibroids have also been shown to impair fertility. Many women seek treatment for fibroids but desire to retain their uterus, whether to preserve future fertility or for other personal reasons. Myomectomy is a curative treatment that allows for uterine preservation but can come at the risk of substantial intraoperative blood loss.

Studies have assessed the utility of GnRH, vasopressin, peri-cervical tourniquet, misoprostol and oxytocin, among others, in reducing intraoperative blood loss (2). Findings from small randomized trials demonstrate significantly lower intraoperative blood loss among women who receive preoperative misoprostol compared to those who receive placebo (4, 6, 7). Other research fails to demonstrate a difference in blood loss following preoperative misoprostol (8) and cites methodologic flaws with existing studies (5). Additionally, no randomized controlled trial has been done in a U.S. population. A double-blinded, randomized, placebo-controlled trial at a tertiary care center in a major U.S. city is an ideal setting for evaluation of this research question.

The aim of this study is to assess the impact of preoperative buccal misoprostol on intraoperative blood loss and clinical outcomes related to blood loss (blood transfusion, protracted hospital stay). Defining the relationship between misoprostol and blood loss during myomectomy would provide insight into the mechanism of uterine contraction and hemostasis and inform optimal preoperative clinical management of patients undergoing this common and potentially morbid procedure.

### 1.2 Study Agent(s)/Devices Background and Associated Known Toxicities

Misoprostol is an analogue of prostaglandin E1 initially developed for treatment of NSAID induced peptic ulcers, which is currently used in a variety of contexts in the field of obstetrics and gynecology including in the FDA approved regimen for medical abortion, cervical ripening, and treatment of postpartum hemorrhage. In non-pregnant women, misoprostol has been widely described for use in cervical preparation prior to hysteroscopy, intrauterine device insertion, and endometrial biopsy.

Multiple routes of administration have been studied including oral, sublingual or buccal, rectal and vaginal administration with peak plasma concentrations less than 30 minutes after administration via the oral or sublingual route. Systemic bioavailablity of sublingual misoprostol is significantly greater than with orally or vaginally administered misoprostol however overall plasma concentrations persist for at least 6 hours at higher concentrations when administered vaginally. Potent uterotonic activity is noted as a result of increased intracellular calcium activating myosin light-chain kinase.

Adverse effects of misoprostol vary and include abnormal vaginal bleeding, lower abdominal pain and cramping, fever or shivering, nausea, vomiting and diarrhea with more uterine cramping and vaginal bleeding associated with vaginal administration (3).

Prior studies evaluating misoprostol effect on intraoperative blood loss at time of either an abdominal and laparoscopic myomectomy have used a single dose of 400mcg misoprostol administered vaginally or rectally pre-procedure and have found a significant decrease in blood loss. 400mcg is the standard dose used for the majority of gynecologic applications and appears to be well tolerated (4-9). There are no additional risks to study participants adding laparoscopic surgery to this study.

### 1.3 Other Agents/Devices

Placebo will be 100mg vitamin B6 (pyridoxine) tablets (see Section 8.2).

### 1.4 Rationale

Abdominal myomectomy is a common procedure that comes with risks of significant morbidity, including intraoperative blood loss at time of abdominal myomectomy as well as numerous postoperative complications including an up to 20% requirement for transfusion and 2% reported conversion to hysterectomy. The significant morbidity associated with this procedure has led to studies evaluating multiple interventions to reducing bleeding during myomectomy. A systematic review of the interventions to reduce blood loss at time of myomectomy found significant reductions in blood loss with use of vaginal misoprostol however included only one randomized controlled trial (2). Since this time, other studies have been done that reproduce these findings (6, 7), though sample size in these trials is small and results are inconsistent (8). This study would augment existing data by employing a larger sample size and double-blinded design in a U.S. population. This study would also assess the impact of a route of misoprostol administration that is less invasive for patients (buccal instead of vaginal or rectal) but offers a similar pharmokinetic profile. Outcomes assessed include estimated blood loss, need for transfusion, prolonged hospitalization, change in postoperative hemoglobin level from preoperative baseline.

### 1.5 Correlative Studies n/a

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Objectives

2.1.1 To determine the effect of 400mcg buccal misoprostol at least one hour pre-procedure on intraoperative blood loss at time of either an abdominal or laparoscopic myomectomy.

### 2.2 Secondary Objectives

2.2.1 To determine the effect of 400mcg buccal misoprostol at least one hour pre-procedure on the need for blood transfusion during or in post-operative course for either an abdominal or laparoscopic myomectomy

2.2.2 To determine the effect of 400mcg buccal misoprostol at least one hour pre-procedure on post-operative fever after either an abdominal or laparoscopic myomectomy.

2.2.3 To determine the incidence of adverse effects, if any, of 400mcg buccal misoprostol at least one hour prior to either an abdominal or laparoscopic myomectomy.

### 2.3 Exploratory Objectives n/a

### 2.4 Endpoints

Estimated blood loss as determined by anesthesia and surgeon at time of abdominal or laparoscopic myomectomy, difference between post-operative and pre-operative hemoglobin, post-operative temperature, and overall length of hospital admission.

## 3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

### 3.1 Inclusion Criteria

3.1.1 Patients presenting for either an abdominal and myomectomy with documented uterine fibroids on pelvic imaging (pelvic ultrasound or MRI) within in last 12 months

3.1.2 Age ≥ 18 years and ≤ 50 years.

3.1.3 Pre-operative hemoglobin >8 g/dl.

3.1.4 Willing to have buccal administration of misoprostol or a placebo at least one hour pre-procedure.

3.1.5 Ability to understand and the willingness to sign a written informed consent.

3.1.6 Admissible medical/surgical history.
a. Can be previously treated with Depo-Lupron, Depo-Provera, or Oral Contraceptive pills
b. Intraoperative use of vasopressin and uterine tourniquet is permissible
c. Can have had prior Cesarean delivery

### 3.2 Exclusion Criteria

3.2.1 Pregnancy. All patients will be required to have a negative urine pregnancy test prior to enrollment.

3.2.2. Patients who have had a prior abdominal myomectomy.

3.2.3 Post-menopausal women.

3.2.4 Patients with known bleeding/clotting disorders.

3.2.5 Patients with a history of gynecologic malignancy.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to misoprostol.

3.2.7 Any cases converted to abdominal hysterectomy orother additional elective surgical procedures performed at time of abdominal or laparoscopic myomectomy will be excluded from data analysis.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

## 4.0 TREATMENT PLAN

### 4.1 Treatment Dosage and Administration

4.1.1 400mcg misoprostol or 100mg vitamin B6 placebo administered buccally at least one hour prior to procedure.

### 4.2 Toxicities and Dosing Delays/Dose Modifications

Given this is a one-time dosing, toxicities will be limited to the immediate intervention period. Any patient who receives treatment on this protocol will be evaluable for toxicity for the entire duration of action of this

medication.

According to published research, serum levels of misoprostol nadir 6 hours following administration and the duration of pharmacologic action is considered to be only 3 hours (3,5). All patients are hospitalized following abdominal myomectomy and laparoscopic such that all patients will be monitored as inpatients for a minimum of 4 hours post-operatively.

### 4.3 Concomitant Medications/Treatments

None.

### 4.4 Other Modalities or Procedures

None.

### 4.5 Duration of Therapy

Pre-operative administration of misoprostol or pyridoxine placebo.

### 4.6 Duration of Follow Up

Patients will be followed for the duration of their hospital admission following abdominal or laparoscopic myomectomy. Patients will be required to stay a minimum of 4 hours post-surgery. Blood will be drawn right before patient leaves the hospital, post operatively.

### 4.7 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. The principal investigator will be notified of any and all patients removed from therapy and the reason for study removal and date the patient was removed will be documented in the Case Report Form. The patient will be followed-up per protocol.

### 4.8 Patient Replacement

If a patient is removed from the study, an additional patient may be enrolled and randomized to replace them.

## 5.0 STUDY PROCEDURES

### 5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within ninety days of registration unless otherwise stated. The screening procedures include:

#### 5.1.1 Informed Consent

Will be obtained for all potentially eligible participants. Please see attached Informed Consent documents, including eConsent, which will be sent through REDCap.

#### 5.1.2 Medical history

Complete medical, surgical, gynecologic and obstetrical history, medications, allergies, social and family history including and history of prior myomectomy and personal or family history of blood dyscrasias,

coagulopathy and bleeding disorders.

**5.1.3 Demographics**

Age, gender, race, ethnicity, gravidity, parity.

**5.1.4 Review subject eligibility criteria**

Refer to section 3.0.

**5.1.5 Review previous and concomitant medications**

**5.1.6 Physical exam including vital signs, height and weight**

Vital signs (temperature, pulse, respirations, blood pressure), height, weight.

**5.1.7 Adverse event assessment**

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

**5.1.8 Baseline Hemoglobin**

Baseline serum hemoglobin will be determined for all patients.

**5.1.9 Pregnancy test** (for reproductive age females)

See section 3.1.6.1 for definition.

**5.1.10 Other**

*Note: Aside from signing of informed consent, all of the above information will be garnered from existent medical records. No additional physical examination, history taking or laboratory testing will be required of study participants.

**5.2 Procedures During Treatment**

Administration of 400mcg Misoprostol or 100mg Pyridoxine (placebo).

**5.3 Follow-up Procedures**

None.

**5.4 Removal of Subjects from Study**

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

**5.5.1** Patient voluntarily withdraws from treatment (follow-up permitted);

**5.5.2** Patient withdraws consent (termination of treatment and follow-up);

**5.5.3** Patient is unable to comply with protocol requirements;

**5.5.4** Patient experiences toxicity that makes continuation in the protocol unsafe;

**5.5.5** Treating physician judges continuation on the study would not be in the patient's best interest;

**5.5.6** Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

**5.5.7** Lost to follow-up. If a research subject decides against undergoing abdominal or laparoscopic myomectomy and/or surgical case is cancelled after receiving misoprostol or placebo, the

subject may be considered lost to follow-up.

### 6.0 Response Criteria

Clinically-documented intraoperative blood loss.

### 6.1 Safety/Tolerability

All patients will be closely monitored by physician and nursing staff in the operating room and post-operative recovery area for the full duration of action of the active medication. Misoprostol is largely considered a safe, well-studied medication (10). The risk profile may be even more favorable when a single dose of misoprostol is administered (11).

The placebo medication, pyridoxine (Vitamin B6), is a safe nutritional supplement with no known side effects of a one-time dose. Additionally, it is absorbed in the jejunum such that absorption when buccally administered (12).

## 7.0 ADVERSE EVENTS

### 7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information. The following information is taken from the FDA website (10).

#### 7.1.1 Contraindications

Pregnancy, history of allergy to prostaglandins or Vitamin B6.

#### 7.1.2 Special Warnings and Precautions for Use

In pregnant women, cytotec can cause birth defects, abortion or premature birth. Uterine rupture has been reported when cytotec has been administered to pregnant women to induce labor or to induce abortion beyond the 8th week of pregnancy. Patients should be advised that cytotec should not be given to others due to its abortifacient properties.

Cytotec may be prescribed if the patient:
• has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
• is capable of complying with effective contraceptive measures.
• has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
• will begin Cytotec only on the second or third day of the next normal menstrual period.

WARNING for off-label uses:
For hospital use only if misoprostol were to be used for cervical ripening, induction of labor, or for the treatment of serious post-partum hemorrhage, which are outside of the approved indication.

#### 7.1.3 Interaction with other medications

Misoprostol is a renally-cleared medication and does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals.

Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant. Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours

apart. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in thetherapeutic range.

### 7.1.4 Adverse Reactions

The FDA reports the following possible side effects with the active medication (Misoprostol):

Gastrointestinal: In subjects receiving Cytotec 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14-40% and in all studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo.

Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported.

Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed.

Gynecological: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. Research studies in obstetrics and gynecology also identify possible side effects of diarrhea, fever and shivering (4,6,7).

Elderly: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence, (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded:
Body as a whole: aches/pains, asthenia, fatigue, fever, rigors, weight changes.
Skin: rash, dermatitis, alopecia, pallor, breast pain.
Special senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.
Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.
Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.
Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.
Hypersensitivity: anaphylaxis
Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.
Genitourinary: polyuria, dysuria, hematuria, urinary tract infection.
Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.
Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.
Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

## 7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- Ø the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- Ø any abnormal laboratory values have returned to baseline;
- Ø there is a satisfactory explanation other than the study drug for the changes observed; or
- Ø death.

## 7.3 Definitions

### 7.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

### 7.3.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

### 7.3.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

**7.3.3.1** Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

**7.3.3.2** Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

**7.3.3.3** Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

**7.3.3.4** Results in persistent or significant disability or incapacity.

**7.3.3.5** Is a congenital anomaly/birth defect

**7.3.3.6** Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

## 7.4 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

## 7.5 Reporting Requirements for Adverse Events

### 7.5.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The office of Risk Management and the IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

Insert your local requirements below:

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.

2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.

3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.

6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

- For IND/IDE trials: The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

### 7.5.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

### 7.6 Unblinding Procedures

Unblinding to occur in the case of serious morbidity or life-threatening illness that may be reasonably attributable to administration of misoprostol, including but not limited to admission to the intensive care unit, hyperpyrexia and repeated or high-grade fevers. While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study therapy is necessary to ensure a subject's safety.

### 7.7 Stopping Rules

This study involves a one-time pre-operative intervention prior to a planned surgical procedure. If a patient develops immediate, intolerable side effects including but limited to emesis, diarrhea, or heavy vaginal bleeding following buccal administration of misoprostol or placebo, therapy will be discontinued.

## 8.0 DRUG/DEVICE INFORMATION

### 8.1 Agent/Device: Misoprostol

- Other names for the drug(s)/device: Cytotec
- Classification - type of agent/device: medication, synthetic Prostaglandin E1 analogue
- Mode of action: Production of uterine contractions
- Storage and stability: Store at or below 25°C (77°F), in a dry area.

· Protocol dose: 400mcg

· Preparation: Tablet

· Route of administration for this study: Buccally, 200mcg on each side

· Incompatibilities: Pregnancy, history of adverse reaction to prostaglandins

· Availability: Commercially available

· Side effects: A brief summary of the adverse events most likely to occur in this study and associated with this agent should be inserted here. Refer the reader to the agent's package insert or Section 7.1 above for a comprehensive list of adverse events.
· Nursing implications: Ensure patient has a negative pregnancy test and confirm list of allergies prior to providing the medication. Day of surgery urine pregnancy testing and verbal confirmation of a patient's allergies are both standard of care practices for reproductive age women undergoing surgery.

**8.2 Agent/Device:** Vitamin B6

· Other names for the drug(s)/device: Pyroxidine

· Classification - type of agent/device: medication, synthetic vitamin

· Mode of action: Vitamin B6 in coenzyme forms performs a wide variety of functions in the body and is extremely versatile, with involvement in more than 100 enzyme reactions, mostly concerned with protein metabolism (12).

· Storage and stability: Store at or below 25°C (77°F), in a dry area.

· Protocol dose: 100mg

· Preparation: Tablet

· Route of administration for this study: Buccally,50 mg on each side

· Incompatibilities: none

· Availability: Commercially available

· Side effects: none

· Nursing implications: none

**8.1.1 Return and Retention of Study Drug/Device**
Active medication will be purchased on a case by case basis from NMH inpatient research pharmacy such that excess misoprostol is not anticipated. In the event of access active medication, this will be disposed per pharmacy protocol.

**8.1.2**
Compliance with administration will be documented by pre-operative nursing staff.

**9.0 CORRELATIVES/SPECIAL STUDIES**
N/A.

## 10.0 STATISTICAL CONSIDERATIONS

### 10.1 Study Design/Study Endpoints

This is a double blinded randomized, controlled trial of women undergoing either an abdominal and laparoscopic myomectomy at a single university-affiliated tertiary care center. Women ages 18-50 years of age with clinically documented, sonographic evidence of uterine fibroids being scheduled for abdominal myomectomy were eligible for inclusion. Eligible participants will be randomized to receive preoperative 400cg buccal misoprostol or placebo on the basis of total fibroid volume, location (intramural or subserosal) and parity. Stratification by fibroid volume (or fibroid size) will be performed prior to randomization. Fibroid volume is defined as the cumulative volume of intramural and subserosal fibroids as measured on preoperative magnetic resonance imaging (MRI), or in the instance of patient contraindication to MRI, transvaginal ultrasound (TVUS). The data collection sheet (addendum) and chart of study variables below include definition of this variable and allow for ease of recording and tracking of this variable in our study database. Women with a history of gynecologic malignancy, critical anemia or blood dyscrasias and those with a history of prior myomectomies will be excluded.

List of Study Variables to be Collected:

| **Outcomes** | **Type** | **Definition** |
|---|---|---|
| Estimated blood loss | Continuous | Intraoperative blood loss as estimated by intra-operative anesthesiologists and surgeons. |
| % drop in Hgb | Continuous | Ratio of the drop in hemoglobin over the starting hemoglobin ($Hg_{post\text{-}op} – Hg_{pre\text{-}op}$)/ $Hg_{pre\text{-}op}$ |
| Duration of hospital stay (days) | Continuous | Number of days inpatient following abdominal myomectomy. |
| Duration of procedure (minutes) | Continuous | Number of days inpatient following abdominal myomectomy. |
| Post-op fever | Dichotomous | If patient has one Temperature >101.4 or two temperatures >100.4, then yes.<br>If not then no. |
| Adverse reaction to misoprostol | Dichotomous | If patient experiences vaginal bleeding, vomiting or diarrhea then yes.<br>If not then no. |

| **Exposures** | **Type** | **Definition** |
|---|---|---|
| Pre-op Misoprostol | Dichotomous | If women randomized to receive misoprostol, then yes.<br>If women randomized to placebo, then no. |

| **Covariates** | **Type** | **Definition** |
|---|---|---|
| Woman's Age | Continuous | Female age in years at time of abdominal myomectomy |
| Volume of fibroids (pre-op) | Continuous | Cumulative volume of intramural and subserosal fibroids based on preoperative imaging<br>Will be used for stratification and randomization. |

| | | |
|---|---|---|
| Mass of fibroids (post-op) | Continuous | Cumulative mass of intramural and subserosal fibroids based on pathology reports<br>-Will be used to account for variability in final models. |
| Pre-treatment with Lupron, Depo-provera, OCPs | Dichotomous | Pre-operative treatment with Lupron, Depo-provera or OCP's |
| Intraoperative treatment with vasopressin or tourniquet | Dichotomous | Use of intraoperative vasopressin or tourniquet during myomectomy. |

| **Other** | **Type** | **Definition** | **Use** |
|---|---|---|---|
| Uterus size in weeks gestation | Ordinal | Uterus size in weeks gestation per pre-operative physical exam | Table 1 characteristic |
| History of Gynecologic Malignancy | Dichotomous | If history of gynecologic cancer (uterine, ovarian or cervical cancer), then yes.<br>If not, then no. | Exclude if yes. |
| Uterine Anomaly | Dichotomous | If septate, unicornuate or bicornuate uterus, then yes.<br>If abnormality is less severe than arcuate uterus or normal then no. | Exclude if yes. |
| Prior Cesarean Section Cycle | Dichotomous | If prior Cesarean delivery, then yes.<br>If no prior Cesarean delivery, then no. | Table 1 characteristic, stratum-specific sub-analyses |
| Gravidity | Count | Number of prior pregnancies | Table 1 population characteristic |
| Gravid | Dichotomous | If number of pregnancies is 1+, then yes<br>If number of pregnancies is 0, then no | Table 1 characteristic, stratum-specific sub-analyses |
| Parity | Count | Number of prior pregnancies | Table 1 population characteristic |
| Living children | Count | Number of living children | Table 1 characteristic |
| Woman's Age (SART categories) | Categorical | Group by age in years at abdominal myomectomy:<br><30<br>30-34<br>35-37<br>38-39<br>40-42<br>43+ | Table 1 population characteristic |
| Race | Categorical | Group by race: White, Black/Africa-American, Hispanic, Asian/Pacific | Table 1 population characteristic |

| | | | |
|---|---|---|---|
| | | Islander, American Indian/Alaskan Native, Middle-Eastern | |

**10.2 Sample Size and Accrual**

Power calculation based on the standard deviation in published reports (5) demonstrates that enrollment of 25 participants per arm is necessary to detect 1 standard deviation difference with 90% power. Further, published results from pilot studies in this population (7) and demonstrates that enrollment of 25 participants per arm is necessary to detect 0.5g/dL difference in hemoglobin with 90% power.

Prentice Women's Hospital of Northwestern Memorial performed over 100 abdominal myomectomies in 2013. Across a year-long study period, we anticipate identifying a minimum of 70 patients to evaluate our primary hypothesis. We have increased our sample size from 50 to 70 to account for the 9 participants that were either consented by a non-study team member, did not get the study drug due to an error at pharmacy or left the hospital after surgery thus we could not obtain a POD 1 which is needed for data analysis.

Following data collection from at least 20 participants in each arm, standard deviation calculations will be performed to confirm that the standard deviations in our sample population is similar. Power calculation will be repeated using the standard deviations in our active and placebo groups and additional participants will be enrolled as needed to achieve adequate power to evaluate our primary outcome of intraoperative blood loss.

**10.3 Data Analyses Plans**

To determine whether women who take a pre-operative dose of misoprostol experince lower blood loss during abdominal myomectomy compared to matched controls who take placebo, we will perform linear regression. We will use this model to assess for the role of numerous covariates, including gravidity, parity and age. Secondary outcomes of percent hemoglobin drop, duration of procedure and length of inpatient hospitalization will be assessed using the T test and further evaluated with multivariate-adjusted linear regression where appropriate. The need for post-operative blood transfusion between groups will be assessed with the Chi-square (Fischer's exact) test. The role of numerous potential covariates will be assessed with Chi-square (Fischer's exact) test for dichotomous variables and T test for continuous variables with $p < 0.05$.

## 11.0 STUDY MANAGEMENT

### 11.1 Conflict of Interest

None to disclosure. All investigators will follow the University conflict of interest policy.

### 11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient

understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form will be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Patients who have their pre-op appointment via telehealth calls will also be able to consent as participants using an eConsent form through the secure Northwestern University REDCap. They will be contacted during or after their pre-op appointment by the research coordinator to discuss the study. The research coordinator will consent the patient over the phone and leave time to answer any questions they have about participating in the study before sending the econsent form through REDCap.

## 11.2 Registration Procedures

N/A.

## 11.3 Data Management and Monitoring/Auditing

N/A.

## 11.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

### 11.4.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

### 11.4.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

### 11.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

### 11.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

### 11.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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## 13.0 APPENDICES

13.1
Data Collection Sheet (see attached)