PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

A comparison of oral misoprostol versus vaginal misoprostol for cervical ripening and induction of labor

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2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
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University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

To study if misoprostol administered orally is at least as effective as misoprostol administered vaginally for cervical ripening and the induction of labor. The main purpose is to show that oral misoprostol administration is non-inferior to vaginal misoprostol administration with respect to the time interval from misoprostol administration to onset of active phase of labor.

1.2 Primary Study Endpoints

The primary endpoint will be the time interval from administration of misoprostol to active phase of labor (greater than or equal to 6 cm dilation).

1.3 Secondary Study Endpoints

1. Time interval from administration of misoprostol to initiation of oxytocin for continued augmentation of labor
2. Time interval from administration of misoprostol to vaginal delivery
3. Cesarean section rate
4. Rate of vaginal delivery within 24 hours
5. Rate of abandoning misoprostol for cervical ripening and switching to mechanical dilation for cervical ripening (ie, Foley balloon)
6. Rate of development of preeclampsia requiring magnesium sulfate administration
7. Rate of tachysystole
8. Rate of tachysystole causing non-reassuring fetal heart tones
9. Rate of need for tocolysis
10. Rate of chorioamnionitis
11. Rate of meconium stained fluid
12. Neonatal morbidity (composite outcome)
    a. Apgar of less than 7 at 5 minutes
    b. Fetal arterial umbilical cord gas with pH of less than 7 or base deficit great than 12
    c. NICU admission within 4 hours of delivery
13. Maternal side effects
    a. Rate of anti-emetic use
    b. Rate of diarrhea
14. Treatment emergent serious adverse events
    a. Uterine rupture
    b. Cesarean hysterectomy
    c. Maternal death during her hospitalization
    d. Neonatal death (0-28 days of life) related to the study drug
15. Adverse events
    a. Postpartum hemorrhage requiring blood transfusion
    b. Maternal surgical ICU admission
    c. Neonatal NICU admission during mother's hospital admission

2.0 Background

2.1 Scientific Background and Gaps

There has always been a push to shorten the time interval a patient is on Labor and Delivery due to the added cost and resources that a patient needs in this setting. Methods used to shorten the time interval on Labor and Delivery need to remain safe, effective, and avoid raising the rate of cesarean delivery. One of the main reasons patients are on the Labor and Delivery unit for extended periods of time is for cervical ripening and induction of labor. Many methods have been studied to shorten the time of latent phase of labor which is normally the longest portion of the induction of labor. A standard method of

cervical ripening and induction of labor is to use misoprostol administered vaginally every 4 hours. Misoprostol was originally approved by the FDA for reducing the risk of NSAID induced gastric ulcers. It does have a black box warning against its use in pregnancy, but then in 2002 had a new label stating its use during pregnancy for cervical ripening and induction of labor. [1] The American Congress of Obstetricians and Gynecologists (ACOG) have also supported the use of misoprostol that it is a safe and effective form of cervical ripening and induction of labor. [2] Misoprostol administered vaginally can have its downfalls due to requiring increased demands on the licensed provider (physician or midwife) to be present to administer the drug, increased amount of vaginal exams that may lead to increased rate of ascending infection, and inconsistency of dosing due to proper placement and use of lubricant, water, or no lubricant upon placement. [3] Since misoprostol administered orally has been proven safe, it may be an effective route of cervical ripening and induction of labor that requires fewer demands on the licensed provider and greater satisfaction for the patient when compared to misoprostol administered vaginally.

2.2 Previous Data

The Cochrane review of "Oral misoprostol for induction of labour" stated that misoprostol administered orally was more effective than placebo, as effective as vaginal misoprostol, and fewer cesarean sections than vaginal dinoprostone or oxytocin. [3] The article stated that more randomized trials are needed, but their optimal dosage of oral misoprostol is 20 to 25 mcg administered in solution every 2 hours. The WHO in 2013 also recommended misoprostol be administered 25 mcg orally every 2 hours for induction of labor. [4] There are multiple studies that look at the oral misoprostol administered as 50 mcg every 4 hours and oral misoprostol as a titration given every 1 hour, but no studies have been reported yet on the oral misoprostol administration of 25 mcg every 2 hours. There is also a pharmacokinetics study of misoprostol with oral versus vaginal administration that showed plasma levels of misoprostol fall sharply after 2 hours when administered orally while the peak plasma levels are sustained for up to 4 hours when administered vaginally. [5] Using the pharmacokinetics data, the oral misoprostol treatment arm will be dosed more frequently than the vaginal misoprostol treatment arm to maintain plasma levels of misoprostol throughout the study period.

2.3 Study Rationale

To show that misoprostol administered orally is at least as effective as misoprostol administered vaginally for cervical ripening and induction of labor, since it is not commonly used at Hershey Medical Center, it can be utilized to lessen the burden on licensed practitioners, decrease infection rate from less vaginal exams, increase patient satisfaction due to less vaginal exams, and test the dosing the oral misoprostol that the Cochrane review and WHO suggest.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Pregnant Female Patients greater than or equal to 18 years of age
2. Induction of labor for a single live intrauterine pregnancy
    a. For medical indications for induction of labor, must be greater than or equal to 37 weeks gestational age and meet one of the following criteria for the induction of labor (taken from ACOG Practice Bulletin Number 107) [2]
        i. Abruptio placentae
        ii. Chorioamnionitis
        iii. Gestational hypertension
        iv. Late term (≥41 weeks) or postterm (≥42 weeks) pregnancy
        v. Maternal medical conditions (eg, diabetes mellitus, renal disease, chronic pulmonary disease, chronic hypertension, antiphospholipid syndrome)
        vi. Fetal compromise (eg, isoimmunization, oligohydramnios)

b. For elective inductions of labor that do not meet the above medical indications, must be greater than or equal to 39 weeks gestational age and meet one of the following criteria.
    i. Ultrasound measurement at less than 20 weeks of gestation supporting gestational age of 39 weeks or greater
    ii. Fetal heart tones documented as present for 30 weeks by Doppler ultrasonography
    iii. 36 weeks since positive serum or urine human chorionic gonadotropin pregnancy test result
    iv. Documented fetal lung maturity
3. Cephalic presentation
4. 20 minute reassuring fetal heart rate (reactive nonstress test (NST))
5. Bishop score based on sterile vaginal exam of less than or equal to 6, for which the cervical dilation is less than or equal to 2 cm.
6. Equal to 3 or less uterine contractions over 10 minutes

3.2 Exclusion Criteria

1. Previous uterine scar from either prior cesarean section or major uterine surgery
2. Contraindication to vaginal delivery
3. Patients with preeclampsia
4. Premature rupture of membranes
5. Suspected intrauterine fetal growth restriction
6. Fetal anomalies
7. Grand multiparity – greater than or equal to 5 live births or stillbirths (greater than or equal to 20 weeks of gestation)
8. Contraindication to misoprostol (history of allergy to prostaglandins, glaucoma)

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Individual subjects who desire to be withdrawn from the study or who withdraw their consent to be in the study at any time will be removed from the study and continue their care in a routine fashion. If the patient experiences an unexpected allergic reaction to the study drug (evidenced by hives, rash, swelling, or difficulty breathing), the patient will be immediately withdrawn from study participation and will no longer receive the study drug. If the patient experiences a serious adverse event (uterine rupture) while taking study drug, she will be removed from the study and no longer receive study drug. Any serious adverse event that occurs after delivery (maternal death during hospitalization, neonatal death during hospitalization, cesarean hysterectomy) does not warrant removal from study since study drug would already be terminated.

3.3.2 Follow-up for withdrawn subjects

Withdrawn subject's data can still be obtained from the subject's chart and incorporated into the data analysis. Subjects who have withdrawn from the study will still have their routine follow-up with their physician.

4.0 Recruitment Methods

4.1 Identification of subjects

When scheduling any term induction of labor in the office, patients can be approached as potential subjects for the study. Offices would include the Women's Health Division at Hope Drive, Camp Hill, Nyes Road, and Mt. Joy along with Maternal Fetal Medicine Department. Also, when on Labor and Delivery term patients coming in for induction of labor can be approached as potential subjects. Patients will be identified by the physicians.

4.2 Recruitment process

Patients will be recruited by physicians that are involved in this study. They will be notified of the study in the office when their induction of labor is scheduled or on Labor and Delivery when they arrive for their induction of labor. While on Labor and Delivery potential subjects must have a Bishop score of less than or equal to 6 and adequate fetal heart rate testing. They will be counseled by the physician about methods of cervical ripening and induction of labor. After potential subjects meet all inclusion/exclusion criteria, they can then be offered to be in this research study.

4.3 Recruitment materials

If subjects meet the inclusion/exclusion criteria they will be offered to be in this research study and will receive a copy of the consent form to review. A flyer and/or PowerPoint slide will be posted in the offices and Labor and Delivery to notify physicians and advance practitioners of potential subjects for the study. The flyer and PowerPoint slide are for faculty and staff only and not patient handouts.

4.4 Eligibility/screening of subjects

If a woman is interested in participating in the study, all procedures will be explained to her before she signs consent. Interested women will be screened for eligibility based on the inclusion/exclusion criteria and will be given the opportunity to ask any questions about the study.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Informed consent will be obtained on the Labor and Delivery Unit at the time prior to the subject's induction of labor.

5.1.1.2 Coercion or Undue Influence during Consent

All methods of cervical ripening and induction of labor must be explained to the patient prior to signing the consent form. Vaginal misoprostol has been shown to have less use of epidural analgesia, more vaginal deliveries in 24 hours, and higher rate of uterine tachysystole as compared to dinoprostone gel or oxytocin. [6] Mechanical ripening with Foley catheter showed no difference when compared to dinoprostone gel. [2] The use of vaginal misoprostol has been associated with higher rates of uterine tachysystole and a Foley catheter has been associated with the lowest rate of uterine tachysystole. [7] Oral misoprostol has been shown to have the lowest rate of cesarean section. [3, 7, 8] Along with that oral misoprostol has been shown to have added safety benefits in a reduction in Apgar score of less than 7 at five minutes and reduced uterine tachysytole when compared with vaginal misoprostol. [6]

Additionally, patients will be informed verbally and in writing that participation in the study is voluntary and they may withdraw from the study at any time. Whether or not patients agree to participate in this study, it will not affect their labor and delivery options available to them.

5.1.2 Waiver or alteration of the informed consent requirement

Waiver of informed consent requested for screening/recruitment purposes only.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written consent will be obtained prior to subject's enrollment. The physician will review the consent form with the subject and ensure that the subject thoroughly understands the study and allows adequate time for the patient to review the consent. The patient and physician will sign and date the consent form on Labor and Delivery at Hershey Medical Center prior to their induction of labor. The patient will then receive a signed and dated copy of the consent and then the consent form will be stored in a doubly locked Maternal Fetal Medicine office to prevent unauthorized access to patient information.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

N/A

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

The inclusion of non-English speaking participants is not planned.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Patient's already sign consent for medical treatment and possible cesarean section, which is standard upon admission into the Labor and Delivery Unit. If these patients are able to sign and understand the consent upon admission to Labor and Delivery, then they have adequate decision making ability to be included in this study.

5.3.2.2 Adults Unable To Consent

If subjects are unable to perform informed consent they will not be included in the study, including those than cannot read or write.

5.3.2.3 Assent of Adults Unable to Consent

Assent will not be required in this study. Only subjects who are able to consent will be included.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

N/A

5.3.3.2 Assent of subjects who are not yet adults

N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Identifiers will include medical record number, patient name, and date of birth. Data will be stored in a secure web application as outlined below. Data will be de-identified with removal of PHI when abstracted and stored on a secure server for statistical analysis.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Without PHI it would be impossible to identify patients who would be eligible for this study.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Without access to the subject's medical record it would be impossible to perform collection of data for this prospective randomized study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Non-inferiority, prospective, open-label, randomized controlled trial.

Subjects included in the study will be randomized to receive misoprostol for cervical ripening and labor induction either orally or vaginally.

In the oral misoprostol group, subjects will receive misoprostol 25 mcg PO every 2 hours (range 2-3 hours). Misoprostol will be administered by the nurse with a sip of water.
In the vaginal misoprostol group, subjects will receive misoprostol 25 mcg vaginally every 4 hours (range 4-5 hours). The physician will place the misoprostol 25 mcg per vagina in the posterior fornix of the vagina with minimal sterile gel for lubricant, usually requiring less than ½ packet of sterile gel.

For redosing for both groups, subject can receive repeat dosing if there are 3 or fewer contractions per 10 minutes and a Category I fetal heart rate tracing.

In the oral misoprostol group, redosing will be considered 2 hours (range 2-3 hours) after a dose of oral misoprostol was given. At the time of evaluation if there are 3 or fewer contractions per 10 minutes and a Category I fetal heart rate tracing, an oral misoprostol dose will be given. If at the time of evaluation there are 4 or more contractions per 10 minute or a Category II fetal heart rate tracing, the provider will wait 2 hours (range 2-3 hours) to reassess if redosing is appropriate. If there is a Category II fetal heart rate tracing and the provider is uncomfortable waiting to reassess, they may proceed with clinical management per the primary team and if deemed appropriate, reassess in two hours. Then upon the reassessment it would be 4 hours since the last oral misoprostol dose and a vaginal exam may occur as part of the assessment for redosing. If at the reassessment for a second time in a row there is a Category II fetal heart rate tracing and misoprostol cannot be given, the protocol can be abandoned and the provider can proceed with induction of labor and/or delivery as they see fit based on their medical judgement. If reassessing for the second time in a row with failure to give a dose of oral misoprostol due to greater than or equal to 4 contractions in 10 minutes, provider may stop misoprostol protocol and transition to oxytocin and titrate up per protocol. Vaginal exams will be timed appropriately to be at every 4 hours (range 4-5 hours) when reassessing oral misoprostol dose.

In the vaginal misoprostol group, redosing will be considered 4 hours (range 4-5 hours) after a dose of vaginal misoprostol was given. At the time of evaluation if there are 3 or fewer contractions per 10 minutes, a Category I fetal heart rate tracing, and a Bishop score of less than 8 or cervical exam less than 4 cm, a vaginal misoprostol dose will be given. At the time of evaluation if there are 4 or more contractions per 10 minutes or a Category II fetal heart rate tracing, redosing will be withheld and reassessed in 2 hours (range 2-3 hours). If there is a Category II fetal heart rate tracing and the provider is uncomfortable waiting to reassess, they may proceed with clinical management per the primary team and if deemed appropriate, reassess in two hours. Ifat time of reassessment misoprostol is again unable to be given due to a Category II fetal heart rate tracing, the protocol can be abandoned and the provider can proceed with induction of labor and/or delivery as they see fit based on their medical judgement. If market time of reassessment vaginal misoprostol is again unable to be given due to 4 or more contractions per 10 minutes, then the provider may stop the misoprostol protocol and transition to oxytocin and titrate up per protocol. Vaginal exams will occur every 4 hours (range 4-5 hours) after a vaginal misoprostol dose was given.

Redosing will be withheld if the Bishop score is greater than or equal to 8, cervical dilation is greater than or equal to 4 cm, active labor is established, if there is a fetal heart tracing that is Category III, or if the subject has spontaneous rupture of membranes. If any of these criteria are met, misoprostol protocol will be stopped and transitioned to oxytocin as appropriate and titrated up per protocol. If there is a Category III fetal heart tracing, the misoprostol protocol will be stopped, and the clinical management will proceed per the primary team.

Subjects may only have a maximum of 6 doses of misoprostol vaginally for a total of 150 mcg and may only have a maximum of 12 doses of misoprostol orally for a total of 300 mcg.

Active labor is when the cervix is 6 cm or greater in dilation with regular uterine contractions.

Oxytocin should not be administered until 4 hours after the last dose of misoprostol if given vaginally or 2 hours after the last dose of misoprostol if given orally. Oxytocin transition and titration will follow the Penn State Hershey Medical Center oxytocin 30units/500mL lactated ringers solution LOW DOSE Regimen protocol which starts at 2 mUnit/min and titrates up by 2 mUnit/min every 30 minutes.

If the patient has spontaneous rupture of membranes while undergoing misoprostol administration they should be transitioned to oxytocin and not receive another dose of misoprostol. The oxytocin will be titrated per protocol. Artificial rupture of membrane may be up to physician discretion after the initiation of oxytocin.

Mechanical dilation, such as Foley catheter or Cook balloon, is not to be used during the induction of labor, unless the patient has reached 24 hours of cervical ripening with misoprostol and no more doses are available.

7.2 Study Procedures

On Labor and Delivery will have continuous fetal heart rate and tocodynanameter monitoring. During misoprostol administration provider will perform sterile vaginal exams approximately every 4 hours (range 4-5 hours). After misoprostol administration is completed, provider will perform sterile vaginal exams every 2 hours (range 1-3 hours). When the subject reaches active labor of greater than or equal to 6 cm dilated, they will be questioned if they had any diarrhea up to this point and it will be documented if an antiemetic was used. Subject's vital signs will be taken every hour as routine protocol at Hershey Medical Center. It will be noted if there is meconium stained amniotic fluid. Umbilical cord gases will be obtained on every subject.

7.2.1 EXAMPLE: Visit 1 or Day 1 or Pre-test, etc. (format accordingly)

In office when scheduling induction of labor may have sterile vaginal exam to see if patient meets inclusion criteria of Bishop score less than or equal to 6.

7.2.2 EXAMPLE: Visit 2 or Day 2 or Post-test, etc. (format accordingly)

On Labor and Delivery will have continuous fetal heart rate and tocodynanameter monitoring. During misoprostol administration provider will perform sterile vaginal exams every 4 hours (range 4-5 hours). After misoprostol administration is completed, provider will perform sterile vaginal exams every 2 hours (range 1-3 hours). Nurse or provider will document every 2 hours if patient subjectively states they are nauseated or have had diarrhea. Nurse or provider will document the amount of times anti-emetics were administered. Subject's vital signs will be taken every hour as routine protocol at Hershey Medical Center. It will be noted if there is meconium stained amniotic fluid. Umbilical cord gases will be obtained on every subject.

7.3 Duration of Participation

The time it takes for the subject's initiation of induction of labor to delivery of infant.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Misoprostol is currently available in 100 mcg tablets. The 100 mcg tablet will be divided into 4 equal pieces to become a 25 mcg tablet. The 25 mcg tablet will be used for the study. There is a small margin of error in creating an exactly 25 mcg tablet since there are no scores on the 100 mcg tablet. When dividing the 100 mcg tablet into four pieces, if any of the ¼ tablets judged to appear uneven based on weight they will be discharged at time of preparation. To assist in this judgment, pharmacy will weigh 10 tablets of misoprostol to calculate what an average ¼ piece should weigh. If a ¼ tablet weighs 5% greater difference than what it's estimated weight should be, it will be discarded. If all 4 pieces appear appropriately sized they will be used. Misoprostol was originally approved by the FDA for reducing the risk of NSAID induced gastric ulcers. It does have a black box warning against its use in pregnancy, but then in 2002 had a new label stating

its use during pregnancy for cervical ripening and induction of labor. [1] The American Congress of Obstetricians and Gynecologists (ACOG) have also supported the use of misoprostol that it is a safe and effective form of cervical ripening and induction of labor. [2]

7.4.2 Treatment Regimen

Subject with either receive misoprostol 25 mcg by mouth every 2 hours (range 2-3 hours) or misoprostol 25 mcg per vagina every 4 hours (range 4-5 hours). The dosing and protocol for each treatment arm is further described in Section 7.1 Study Design.

7.4.3 Method for Assigning Subject to Treatment Groups

The randomization scheme for this study will use variable-size, random permuted blocks to ensure that the number of participants in each treatment arm is balanced after each set of *B* randomized participants, where *B* is the block size. Furthermore, the randomization will be stratified by whether the participant is nulliparous or multiparous. A randomization order will be made for oral or vaginal misoprostol through REDCap software. After meeting eligibility criteria and being consented for the study, a subject will be ready to be randomized. Team members that have REDCap access with access REDCap to carry out the randomization assignment. If they do not have access, and a fellow team member is present with access to REDCap, the fellow team member will carry out the randomization assignment. If no team member is available with REDCap access the Co-PI will be contacted and will enter the relevant subject information into REDCap and REDCap will return a randomization assignment. The randomization will then be relayed to the study team member to carry out the assigned randomization. If co-PI is not available, the PI (Jaimey Pauli) will be contacted to enter the subject's relevant information into REDCap and receive a randomization assignment. If REDCap is offline and unavailable at the time of randomization, or the co-PI and Jaimey Pauli were not able to be contacted, Investigational Drug Services Pharmacy at Penn State Hershey Medical Center will have randomization assignments on paper as a backup hardcopy in order to randomize a patient.

7.4.4 Subject Compliance Monitoring

When the medication is administered, a registered nurse will administer the oral misoprostol and a physician will administer the vaginal misoprostol, for which both medications will be properly documented as of their time of administration by nursing.

7.4.5 Blinding of the Test Article

There will be no blinding in this study.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The misoprostol tablets will be obtained, prepared, dispensed, returned and destroyed by Investigational Drug Services Pharmacy at Penn State Hershey Medical Center. Misoprostol 100mcg tablets will be purchased from a pharmacy distributor. The Investigational Pharmacy will divide the 100mcg tablet into four pieces under a vertical laminar flow hood and then unit dose the 25mcg ¼ tablets. Each quarter tablet that was produced from the splitting will be weighted and the weight will be recorded. Any ¼ tablets judged to be uneven will be discarded at the time of preparation. To assist in this judgment, pharmacy will weigh 10 tablets of misoprostol to calculate what an average ¼ piece should weigh. If a ¼ tablet weighs 5% greater difference than what it's estimated weight should be, it will be discarded. If all 4 pieces appear appropriately sized they will be used.

7.4.6.2 Storage

Prepared misoprostol doses will be stored at controlled room temperature with other inpatient investigational medications in Penn State Hershey Medical Center Pharmacy. The Investigational Pharmacy will be responsible for maintaining and managing the storage, preparation, dispensation, and destruction of the misoprostol for this study following their standard operating procedures.

7.4.6.3 Preparation and Dispensing

The Investigational Pharmacy will divide the 100mcg misoprostol tablet into four pieces under a hood and then unit dose the 25mcg ¼ tablets. Each quarter tablet that was produced from the splitting will be weighed and the weight will be recorded. Any ¼ tablets judged to be uneven will be discarded at the time of preparation. To assist in this judgment, pharmacy will weigh 10 tablets of misoprostol to calculate what an average ¼ piece should weigh. If a ¼ tablet weighs 5% greater difference than what it's estimated weight should be, it will be discarded. If all 4 pieces appear appropriately sized they will be used. Pharmacy will dispense six ¼ tablets labeled for the specific subject at a time. For subjects randomized to receive oral administration of misoprostol, six additional ¼ tablets may be dispensed as needed. The prepared misoprostol ¼ tablets (=25mcg) will be the same in both administration arms. Randomization ordering will determine whether the subject receives misoprostol orally administered by the registered nurse or vaginally placed by the physician.

7.4.6.4 Return or Destruction of the Test Article

Misoprostol will be dispensed by pharmacy following receipt of a written study order. Any unused tablets will be returned to pharmacy. Pharmacy will be responsible for proper destruction of the product when applicable.

7.4.6.5 Prior and Concomitant Therapy

Any medication therapy that is required by the subject for their medical history or labor course is permitted during the study. If the subject receives magnesium sulfate for seizure prophylaxis due to preeclampsia during their labor course, that subject will be accounted for in an intent to treat analysis.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

A total of 110 subjects will be randomized.

From looking at previous data collected at Penn State Hershey Medical Center, there were about 350 induction of labors using misoprostol over one year's time. Due to inclusion/exclusion criteria it is estimated that only 60% of the induction of labors will qualify for the study. That leaves about 210 patients able to participate in the study. Potentially the study could be completed within six months.

8.2 Sample size determination

With respect to the primary study endpoint of the time interval from administration of misoprostol to active phase of labor (greater than or equal to 6 cm dilation), shorter times are considered better. Based on a previous published data, the mean time interval from vaginal misoprostol administration to active phase of labor was 12.0 hours (standard deviation (SD)=5.9 hours) [9] and the mean time interval from oral misoprostol administration to active phase of labor was 9.9 hours (SD=7.1 hours). [10] Using these standard deviations and a non-inferiority margin of 4 hours, a sample size of 92 patients (46 per group) would provide 80% power to

detect non-inferiority of oral misoprostol compared to vaginal misoprostol with respect to the time interval from administration of misoprostol to active phase of labor using a one-sided Mann-Whitney test having a significance level of 0.025. Factoring in a 15% drop-out rate, our target sample size is 110 subjects.

8.3 Statistical methods

Analyses will invoke an intent-to-treat paradigm, wherein all randomized subjects are included according to their randomized treatment arm, regardless of actual treatment received. Data will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, and percentiles) and frequency statistics (frequencies and percentages) for categorical variables. Univariate and bivariate distributions will be inspected in order to address any missing data, inconsistent responses, outliers, and data entry errors.

The primary study endpoint will be the time interval from administration of misoprostol to active phase of labor (greater than or equal to 6 cm dilation) and shorter time is considered better. The difference between the treatment arms (oral misoprostol – vaginal misoprostol) will be denoted by Δ and the non-inferiority margin will be set to δ=4 hours. Thus to test for non-inferiority of oral misoprostol compared to vaginal misoprostol the null hypothesis is H_o: $\Delta \geq 4$ hours and the alternative hypothesis is H_a: $\Delta < 4$ hours. The distribution of the time interval from administration of misoprostol to active phase of labor (greater than or equal to 6 cm dilation) is expected to be skewed. Therefore, to test for non-inferiority of oral misoprostol compared to vaginal misoprostol with respect to the primary endpoint, a one-sided Mann-Whitney test will be used where the non-inferiority margin will be set to 4 hours. The upper bound of the one-sided 97.5% confidence interval for testing non-inferiority will be constructed using the Mann-Whitney test as described by Rothman et al. [11] If the upper bound of the one-sided 97.5% confidence interval is less than the non-inferiority margin of 4 hours, then the null hypothesis will be rejected. In the event the primary endpoint is normally distributed, a one-sided, two-sample t-test will be utilized to test for non-inferiority with corresponding one-sided 97.5% confidence interval.

As detailed in Section 1.3, there are numerous secondary endpoints for this study. Secondary continuous outcomes (e.g., time interval from administration of misoprostol to initiation of oxytocin for continued augmentation of labor and time interval from administration of misoprostol to vaginal delivery) will be compared between the two treatment groups using a two-sample t-test or Mann-Whitney test, as appropriate, based on the distribution of the outcome. Additionally, as a secondary analysis, Kaplan-Meier survival curves will be constructed for these two time to event outcomes. Secondary categorical outcomes (e.g., Section 1.3 secondary endpoints 3-15 which includes Cesarean section rate and rate of tachysystole) will be compared between the two groups using a chi-square test (or Fisher's exact test if the expected cell counts are small).

While every attempt will be made to collect complete data and prevent participant drop-out, there is the possibility of drop-outs and other missed information. We expect the underlying mechanism of any missing data for this particular study to arise due to data that are missing-at-random (MAR). One reason the MAR assumption is expected for this study is because the two treatment arms are providing the same drug (misoprostol) but via different routes (oral vs. vaginal). The statistical methods and analyses that are planned for the primary and secondary outcomes are appropriate, and provide valid inference, under the MAR assumption. Although not expected for this study, if it appears the MAR assumption is not reasonable then we will use multiple imputation to handle the issue of missing data for analyses.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

This study involves minimal risk to subjects as it involves standard methods for cervical ripening and induction of labor as stated by multiple collaborations including American College of Obstetricians and Gynecologists, Cochrane Review, and World Health Organization. Oversight for the conduct of the study will be provided by the PI, co-PI, and her mentoring team. They will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation in study and that all study procedures and adverse event reporting occur according to the IRB approved protocol.

10.2 Data that are reviewed

Data collection for safety monitoring: Treatment emergent serious adverse events (TESAEs) are defined as uterine rupture, maternal death during her hospitalization, neonatal death (0-28 days of life) related to the study drug, and cesarean hysterectomy, and will be reported to the IRB within 24 hours of occurrence. Other adverse events that will be reviewed include postpartum hemorrhage requiring blood transfusion, surgical ICU admission, and neonatal NICU admission during mother's hospital admission.

10.3 Method of collection of safety information

All TESAEs (uterine rupture, maternal death during her hospitalization, neonatal death (0-28 days of life) related to the study drug, and cesarean hysterectomy) will be documented on study specific case report forms. Co-PI, with Jaimey Pauli as second contact, will be notified immediately to begin process of notifying the IRB within 24 hours if the event is a TESAE.

10.4 Frequency of data collection

Data will be collected as the patient is on Labor and Delivery during the time of study. Collected data should be entered into the REDCap system within one month's time of the subject participating in the study.

10.5 Individuals reviewing the data

The PI, Dr. Jaimey Pauli and Co-Investigator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk:benefit ratio to the IRB immediately. The PI's will be assisted in reviewing the data by Allen Kunselman and Christy Stetter with the Department of Public Health Sciences in the Division of Biostatistics and Bioinformatics.

10.6 Frequency of review of cumulative data

The data between the two study groups will be compared on six month intervals.

10.7 Statistical tests

At six month intervals, the percentage of participants experiencing adverse events will be compared between the two groups using Fisher's exact tests; however, stopping of the study will not be based on statistical significance. The statistical tests will be used as an aid to help inform the PIs of the safety of the study.

10.8 Suspension of research

If the total number of subjects experiencing one or more TESAE (defined as uterine rupture, maternal death during her hospitalization, neonatal death (0-28 days of life) related to the study drug, and cesarean hysterectomy) reaches 5, the trial will be stopped. This reflects a 2.3% prevalence rate (110 subjects with 110 singleton neonates are included in the trial for a prevalence of 5/220 subjects). Or if any two cases of uterine rupture, two cases of maternal death during her hospitalization, or two cases of neonatal death (0-28 days of life) related to the study drug, the trial will be stopped.

11.0 Risks

Subjects may experience nausea and diarrhea, which is a side effect of misoprostol; subjects may have a higher incidence of meconium stained fluid while using misoprostol; uterine tachysystole with or without nonreassuring fetal heart tones; development of chorioamnionitis; need for cesarean section; neonatal morbidity or death. All of these risks are standard risks of labor and delivery should not be any higher incidence due to the study. There is always a discomfort with sterile vaginal exams. As part of the randomization, if the subject is selected to be in the misoprostol administered per vagina, the placement of the medication may cause more discomfort than the subjects that take the medication by mouth.

Side Effects/Risks of Misoprostol:

- Diarrhea: when taking misoprostol 800 mcg daily, trials have shown an incidence of diarrhea of about 13%. In this study you will be not receive more than 300 mcg of misoprostol. [1]
- Use of vaginal misoprostol has a higher rate of uterine contractions, with contractions being more frequent than every 2 minutes when compared with placebo (RR 3.52), dinoprostone gel (RR 1.99), or oxytocin (RR 2.24) for induction of labor. [6] Induction with Foley catheter has a decreased risk of uterine contractions happening greater than every 2 minutes when compared to vaginal misoprostol (RR 0.15). [7]
- Increased risk of meconium staining of amniotic fluid, but no difference in neonatal outcome. [3,6]
- Uterine rupture [1]

Side effects of misoprostol when taken as prescribed for prevention of gastric ulcers that have an incidence greater than 1%, but no difference than placebo. [1]

- Nausea – 3.2%
- Flatulence – 2.9%
- Headache – 2.4%
- Dyspepsia – 2%
- Vomiting – 1.3%
- Constipation – 1.1%

There is a risk, as with any medication, of an unexpected allergic reaction to the study drug (defined as the development of hives, rash, swelling, or difficulty breathing) which will be treated with antihistamines in a standard fashion and lead to immediate withdrawal of the subject from the trial.

There is a risk of loss of confidentiality if protected health information or identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Subjects may benefit from a faster labor induction, less need for vaginal exams, easier to administer misoprostol for induction of labor, less risk of infection, and decreased rate of cesarean section.

12.2 Potential Benefits to Others

This research may show that misoprostol has a similar or better effect when given orally as compared to vaginal administration. Given orally may result in better patient satisfaction, less demand on licensed practitioner during induction of labor, less rate of infection, and less cesarean section rate.

13.0 Sharing Results with Subjects

There are no results from diagnostic studies that will be obtained. The study results will be shared with the subjects at the end of the project.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

There is no compensation or reimbursement that will be given to these subjects.

15.0 Economic Burden to Subjects

15.1 Costs

The misoprostol medication will be provided to the subjects at no cost. There are no extra costs that subjects are responsible for because of their participation in this research study. Subjects will assume the normal charges from the hospital and staff for Labor and Delivery and Postpartum care.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Identification and notification of subjects will take place at all office locations within the Penn State Women's Health Division, including Hope Drive, Nyes Road, Camp Hill, and Mt. Joy office. Recruitment, consent, and study procedures will be performed at Penn State Hershey Medical Center, Labor and Delivery Unit.

16.2 Feasibility of recruiting the required number of subjects

From previous data at Penn State Hershey Medical Center it is estimated that there was about 350 inductions of labor over one year's time. Accounting for inclusion/exclusion criteria it is estimated only 60% of patients will qualify for the study. That leaves 210 patients eligible for the study. Of the 210 potential subjects, 52% would need to be recruited to complete the study for the projected sample size of 110 subjects.

16.3 PI Time devoted to conducting the research

The Co-Investigator will engage in the study over training remaining at Penn State Hershey Medical Center. During her training, there is devoted research time in her residency program for a research project such as this one. Assistance from other project members will be provided including Dr. Pauli, PI of this project who has dedicated research time. Dr. Pauli when not in clinic, will have devoted time dedicated to research projects. As PI, she will ensure that an allotted time will be well suited to oversee the project with the Co-PI.

16.4 Availability of medical or psychological resources

Routine intrapartum and postpartum care. There is no foreseeable extra medical or psychological resources needed.

16.5 Process for informing Study Team

All study members will have access to the IRB approved protocol and supporting documents. A copy of the study protocol will be available on the Labor and Delivery Unit and in secure location on hersheymedfiles.net. We will have training sessions for all parties involved, study members, physicians and nurses, to review the study protocol. We will have ongoing meetings with research team members

for discussions on progress of study and to clarify their duties and expectations to ensure timely completion of study.

17.0 Other Approvals

17.1 Other Approvals from External Entities

N/A

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of the Use of Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Research Center (CRC) Advisory Committee – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload the Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☒ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

N/A

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

19.2 Recording of Adverse Events

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.5 Unblinding Procedures

The study is not blinded, therefore N/A

19.6 Stopping Rules

If the total number of subjects experiencing one or more serious adverse events (defined as uterine rupture, maternal death during her hospitalization, neonatal death during maternal hospitalization, and cesarean hysterectomy) reaches 5, the trial will be stopped. This reflects a 2.3% prevalence rate (110 subjects with 110 singleton neonates are included in the trial for a prevalence of 5/220 subjects). Or if any two cases of uterine rupture, two cases of maternal death during her hospitalization, or two cases of neonatal death (0-28 days of life) related to the study drug, the trial will be stopped.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The study will be monitored by Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject, after enrollment of the fifth subject and then after every 10 subjects enrolled or at a frequency developed by the Public Health Sciences monitoring team.

20.1.2 Safety Monitoring

On the listed protocol that investigators will follow while carrying out the study, will be the list of treatment emergent serious adverse events (TESAEs). Treatment emergent serious adverse events are defined as maternal death during hospital admission, neonatal death (0-28 days of life) related to the study drug, uterine rupture, or cesarean hysterectomy. If a TESAE happens the Co-investigator will be immediately paged and notified. If no response within 4 hours, the Principal Investigator, Jaimey Pauli, will be paged.

The Principal Investigator will confirm that the TESAE are correctly entered into the adverse event (AE) case report forms by the Co-investigator; be available to answer any questions that the Co-investigator may have concerning AEs; and will notify the IRB and FDA all TESAEs. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The Co-investigator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB and FDA of all Unanticipated Problems/TESAE's.

The Clinical Trial Monitoring Team will confirm that the TESAEs and AEs are correctly entered into the case report forms. The monitoring team will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored
N/A

21.2 Location of storage
N/A

21.3 Duration of storage
N/A

21.4 Access to data and/or specimens
N/A

21.5 Procedures to release data or specimens
N/A

21.6 Process for returning results
N/A

22.0 References

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Version Date: 2/1/2021

CONSENT FOR RESEARCH

Penn State College of Medicine
The Milton S. Hershey Medical Center

Title of Project: A comparison of oral misoprostol versus vaginal misoprostol for cervical ripening and induction of labor.

Principal Investigator: Jaimey M. Pauli, MD
Co-Principal Investigator: Courtney Birchall, MD

Address: 500 University Drive, M/C H103
Hershey, PA 17033

Telephone Numbers: Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-3503 or (717) 531-8521 and pager 3192
After hours call (717) 531-8521. Ask for the OB/GYN doctor on 24-hour call.

Subject's Printed Name: _____

We are asking you to be in a research study.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

1. Why is this research study being done?

We are asking you to be in this research because you are scheduled for a term induction of labor at Penn State Hershey Medical Center.

This drug, misoprostol, has been approved by the Food and Drug Administration for the treatment of reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin) induced gastric ulcers in patients at high risk of complications from gastric ulcers and is commercially available. Misoprostol is routinely used and approved by The American College of Obstetricians and Gynecologists as a cervical ripening agent for the induction of labor. A cervical ripening agent is a process to aid one's body in preparing for labor. The purpose of this study is to compare the effects of misoprostol on cervical ripening and induction of labor when it is administered either via the standard method, vaginally, or the experimental method, by mouth.

Approximately 110 people will take part in this research study Hershey Medical Center.

2. What will happen in this research study?

In the office at one of your prenatal visits, your physician or advanced practitioner may have reviewed the study with you. If he/she felt you are eligible to continue in the study, when he/she schedules your induction of labor, a form is routinely sent to our schedulers. A notation will be made on the form stating potential misoprostol study candidate for which it will be a reminder to the physicians on Labor and Delivery to discuss with you participating in the study if you qualify.

Upon arrival to Labor and Delivery at Hershey Medical Center you will undergo standard check-in process with nursing and physician. You will have routine electronic fetal monitoring (EFM), monitoring for contractions, hemoglobin level, blood type, a peripheral intravenous line started, sterile vaginal exam, and review and sign Cesarean Section Consent. All of these screening tests would be done even if you do not take part in this research study. These tests are routine for patients when you arrive for induction of labor who are about to start therapy. If you meet the inclusion criteria for the study you will be randomly assigned to receive one of the two study treatments. This means that whichever study treatment you receive will be determined purely by chance, like flipping a coin. Either you will be in the research arm and given misoprostol 25 micrograms (mcg) orally every two hours or in the standard arm and given misoprostol 25 mcg vaginally every four hours.

Once consented for, randomized, and participating in the study, the research team will be following the below guidelines:

- During misoprostol administration there will be a sterile vaginal exam every 4 hours which is standard of care.
- Once you reach a sterile vaginal exam with a Bishop score of greater than or equal to 8 or your cervix dilates to greater than or equal to 4 cm, misoprostol will be discontinued and oxytocin will be initiated 2 or 4 hours after the last dose of misoprostol if indicated for further augmentation of labor.
- If receiving misoprostol per vagina, you may only have a max of 6 doses of misoprostol for at total of 150 mcg. If receiving misoprostol per mouth, you may only have a max of 12 doses of misoprostol for a total of 300 mcg.
- After misoprostol is discontinued and/or oxytocin is initiated, you will have a sterile vaginal exam every 2 hours which is the standard of care.
- If you do not undergo spontaneous rupture of membranes, the physician may augment your labor with artificial rupture of membranes after the initiation of oxytocin.
- Your labor induction, augmentation, and delivery will be monitored and treated with Hershey Medical Center's standard protocol.

What are my responsibilities if I take part in this research?

If you take part in this research, your major responsibilities will include:

- Follow the instructions of the research team as outlined above.

3. What are the risks and possible discomforts from being in this research study?

You will be assigned to a treatment program by chance. The treatment you receive may prove to be less effective or to have more side effects than the other research treatment(s) or other available treatments.

There is always a discomfort with sterile vaginal exams. As part of the randomization, if you selected to be in the misoprostol administered per vagina, the placement of the medication may cause more discomfort than if you had to take the medication by mouth. The risk for possible cesarean section throughout the course of your induction of labor, chorioamnionitis, neonatal morbidity or death is standard and you would have these risks with or without this research study.

Side Effects/Risks of Misoprostol:

- Diarrhea: when taking misoprostol 800 mcg daily, trials have shown an incidence of diarrhea of about 13%. In this study you will be not receive more than 300 mcg of misoprostol.

- Use of vaginal misoprostol has a higher rate of uterine contractions, with contractions being more frequent than every 2 minutes when compared with placebo, dinoprostone gel, or oxytocin for induction of labor. Induction with Foley catheter has a decreased risk of uterine contractions happening greater than every 2 minutes when compared to vaginal misoprostol.
- Increased risk of meconium staining of amniotic fluid, but no difference in neonatal outcome. Meconium staining means that your infant had a bowel movement inside the womb prior to birth. It happens in about 12-22 percent of the time.
- Uterine rupture

Side effects of misoprostol when taken as prescribed for prevention of gastric ulcers that have an incidence greater than 1%, but no difference than placebo.

- Nausea – 3.2%
- Flatulence – 2.9%
- Headache – 2.4%
- Dyspepsia – 2% (indigestion or heartburn)
- Vomiting – 1.3%
- Constipation – 1.1%

There is a risk, as with any medication, of an unexpected allergic reaction to the study drug (defined as the development of hives, rash, swelling, or difficulty breathing) which will be treated with antihistamines in a standard fashion and lead to removal from the trial to prevent any further allergic reaction to the medication.

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?

There is no guarantee that you will benefit from this research. The possible benefits you may experience from this research study include A faster labor induction, less need for vaginal exams, easier to administer misoprostol for induction of labor, less risk of infection, and decreased rate of cesarean section.

4b. What are the possible benefits to others?

The results of this research may gain further understanding of using oral misoprostol for induction of labor with the new recommended dosing to provide better patient satisfaction, fewer vaginal exams, less rates of infection, decreased rate of cesarean section and decreased uterine tachysystole.

5. What other options are available instead of being in this research study?

You do not have to take part in this study to be treated for your condition. Instead of participating in this research, you could:

- Receive the routine standard induction of labor as discussed with your provider. Options are vaginal misoprostol at the same dosing without participating in the study, use of a Foley catheter causing mechanical dilation, or oxytocin.

Before you decide if you want to be in this research, we will discuss the other choices that are available to you. We will tell you about the possible benefits and risks of these choices.

The therapy (vaginal dosing) offered in this research is available to you without taking part in this research study. The oral misoprostol dosing is not available to you at this site outside of this research study.

6. How long will I take part in this research study?

If you agree to take part, it will take you approximately 12-36 hours and up to 72+ hours to complete this research study, which is the normal time frame for an induction of labor. Once your infant is delivered there is no further time commitment to this study.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?

7a. What happens to the information collected for the research?

Efforts will be made to limit the use and sharing of your personal research information. In our research files at The Milton S. Hershey Medical Center (HMC) and Penn State College of Medicine (PSU) we will include these identifiers; your name, date of birth, medical record number, and a code number.

- A list that matches your name with your code number will be kept in a locked file in the Penn State Milton S. Hershey Medical Center, Maternal Fetal Medicine Office.
- Your research records will be labeled with your code number, name, date of birth, and medical record number and will be kept in a safe and locked area in the Maternal Fetal Medicine Office.
- A copy of this signed consent form will be included in your HMC medical record. This means that other HMC healthcare providers will know you are in this study.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

7b. How will my identifiable health information be used?

If you give your consent, health information that can be traced to you will be collected for this research study. In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so. We will use and disclose your information only as described in this form and in the HMC Privacy Notice.

The research team may use the following health information:

- Past, present, and future medical records
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- HMC/PSU research staff involved in this study
- The HMC/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The HMC/PSU Human Subjects Protection Office
- The HMC/PSU Research Quality Assurance Office
- Non-research staff within HMC/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)

- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, the National Institutes of Health, and other U.S. or foreign government bodies that oversee or review research)
- The HMC/PSU pharmacy
- A group that oversees the data (study information) and safety of this research
- Organizations that provide independent accreditation and oversight of hospitals and research

These groups may also review and/or copy your original PSU/HMC records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:

- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.
- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?

For costs of tests and procedures that are only being done for the research study:

- The misoprostol drug will be provided by the Investigational Drug Services Pharmacy at Penn State Hershey Medical Center at no cost to you while you take part in this study. Although the study drugs are provided at no cost, there may be costs for drug administration. You or your insurance company will be responsible for these costs.
- There are no extra tests or procedures that are required as part of the research that are outside the standard of care (what is normally done) for an induction of labor.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.

- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies may not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

8b. What happens if I am injured as a result of taking part in this research study?

It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and the principal investigator will arrange for medical treatment.

<u>HMC/PSU compensation for injury</u>

- There are no plans for HMC/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Costs will be charged to your insurance carrier or to you.
- Some insurance companies may not cover costs associated with research injuries.
- If these costs are not covered by your insurance, they will be your responsibility.

When you sign this form you are not giving up any legal right to seek compensation for injury.

9. Will I be paid to take part in this research study?

You will not receive any payment or compensation for being in this research study.

10. Who is paying for this research study?

The institution and investigators are not receiving any funds to support this research study.

11. What are my rights if I take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

If you decide to leave the research, contact the investigator or study team so that the study team and physicians can continue your induction of labor as you both seem fit to the standard of care.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect medical information from your routine medical care. If you agree, this data will be handled the same as research data. If you withdraw completely from the research study, no further information will be collected and your participation will end. You may

discontinue taking part at any time without penalty or loss of benefits to which you are otherwise entitled.

Your research doctor may take you out of the research study without your permission.

- Some possible reasons for this are: allergic reaction to misoprostol, uterine tachysystole (too many contractions within a 10 minute period), or nonreasurring fetal heart tones.
- Also, the sponsor of the research may end the research study early.
- If your participation ends early, you will receive routine care during labor, delivery, and postpartum period at Penn State Hershey Medical Center.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?

Please call the Co-Principal Investigator of the research study, Dr. Courtney Birchall at 717-531-3503 or the OB/GYN doctor on 24-hour call at 717-531-8521 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the research protection advocate in the HMC Human Subjects Protection Office (HSPO) at 717-531-5687 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the HSPO's web site at http://pennstatehershey.org/irb under research subject information for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization
Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name