

Outpatient Foley Catheter
Compared to Usual Inpatient
Care for Cervical Ripening: A
Non-Randomized Prospective
Study

NCT02546193

November 16, 2016

OUTPATIENT FOLEY CATHETER COMPARED TO USUAL INPATIENT CARE FOR CERVICAL RIPENING: A NON- RANDOMIZED PROSPECTIVE STUDY

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Study Product: Transcervical single balloon Foley catheter

Protocol Number: (IRBe) 14-008988

IND Number: Not applicable

Initial version: 7/6/15 Version (1.1)

Modification 4 11/20/2015 Version (1.6)

Modification 5 2-15-16 Version (1.7)

Modification 8, Change in PI, 4-28-16 Version (1.8)

Modification 9, Prospective study design Version (1.9) IRB approved 11-16-16

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	Outpatient Foley catheter compared to usual inpatient care for cervical ripening: A non-randomized prospective study
Running Title	Outpatient vs. inpatient cervical ripening
Protocol Number	14-008988
Phase	Pivotal
Methodology	Prospective
Overall Study Duration	24 months
Subject Participation Duration	4-36 hours
Single or Multi-Site	Single site
Objectives	To compare the length of pre-delivery hospitalization in pregnant women undergoing cervical ripening with a Foley catheter in the outpatient setting compared with standard methods administered in the inpatient setting.
Number of Subjects	40 Outpatient Foley Subjects + 160 standard of care subjects Total of 400 women and their babies
Diagnosis and Main Inclusion Criteria	Pregnant women at ≥ 37 weeks gestation who are scheduled for induction of labor and who have an unfavorable cervical exam (Bishop score < 9 and cervical dilation < 3 cm)
Study Product, Dose, Route, Regimen	The Foley catheter is a single balloon catheter that is placed transcervically by a provider and inflated with 60cc of normal saline. It mechanically dilates the cervix to 3-4cm over several hours.
Duration of Administration	The device will remain in place until it passes through the cervix, generally when the cervix is dilated to 3-4 cm, which typically occurs 3-12 hours after placement.
Reference therapy	Cervical ripening in the inpatient setting with either a Foley catheter and/or vaginal misoprostol 25 mcg tablets every 4 hours.
Statistical Methodology	The mean time of pre-delivery hospitalization between outpatient Foley catheter and inpatient usual care groups will be compared using a two sample t-test or the nonparametric equivalent Wilcoxon rank sum test. Secondary endpoints will be compared using two sample t-tests or the nonparametric equivalent Wilcoxon rank sum test for continuous endpoints or the chi-Square or Fisher's exact test for categorical endpoints.

1 Introduction

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

1.1 Background

In 2012, 23% of pregnant women underwent induction of labor in the United States [1]. Induction of labor is the use of pharmacologic and/or mechanical methods to initiate labor [2]. Cervical ripening generally refers to the early part of labor induction in cases where methods are required to achieve a “favorable cervix,” variably defined at ≥ 6 or ≥ 8 by Bishop score (a scoring system based on 5 components including cervical dilation, effacement, position, consistency, and fetal station with a range of 0-13) [3]. Cervical ripening in women with unfavorable cervical examinations has been shown to decrease cesarean delivery compared with oxytocin alone [4]. Vaginal prostaglandins and the transcervical catheter are the two most common methods of cervical ripening. Cervical ripening can be a lengthy process, though often a passive one requiring little provider intervention. It is conventionally performed in an inpatient setting; however, there has been an increasing amount of research investigating cervical ripening in the outpatient setting [5]. Although cervical ripening has traditionally been performed in the inpatient setting, the medical necessity of this practice is unproven [6]. Increasing the time a woman spends in her home environment has the potential to decrease the length of hospital stay and associated healthcare costs as well as improve maternal satisfaction.

A recently published study comparing inpatient versus outpatient cervical ripening with vaginal prostaglandin E2 gel found no difference in clinical outcomes including oxytocin use, cesarean delivery, and vaginal delivery within 24 hours [6]. Importantly, though, women in the outpatient group were more likely to have tachysystole (more than 5 contractions in 10 minutes) with fetal heart rate changes, and less than half remained at home overnight. The authors state, and we agree, that prostaglandins may not be the safest agent for outpatient cervical ripening. Compared to prostaglandins, the Foley catheter is associated with a decreased rate of uterine tachysystole with fetal heart rate changes [7]. There is no difference in the rate of chorioamnionitis, endometritis, undelivered women at 24 hours, meconium passage, or serious maternal or neonatal morbidity [7]. The Foley catheter has been shown to be comparable to prostaglandins with regard to cesarean delivery rates [8]. Thus, because the Foley catheter does not cause tachysystole with fetal heart rate changes and does not require interval dosing, it is a potentially promising option for outpatient cervical ripening.

A recent retrospective review of 1,905 low risk women undergoing cervical ripening with the Foley catheter examined adverse effects occurring in the first 12 hours after Foley placement [9]. Of the 1,905 women studied, only 3 underwent cesarean delivery following Foley placement and post-placement monitoring (1 for face presentation and 2 for arrest of dilation). All 3 women would have been excluded from an outpatient trial based on rupture of membranes or spontaneous labor at the time of Foley placement. There were no stillbirths and no cesareans performed for abruption or nonreassuring fetal heart tracing. Based on this study, the Foley catheter is a safe method of cervical ripening with no reported adverse fetal or maternal effects and should be considered for use in the outpatient setting.

Sciscione et al. performed the first prospective randomized controlled trial comparing the use of a Foley catheter in the inpatient versus outpatient setting [10]. A total of 111 women were enrolled; 61 were randomized to the outpatient setting. All women had a number 16 Foley catheter filled with 30cc of sterile saline placed by sterile speculum exam. The primary outcome was difference in Bishop score from the first cervical exam to the cervical exam the next morning. They found no significant difference in the change in Bishop score, pain scores, or total induction time between the groups. The inpatient admission time was 9.6 hours longer in the inpatient group compared to the outpatient group. Only 8% (n=5) returned overnight for either rupture of membranes or labor.

A similar, more recent trial by Henry et al. compared outpatient Foley catheter placement to inpatient PGE2 vaginal gel in 101 women [11]. The outpatient group spent 11.1 fewer hours in the hospital prior to delivery compared to the inpatient group ($p<.001$). They also felt less pain and got more sleep during cervical ripening. Oxytocin was required for induction more often in the outpatient group. No adverse neonatal or maternal outcomes were associated with outpatient Foley catheter allocation. Only one woman in the outpatient group returned to the hospital earlier than scheduled (for regular, painful contractions).

The trials by Sciscione et al. and Henry et al. have limitations, though. First, neither utilized a standard protocol for labor induction. Second, the inpatient control group was allocated to either Foley usage alone (Sciscione et al.) or prostaglandin PGE2 gel alone (Henry et al.). We believe the most appropriate comparison group is “usual care” wherein women may receive either the Foley catheter or prostaglandins based on patient and provider preference.

The use of a Foley catheter for cervical ripening in the outpatient setting has the potential for substantial advancement to the induction process for the patient, provider, and healthcare system. The Foley catheter is a safe, inexpensive method of cervical ripening that causes less fetal heart rate effects than other ripening methods [7, 8]. Women may find gratification by being in their home environment during more of their labor course [12]. Providers and healthcare systems may be better able to allocate their resources with decreased length of stay during the early induction phase. A 2013 Cochrane review of outpatient cervical ripening concluded that more studies are required to demonstrate its efficacy and safety in this setting [5]. Our study will provide additional evidence of safety and efficacy to transition cervical ripening to the outpatient setting.

1.2 Investigational Agent

The Foley catheter is a device used to achieve cervical ripening to start labor induction. It is the most common mechanical method used for cervical ripening in the third trimester. It is a single balloon catheter placed transcervically by a provider, either digitally or using a speculum for visualization. The balloon is placed above the internal os but below the fetal head, amniotic membranes, and placenta and is inflated with 30-80 mL of normal saline. Traction is placed on the catheter, either by taping the catheter to the patient's thigh and/or intermittently by a provider. Over several hours, the balloon gradually dilates the cervix. The catheter is expelled when the cervix is 3-4 centimeters. At this dilation, oxytocin (Pitocin) is much more effective.

1.3 Clinical Data to Date

Please refer to section 1.1 and 1.2.

1.4 Dose Rationale and Risk/Benefits

Only one Foley catheter is placed during a patient's labor induction course. The single balloon can be filled with 30-80 mL of normal saline. Our equipment best facilitates 30-60 mL. A study by Delaney et al. demonstrated that inflation with 60 mL increased the likelihood of delivery within 12 hours compared to 30 mL without any adverse maternal or neonatal outcomes [13]. Therefore, 60 mL was elected for this study.

Common adverse effects of transcervical Foley catheters include discomfort and vaginal spotting. The patient may feel uncomfortable during placement of the Foley catheter and while the Foley catheter is in place. Similarly, women in the inpatient group can expect discomfort during the initiation of their labor induction as well, whether with the Foley catheter or vaginal misoprostol. Pain control options as described elsewhere in this document will be available for patient comfort. Available data suggests that the Foley catheter is tolerable from a pain perspective. Pennell and colleagues evaluated pain associated with the Foley catheter and found that pain with insertion was rated as 4/10 and pain during cervical ripening was 2/10 [14]. Overall satisfaction with induction of labor for Foley catheter was 8/10, which was equivalent to the other cervical ripening agents studied.

Patients may also commonly experience vaginal spotting after placement of a Foley catheter. This is typically from cervical manipulation rather than clinically significant placental abruption. In the majority of cases, these etiologies can be distinguished by experienced clinical evaluations. If there is suspicion that vaginal bleeding represents placental abruption, the patient will be excluded from the trial and kept in the inpatient setting until delivery. The amount of blood lost from vaginal spotting is not clinically significant and is common during induction of labor in the inpatient setting.

Less likely risks include the following: artificial or spontaneous rupture of membranes, initiation of spontaneous labor, and placental abruption, both clinically significant and insignificant. The patient will be educated regarding these risks. Should any of these events be diagnosed while the patient is in the Family Birth Center for post Foley monitoring, she will be kept as an inpatient until delivery and excluded from the trial. Should any of these occur at home, the patient will return immediately to the Family Birth Center as outlined in both verbal and written instructions.

2 Study Objectives

2.1 Primary Objective

The primary objective of the study is to compare the mean length of pre-delivery hospitalization among women undergoing induction of labor with a Foley catheter in the outpatient setting as compared to usual care in the inpatient setting.

2.2 Secondary Objective

Our secondary objectives are as follows:

- 1) To compare the cesarean delivery rate among women undergoing outpatient Foley versus inpatient cervical ripening.
- 2) To compare other maternal outcomes including: postpartum hemorrhage, infection, hospital readmission, and satisfaction with the induction process.
- 3) To compare neonatal outcomes including: APGAR scores, umbilical artery pH, and nursery disposition.

3 Study Design

3.1 General Design

The study began as a randomized control trial. The intervention group was comprised of low risk pregnant women who had a Foley catheter placed followed by dismissal home with return in approximately 12 hours for continuation of the labor induction process. The control group consisted of women who remained inpatient during the entire cervical ripening phase followed by continuation of the labor induction process in the inpatient setting.

Due to difficulty enrolling women for the randomized control trial, a prospective design with an outpatient intervention group (Foley catheter) and matched inpatient control comparison group is proposed. Low risk pregnant women will be invited to participate in an outpatient Foley catheter intervention to begin their induction of labor process. Maternal/Neonatal outcomes and maternal satisfaction with the induction experience will be assessed. The comparison group will be enrolled to participate in the study in a limited way, providing responses to a maternal satisfaction of induction survey and allowing their and their baby's electronic medical record to be followed for maternal/neonatal health outcomes and total hospital time.

- I. Enrollment of participants (Randomized Control Trial)
 - A. Clinic nurses, clinical assistants who room patients, and the patient's obstetric provider will refer eligible patients to the research coordinator.
 - B. The Co-PI (Dr. Joy Beissel) will monitor the induction scheduling book in the Family Birth Center two weeks in advance to identify patients who may be eligible for the study. She will communicate the patient's next clinic appointment to the research coordinators so these patients can be approached in clinic.
 - C. Patients who receive their care in Mayo Clinic Family Medicine clinics will be eligible for this study. Their providers will be educated regarding this trial.
- II. Patient education, consent, and randomization
 - A. The patients will be educated about induction of labor, the Foley catheter, and the proposed research study.
 1. The patient will be approached for this education during their last or second to last clinic visit before planned induction of labor.
 2. The education will be performed by a trained research coordinator, Principal Investigator, Co-Principal Investigator, or authorized obstetric provider.
 - B. If the patient elects participation, she will undergo informed consent at that time.
 1. Informed consent will be obtained by a trained research coordinator, Principal Investigator, Co-Principal Investigator, or authorized obstetric provider.
 - C. Randomization
 1. Randomization will occur the day before the planned induction to decrease drop out (for example: from spontaneous labor between the clinic visit and planned induction).
 2. The randomization will be computer generated.
 3. The patient's randomization status will be accessed by the research coordinator.
 4. The research coordinator will contact the patient by phone to inform her of her randomization group.

5. Randomization will be stratified by parity (primiparous vs. multiparous) and by body mass index (current body mass index $<30 \text{ kg/m}^2$ vs. $\geq 30 \text{ kg/m}^2$).

III. Enrollment of participants (Prospective Study)

A. Enrollment of outpatient intervention participants

1. Clinic nurses, clinical assistants who room patients and the patient's obstetric provider will refer eligible patients to the research coordinator.
2. The study coordinator will screen the induction scheduling book in the Family Birth Center weekly to identify patients who may be eligible for the study. She will communicate with eligible women by telephone share general information about the study. If women are interested in learning more, she will meet with them at the patient's next clinic appointment.
3. Patients who receive their care in Mayo Clinic Family Medicine clinics will be eligible for this study. Their providers will be educated regarding this study. These women will be enrolled in the same manner as women from the antenatal clinic.

(a) Patient education and consent

- (a) The patients will be educated about induction of labor, the Foley catheter, and the proposed research study.
- (b) If the patient elects participation, she will undergo informed consent at that time by a trained research study coordinator, Principal Investigator, Co-Principal Investigator, or authorized obstetric provider.
- (c) Parity (primiparous vs. multiparous) and BMI (current body mass index $<30 \text{ kg/m}^2$ vs. $\geq 30 \text{ kg/m}^2$) will be recorded based on the stratification used in the Randomized Control Trial design.

B. Enrollment of inpatient comparison (usual care) participants

1. Women who decline participation in the outpatient intervention study may be approached to participate in a limited way as inpatient comparison control participants.
2. The study coordinator will screen the OB White Board daily in the Family Birth Center to identify patients presenting for induction of labor who may be eligible for the study, but not captured during the weekly screening process. Eligible women will be approached, after discussion with their attending obstetric provider, to participate in the study as inpatient comparison usual care participants.
3. Four inpatient comparison control participants will be enrolled with the same parity and BMI strata for every outpatient intervention patient enrolled (see III. A. 3. c. above).

(a) Patient education and consent

- (a) The patients will be educated the proposed research study.
- (b) If the patient elects participation, she will undergo informed consent at that time by a trained research study

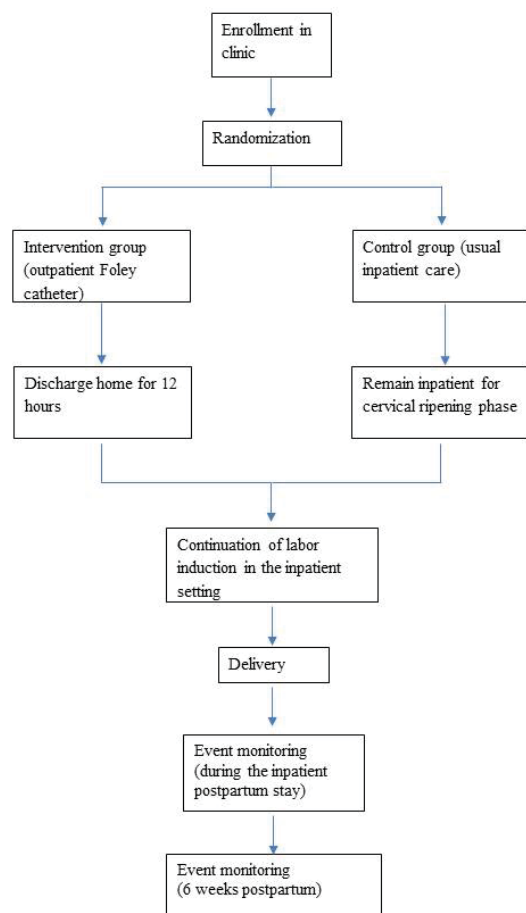
coordinator, Principal Investigator, Co-Principal Investigator, or authorized obstetric provider.

IV. Protocol for the intervention group (Both Randomized Control Trial and Prospective Study)

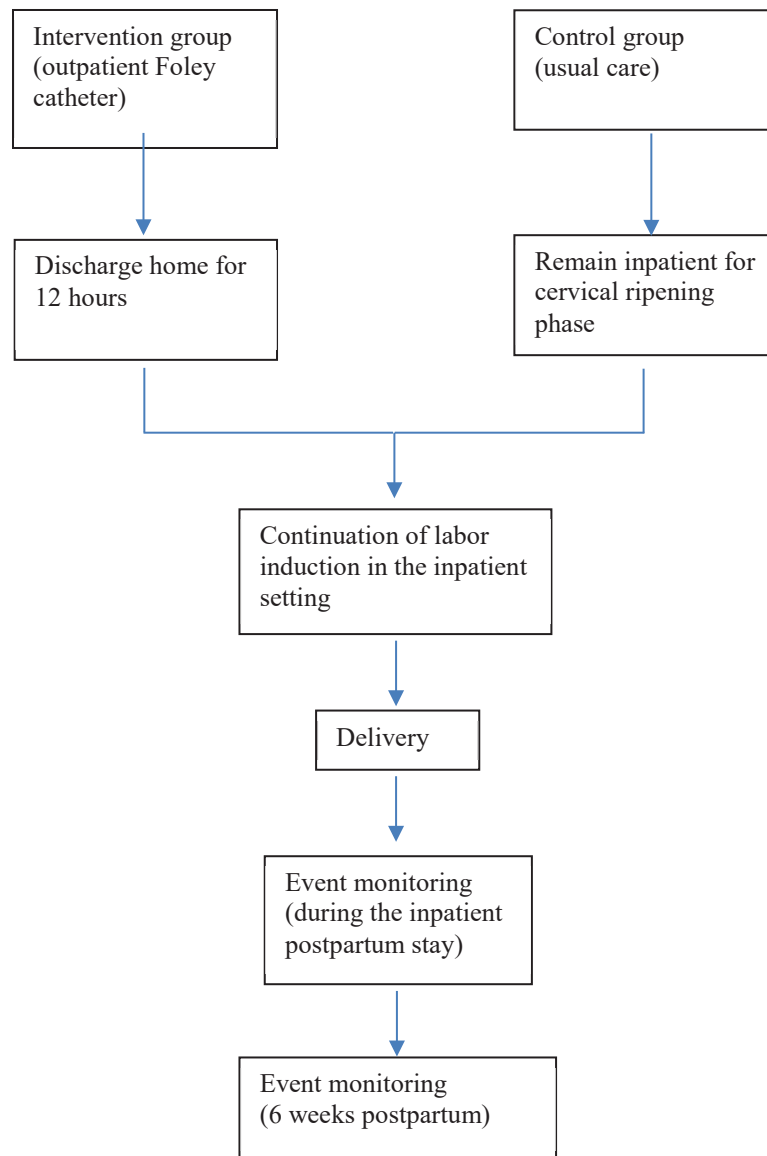
- A. The patient will present to the Family Birth Center at 0730 or 1930.
- B. A nonstress test (NST) will be performed
 1. The fetal heart rate (FHR) is observed by external monitoring for at least 20 minutes. The FHR is observed for the presence of accelerations, at least 2 in 40 minutes that peak at least 15 beats per minute above the baseline and last for at least 15 seconds. The absence of at least 2 accelerations in up to 40 minutes is considered nonreactive.
 2. A nonreactive NST, the presence of ≥ 3 variable decelerations in a 20 minute period, late-appearing decelerations, or any deceleration lasting ≥ 1 minute should be considered criteria for exclusion.
- C. An ultrasound will be performed for fetal presentation and amniotic fluid index.
- D. A cervical exam will be performed with calculation of a Bishop score.
- E. The patient will be asked the following standard questions.
 1. Are you experiencing any of the following: regular, painful contractions? Decreased fetal movement? Vaginal bleeding? Leakage of fluid from the vagina concerning for rupture of membranes? Fevers or chills?
 2. She will be excluded from the trial based on her answers, as described in section 4.2 “Exclusion Criteria.”
- F. A Foley catheter will be placed if the following criteria have been met: the nonstress test is reactive, the fetal presentation is cephalic, the amniotic fluid index is 5 centimeters or more, the Bishop score is <9 , the cervical dilation is <3 cm, and she has no other clinical characteristics that exclude her from the trial.
- G. An obstetric provider will place a 16 French Foley catheter through the internal os. The balloon will be inflated with 60cc of normal saline. The distal end of the Foley will be taped to the patient’s inner thigh.
- H. The fetal heart rate tracing will be monitored for 1 hour after Foley placement.
- I. The patient will be sent home if the following criteria are met: the fetal heart rate tracing is reactive and category I; there is no evidence of rupture of membranes, spontaneous labor, or vaginal bleeding more than spotting; and maternal vital signs are within normal range.
- J. Pain control options
 1. While the Foley catheter is in place, the patient can use the following non pharmacologic methods to decrease discomfort: warm baths, massage, frequent position changes in a comfortable environment, relaxation techniques, and gentle stretching
 2. Pharmacologic methods available to the patient include:
 - (a) Tylenol 1000mg orally q6 hours as needed for pain
 - (b) Morphine 10 mg IM once prior to dismissal
- K. The patient will be instructed to return to the Family Birth Center approximately 12 hours following their Foley bulb placement.
- L. The patient will be given verbal and written instructions as follows:

1. To return immediately to the Family Birth Center if she feels decreased fetal movement, if she is concerned her membranes ruptured, if she has vaginal bleeding more than spotting, if she has regular, painful contractions, if she has severe pain, if she develops a fever of $\geq 100.4^{\circ}\text{F}$ or $\geq 38.0^{\circ}\text{C}$, or if she develops any symptoms concerning to her.
 2. If the Foley catheter is expelled at home, she is to record the time of expulsion. She does not need to return to the Family Birth Center earlier than planned due to expulsion.
 3. She will be provided with the 24 hour direct access line for the Family Birth Center to call with any questions or concerns.
- M. On arrival to the Family Birth Center at 12 hours later, the induction will be continued.
1. The providing team will decide to proceed with oxytocin and/or artificial rupture of membranes.
 2. The oxytocin dose will be increased as determined by the Family Birth Center oxytocin low dose infusion regimen.
 3. The patient will have continuous electronic fetal monitoring.
 4. The remainder of her care during the first, second, and third stages of labor will be at the discretion of the providing team.
 5. If the Foley is still in place when the patient arrives, a provider should gently tug on it. If it does not come out, the providing team may choose to deflate and remove the Foley catheter (and then proceed with artificial rupture of membranes or oxytocin) OR leave the Foley in situ and place vaginal misoprostol.
- N. All patients' labor progress will be monitored using a partogram. Cesarean delivery will not be performed for arrest of labor or failed induction unless all criteria have been met as outlined by the Family Birth Center Workgroup protocol made effective 6/2/14.
- V. Protocol for the control group (Randomized Control Trial)
- A. If the patient is in the outpatient control group, she will arrive to the Family Birth Center at a standard, predetermined time (typically 0730 or 1930) to undergo induction of labor.
 - B. Method of cervical ripening
 1. The only pharmacologic cervical ripening agent to be used is vaginal misoprostol, 25 mcg every 4 hours with a maximum of six doses.
 2. She may or may not have a Foley catheter placed as a method of cervical ripening based upon the providing team's discretion.
 3. A Foley catheter will be favored during the cervical ripening phase if there is tachysystole and/or a nonreassuring fetal heart tracing precluding further misoprostol administration, provided the Bishop score is still <6 .
 - C. After cervical ripening is achieved, oxytocin and/or artificial rupture of membranes will be used at the discretion of the providing team.
 - D. If oxytocin is used during the labor induction, the dose will be increased as determined by the Family Birth Center Oxytocin low dose infusion regimen.
 - E. The remainder of her care during the first, second, and third stages of labor will be at the discretion of the providing team.

- F. All patients' labor progress will be monitored using a partogram. Cesarean delivery will not be performed for arrest of labor or failed induction unless all criteria have been met as outlined by the Family Birth Center Workgroup protocol made effective 6/2/14.
- VI. Protocol for the inpatient usual care group (Prospective Study)
- A. All methods of cervical ripening and labor augmentation will be at the discretion of the providing team. Cervical ripening will occur as described above with vaginal misoprostol and a Foley catheter; dinoprostone (vaginal prostaglandin, brand name Cervidil) is infrequently used in the Family Birth Center but would now be an option as well. Oxytocin dosing will be increased by the FBC oxytocin low dose infusion regimen, labor will be monitored using a partogram, and Cesarean delivery will continue to be determined by the criteria as described above.
- VII. Follow-up
- A. Inpatient follow-up
1. We will obtain maternal consent to abstract secondary endpoints as described in section 3.3 from the fetal and maternal electronic medical record.
- B. Follow-up over 6 weeks
1. Secondary endpoints from section 3.3 will be abstracted from the EMR.
 2. Data collection will stop at 42 days after the patient's delivery or the date of the patient's final postpartum clinic visit, whichever comes last.
- VIII. Flow chart for Randomized Control Trial



IX. Flow chart for Prospective Study



3.2 Primary Study Endpoints

The primary endpoint is the mean time from admission to delivery.

Please note that the time the intervention (outpatient) group spends in the Family Birth Center the night before (for fetal heart rate monitoring, Foley placement, etc) will be added into the total time of inpatient admission

3.3 Secondary Study Endpoints

- I. Baseline maternal data
 - A. Date of birth

- B. Race and ethnicity
- C. Pre pregnancy body mass index
- D. Gravidity
- E. Parity
- F. Medical comorbidities
- G. Surgical history
- H. Major complications during this pregnancy (i.e. gestational diabetes)
- II. Intervention (outpatient)group data
 - A. Method of Foley catheter insertion: digital or sterile speculum
 - B. Foley catheter expulsion at home: yes/no, time of expulsion
 - C. Return to the Family Birth Center earlier than scheduled and reason (labor, rupture of membranes, decreased fetal movement, vaginal bleeding, pain, fever, or other)
 - D. Bishop score before Foley placement
 - E. Bishop score on the morning of admission for continuation of the labor induction
 - F. First induction method used after admission in the morning
 - a. Oxytocin
 - b. Artificial rupture of membranes
 - c. Oxytocin + artificial rupture of membranes
 - d. If Foley catheter still in place, Foley + oxytocin
- III. Procedural data for both groups
 - A. Gestational age at delivery
 - B. Primary providing team in the Family Birth Center (Obstetrics, Midwifery, or Family Medicine)
 - C. Use of Foley catheter: yes/no, date and time
 - D. Use of pharmacologic cervical ripening: yes/no, date and time, number of doses
 - E. Use of oxytocin: yes/no, date and time, maximum dosage
 - F. Rupture of membranes: spontaneous or artificial, date and time
 - G. Epidural placement: yes/no, date and time
 - H. IV pain medication administration prior to delivery—time, medication, and dose
 - I. Date and time of delivery
 - J. Number who delivered within 12, 24, 36, 48 hours from initiation of cervical ripening
 - K. Number who delivered before midnight of the following day
 - L. Meconium passage prior to delivery: yes/no, thin or thick
 - M. Total number of cervical exams
 - N. Mode of delivery
 - 1. Normal spontaneous vaginal delivery
 - 2. Vacuum assisted vaginal delivery and indication
 - 3. Forceps assisted vaginal delivery and indication
 - 4. Cesarean delivery
 - O. If a cesarean delivery was performed:
 - 1. Indication for cesarean (non-reassuring fetal heart status, umbilical cord prolapse, uterine rupture, placental abruption, failed operative delivery, arrest of dilation, arrest of descent, and other)
 - 2. Type of cesarean—emergent, urgent, or non-urgent (“Alpha,” “Beta,” or “Charlie”)
 - 3. Cervical dilation at the time of cesarean, if known

4. Stage of labor at the time of cesarean
- IV. Maternal outcomes
 - A. Intrapartum complications
 1. Intrapartum fever
 2. Chorioamnionitis
 3. Suspected or confirmed placental abruption
 4. Category II or category III fetal heart tracing requiring in utero resuscitation as documented in the electronic record during the cervical ripening phase only
 - B. Estimated blood loss at delivery
 - C. Postpartum hemorrhage: yes/no, if pharmacologic or surgical treatments required
 - D. Infection (endomyometritis, wound infection, or urinary tract infection within 30 days)
 - E. Readmission within 6 weeks of delivery and reason
 - F. Length of inpatient hospital stay (in hours from time of admission to noon on the day of discharge)
- V. Fetal outcomes
 - A. Sex
 - B. Birth weight (grams)
 - C. Position at delivery (occiput anterior, occiput posterior, occiput transverse, or unknown)
 - D. APGAR scores at 1 and 5 minutes
 - E. Umbilical cord blood gas-pH and base excess
 - F. Disposition after delivery: level I, II, or III. If II or III, reason for admission.
 - G. Day of life on which discharge occurred
 - H. Neonatal death within 30 days and reason
- VI. Maternal satisfaction data
 - A. Average scores for each question on the maternal satisfaction survey (see attached)

3.4 Primary Safety Endpoints

The primary safety outcomes are as follows: heavy vaginal bleeding, severe pain (return to hospital overnight for unrelieved pain), mode of delivery, intrapartum complications (as described above), and fetal outcomes (as described above). These will include overall fetal and maternal survival rates. Based on previous studies, we do not anticipate any difference between safety endpoints in the inpatient vs. outpatient groups.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Pregnant women at ≥ 37 weeks gestation by reliable dating criteria as determined by the American College of Obstetricians and Gynecologists (i.e. gestational age supported by one of the following: ultrasound prior to 20 weeks of gestation, fetal heart tones auscultated by Doppler for 30+ weeks, or documented serum or urine pregnancy test 36+ weeks ago)

2. Scheduled induction of labor with indication and timing supported by the Family Birth Center induction of labor guideline entitled “Induction of labor: Indications and Timing”
3. Singleton gestation
4. Cephalic presentation
5. Amniotic fluid index greater than or equal to 5 centimeters
6. Formal prenatal ultrasound documenting the absence of placenta previa
7. Bishop score ≤ 9 and cervical dilation ≤ 3 cm
8. The woman is able to give appropriate consent and has undergone an informed consent process.
9. Maternal age ≥ 18 years old at the time of consent.

4.2 Exclusion Criteria

1. New diagnosis requiring immediate hospitalization for monitoring (such as preeclampsia)
2. Vaginal bleeding
3. Active labor
4. Premature rupture of membranes as determined by positive ferning and as supported by pooling of fluid in the vaginal vault.
5. Uterine tachysystole (>5 contractions in 10 minutes)
6. Nonreassuring fetal heart tracing before or after Foley placement
7. Chorioamnionitis or maternal fever
8. Intrauterine fetal demise
9. Contraindication to vaginal delivery, relative or absolute (i.e. transfundal uterine surgery)
10. Abnormal placentation including a low lying placenta
11. Prior cesarean delivery
12. Intrauterine growth restriction (growth $<10^{\text{th}}$ percentile by formal ultrasound)
13. Known major fetal anomaly
14. Human immunodeficiency virus, Hepatitis C, or active herpes infection
15. Maternal cardiopulmonary disease requiring cardiac monitoring during labor
16. Pregestational diabetes
17. Rh isoimmunization
18. Non-English speaking

4.3 Subject Recruitment, Enrollment and Screening

We anticipate a targeted population of 400, which includes 200 mothers and their 200 infants. Data will be collected from these 400 charts after delivery.

We anticipate that 250 women in total will provide informed consent before giving birth to their babies. That is, we estimate that 50 women who are initially consented for the study will become ineligible for inclusion in the trial, for example due to spontaneous onset of labor, prior to induction of labor. These women will be considered screen failures.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A patient may be withdrawn from the study for several reasons.

First, the patient may decide at any time to cease participation in the trial. She will receive all appropriate medical cares without consequence of her participation in the trial. If she is randomized to the outpatient group, for example, but decides to withdraw before Foley placement, her induction of labor will occur in the standard, inpatient fashion. The induction will commence either that evening or the next morning, as staffing, unit flow, maternal status, and fetal status allow. Similarly, if a woman in the intervention group declines participation in the trial after the Foley catheter has been placed, the Foley catheter can be removed with pursuit of standard, inpatient cervical ripening. Alternatively, she can keep it in place and elect pain management options such as an epidural outside the realm of this study (thereby excluding her from the study and committing her to inpatient management).

Second, the patient may become excluded from the trial for several reasons. A pregnant woman may be found to be an eligible participant when she is approached at her clinic visit; however, before her scheduled induction of labor that will occur several days later, she may become excluded for any of the following reasons:

- 1) She develops a new diagnosis (such as preeclampsia) requiring immediate hospitalization for monitoring
- 2) She develops vaginal bleeding that is unexplained and concerning for labor or placental abruption
- 3) She spontaneously labors and is admitted for anticipated delivery
- 4) She undergoes premature (pre-labor) rupture of membranes
- 5) During indicated fetal heart rate monitoring, the tracing becomes non reassuring such that outpatient management is not recommended
- 6) She develops a fever and/or chorioamnionitis
- 7) There is an intrauterine fetal demise
- 8) She develops a contraindication to vaginal delivery, such as new active genital herpetic lesions
- 9) Intrauterine growth restriction is diagnosed

Finally, the pregnant woman may become excluded from study shortly after arrival to the Family Birth Center for initiation of the planned induction of labor. Any of the above-listed reasons (vaginal bleeding, spontaneous labor, premature rupture of membranes, etc) diagnosed at presentation will be reason to exclude the woman from participation. Furthermore, *after* Foley catheter placement, a patient may be excluded from the trial should any of the following occur:

1. She is diagnosed with a condition that requires immediate admission for induction of labor (such as gestational hypertension or preeclampsia)
2. She develops vaginal bleeding more than spotting that is clinically concerning for placental abruption
3. She spontaneously labors
4. She undergoes premature rupture of membranes
5. The post-placement fetal heart tracing is non reassuring such that outpatient management is not recommended
6. She develops a fever and/or chorioamnionitis

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Data will not be collected from women who electively withdraw from the study. Data will be collected on all women who are randomized to a treatment group. Should patients from the outpatient group cross over to the inpatient group (i.e. if they meet exclusion criteria), analysis will be by intention to treat.

5 Study Drug

5.1 Description

Please see section 1.2 for a description of the Foley catheter.

At Mayo clinic, the Foley bulb costs \$5.51 for the catheter and all necessary supplies. All resident level providers are trained in their first year to insert these catheters at Mayo clinic both in simulation models and in the Family Birth Center.

Please see section 1 for description of previous studies examining the Foley catheter as a means of cervical ripening in the outpatient setting.

5.2 Treatment Regimen

Please see sections 1.2 and 1.4.

5.3 Method for Assigning Subjects to Treatment Groups in the Randomized Control Trial

Through computer-generated randomization, women will be randomized on the morning of planned induction. They will be notified via telephone by the research coordinator. The randomization will be stratified by parity (primiparous vs. multiparous) and by body mass index ($<30 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$).

5.4 Preparation and Administration of Study Drug

The following supplies should be gathered prior to insertion of the Foley catheter: one 16 French Foley catheter, one catheter plug, 60 cc of normal saline, one 60 cc syringe, sterile gel, and one pair of sterile gloves. The patient is appropriately for a pelvic exam. The examiner dons sterile gloves. He or she uses sterile gel and locates the cervical opening digitally. The tip of the Foley catheter is guided into cervix and through the internal os. The nurse then places the catheter plug in the outflow tract and injects 5 cc of normal saline into the inflow tract. The provider confirms that the balloon is in the appropriate position above the internal os. Then, the other 55 cc of normal saline are injected. The end of the catheter is taped to the patient's leg using foam tape.

Alternatively, depending on provider preference, the catheter can be placed using a speculum for guidance. In this case, the patient is placed in the lithotomy position. A speculum is inserted after the provider dons sterile gloves. Once the cervix is located, a ring forceps is placed on the anterior lip of the cervix. Another ring forceps is placed onto the tip of the catheter and is used to guide the catheter into the cervical os. Then, the balloon is inflated with 60 cc normal saline as above. Direct visualization confirms appropriate placement of the catheter. All other steps as described above are utilized.

5.5 Subject Compliance Monitoring

Not applicable.

5.6 Prior and Concomitant Therapy

Information about concomitant pharmacologic pain control therapies will be collected. Please see the “protocol for the intervention group” in the section 3.1 above for a description of pain control options for the outpatient group. As this section states, non pharmacologic options (warm baths, massage, frequent position changes, relaxation techniques, gentle stretching), Tylenol, and Morphine 10 mg IM once before discharge are permitted for the intervention group. The inpatient group will have the standard array of pain control options that will be left to provider discretion.

5.7 Packaging

The Foley catheter will be packaged by the manufacturer. A single device will be in a sterile, transparent wrapping.

5.8 Masking/Blinding of Study

There is no blinding in this study. It is not logistically possible to blind either the subjects or their providers.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Storage

The Foley catheters are already in use commonly on the Family Birth Center, and storage will not change. They are not removed from their package until minutes prior to their intended use. They may be exposed to light. They are stored in the Family Birth Center supply room, which is accessed only by a list of approved personnel using their identification badges.

5.9.2 Dispensing of Study Drug

The Foley catheters are already in use commonly on the Family Birth Center, and dispensing will not change. The Foley catheters are stored in the Family Birth Center supply room. They will be obtained from this supply area individually for placement in each patient. If they are damaged inadvertently, they will not be utilized. If they are damaged during placement, the device will be discarded and a new catheter will be used.

6 Study Procedures

6.1 Clinic visit

Eligible patients will be identified, educated, and consented as described above in the Study Design section (3.1).

6.2 Initial arrival to the Family Birth Center (both groups)

Please see the Study Design section under the headings “Protocol for the intervention (outpatient) group” and “Protocol for the inpatient (usual care) comparison/control group.” Briefly, all patients will undergo the following upon arrival:

1. Non stress test
2. Ultrasound for fetal presentation
3. Ultrasound for amniotic fluid index

- (a) Not routinely completed in usual care of induction of labor.
- 4. Cervical exam
- 5. A set of standard questions as described in section 3.1
- 6. Maternal vital signs

6.3 Return to the Family Birth Center after dismissal home (intervention (outpatient) group only)

When a patient in the intervention (outpatient) group is admitted to the hospital, either the next morning or any time in the middle of the night, she will undergo the following:

- 1. Non stress test
- 2. Ultrasound for fetal presentation
- 3. Cervical exam
- 4. Maternal vital signs

6.4 Inpatient postpartum stay

Patients typically remain in the hospital between 24-72 hours after their delivery depending on mode of delivery and patient preference. During their inpatient stay, they will have their vitals checked per current protocol. Secondary endpoints will be collected during this time frame.

All subjects will be given the maternal satisfaction survey to complete prior to dismissal from the hospital. All efforts will be made by the research team to ensure the patient has completed the survey. If she does not complete the survey while in the hospital, she will be contacted by phone within the following 2 weeks by a member of the research team to complete it over the phone.

The maternal satisfaction survey has been adapted from the survey utilized by Henry et. al [11].

6.5 Postpartum follow up

Secondary endpoints will be collected during the postpartum period. This is defined as 42 days after delivery or the final postpartum visit (typically at 6 weeks), whichever occurs later.

For patients who do not present to their postpartum visit, all available information in the electronic medical record will be used to determine the nature of the patient's postpartum course. A significant majority of low-risk obstetric patients live locally; therefore, we do not anticipate that adverse events will commonly be diagnosed and treated in other hospital systems.

7 Statistical Plan

7.1 Sample Size Determination for Randomized Control Trial

A power analysis was performed. With 64 patients per arm, we would have 80% power to detect a ½ standard deviation reduction in the hospitalization time for the outpatient group vs. the inpatient group, assuming a standard deviation of 8 (hours) and a reduction in the mean hospitalization time from 16 to 12 (hours) for the inpatient and outpatient groups, respectively. This also assumes a 2-sided significance level of 0.05.

This is a conservative estimate of the effect of the Foley catheter in the outpatient setting on pre-delivery hospitalization time, our primary outcome. The trial by Sciscione et al. [10]

observed that there was a reduction of 9.6 hours; Henry et al. found a reduction of 11.1 hours [11]. If we replicate this finding, we would be able to detect a difference in the primary outcome with a smaller number of patients, should we not meet desired enrollment.

7.2 Sample Size Determination for Prospective Study

A power analysis was performed and assumed a standard deviation of 8 hours. With 40 subjects in the Foley intervention arm and 160 subjects in the standard of care group, we would have 80% power to detect a $\frac{1}{2}$ standard deviation reduction in the predelivery hospitalization time from 16 to 12 hours in the standard of care and intervention groups, respectively. This also assumes a 2-sided significance level of 0.05.

7.3 Statistical Methods

Descriptive Statistics

Baseline characteristics will be descriptively summarized using mean and standard deviation for continuous variables that have a normal Gaussian distributions, and median and interquartile range for continuous variables with a skewed distribution. Frequencies and percentages will be used to summarize categorical baseline characteristics. Baseline characteristics will be compared between the intervention and control groups using the two-sample t-test, Wilcoxon rank sum test, and chi square test, as appropriate.

Handling of Missing Data

Subjects with missing data for the primary outcome will be excluded. Otherwise, missing data will be tracked and reported separately. If the amount of missing data within an analysis is greater than 10%, imputation methods will be used and the data re-analyzed as a sensitivity analysis.

Multiplicity

We will only evaluate outcomes determined a priori and will report all analyses.

Primary Hypothesis:

We hypothesize that the mean pre-delivery length of stay will be significantly less in the intervention group as compared to the control group. The mean time spent in the hospital between the groups will be compared using a 2-sample t-test or the nonparametric equivalent (Wilcoxon Rank-Sum test).

Secondary Hypotheses:

The secondary hypotheses are described below, followed by the statistical tests we plan to utilize.

1. Cesarean delivery rates will not differ between the two groups. This hypothesis will be tested using the Chi-Square or Fisher's exact test. Graphical and statistical methods will be used to show the data descriptively. We will report frequencies and percentages.

2. Maternal outcomes (including but not limited to postpartum hemorrhage, infection, hospital readmission rates, and satisfaction scores) will not be differ between the two groups. These hypotheses will be assessed using the Chi-Square or Fisher's exact test for categorical endpoints. For continuous endpoints, a 2-sample t-test or the nonparametric equivalent (Wilcoxon Rank-Sum test) will be used. Graphical and statistical methods will be used to show the data descriptively. For continuous data, we will also report means, medians, standard deviations, and ranges. For categorical data, we will report frequencies and percentages.

3. Fetal outcomes (including but not limited to APGAR scores, umbilical artery pH, and nursery disposition) will not differ between the two groups. These hypotheses will be assessed using the Chi-Square or Fisher's exact test for categorical endpoints. For continuous endpoints, a 2-sample t-test or the nonparametric equivalent (Wilcoxon Rank-Sum test) will be used. Graphical and statistical methods will be used to show the data descriptively. For continuous data, we will also report means, medians, standard deviations, and ranges. For categorical data, we will report frequencies and percentages.

7.4 Subject Population(s) for Analysis

We will analyze all subjects who were randomized in the randomized control trial design stage of the study, except those who electively withdrew from the trial. We will analyze all subjects enrolled in the prospective stage of the study, who do not electively withdraw.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

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

Adverse Event

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

Serious Adverse Event

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

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

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

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

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 42 days following delivery, or the date of the final postpartum visit (typically at 6 weeks), whichever comes last.

Preexisting Condition

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

General Physical Examination Findings

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

Post-study Adverse Event

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

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in

this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

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

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

-Hospitalization or prolonged hospitalization for diagnostic procedures, therapy, and/or surgery for all intrapartum and postpartum events, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

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

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

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

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

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

Information collected on the adverse event worksheet:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:

- The severity of the adverse event:
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.4 Unmasking/Unblinding Procedures

This study is not blinded.

8.5 Medical Monitoring

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

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Those regulations require a signed subject authorization informing the subject of the following:

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

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

9.2 Source Documents

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

records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use “white-out” for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

All data will be manually abstracted from the electronic medical record and recorded in the RedCap database by the Co-Principal Investigator.

Data Security and Confidentiality

Only necessary research team members will have access to the data for data entry or analysis. All data collection and analysis will be performed behind the Mayo firewall.

Data Quality Assurance

One trained team member, , will perform all data entry. A second team member will independently collect data on every 50th patient, and a comparison of data points between the first and second team members will be performed for quality assurance.

Data Clarification Process

Incomplete and outlying data points will be corrected as needed by reviewing the patient’s electronic medical record.

9.4 Records Retention

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

Subject-specific data and Case Report Forms will be identified by the patient’s medical record number and a unique number given in order of patient randomization; the patient’s name will not be included. The subject identification list will be stored behind the Mayo firewall.

Subject names and other directly identifiable information will not on any reports, publication, or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports:

1. As outlined in the Mayo Clinic Research Policy Manual –“Retention of and Access to Research Data Policy”

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

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

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

10.2 Auditing and Inspecting

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

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

11 Ethical Considerations

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

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

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

This study involves a vulnerable population, namely pregnant women. All criteria as specified in “Special categories of research: Pregnant women, human fetuses, and neonates” delineated by the Mayo Clinic Office for Human Research Protection have been met to perform research involving pregnant women.

12 Study Finances

12.1 Funding Source

This study is financed through grants from both the Obstetrics and Gynecology Research Committee and the Obstetrics and Gynecology Education Committee.

12.2 Conflict of Interest

None of the authors or study team members have a conflict of interest with this study including financial gain.

13 Publication Plan

There are no specific publication requirements from the funding agencies for this study. Dr. Vanessa Torbenson, replacing Dr. Mary Catherine Tolcher upon her departure from Mayo Clinic in June of 2016, holds primary responsibility for publication of the results this study. Her approval is required before any information can be published, used, or passed on to a third party.

This study will be registered to ClinicalTrials.gov prior to subject enrollment in the trial. The primary results will be posted to ClinicalTrials.gov within 12 months of final data collection.

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