STUDY PROTOCOL

A Trial of Cervidil (Dinoprostone PGE 2 Insert) for Outpatient Pre-induction Cervical Ripening in Women at 39.0-41.6 weeks gestation

Study Sponsor:	Ferring Pharmaceuticals
Study Contact Information:	Dixie Regional Medical Center/High Risk Obstetrics
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Principal Investigator Signature **Date**

Principal Investigator Printed Name

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1 - INTRODUCTION

1.1 Study Abstract

Induction of labor is a frequently planned obstetric procedure. Induction for women with an unfavorable cervix (bishop score <6) increases the risk of cesarean section. This risk may be reduced by ripening or softening the cervix before the induction of labor. This protocol outlines a randomized trial of 200 women evaluating the placement and use of Cervidil to the post vaginal fornix to soften the cervix in preparation for induction.

This trial is looking at inpatient vs outpatient pre-induction cervical ripening using Cervidil and the effects on:

- Maternal and newborn outcomes including time of admission to delivery
- System healthcare cost
- Cost to patient
- Patient satisfaction

1.2 Study Hypotheses

When compared to patients admitted to the hospital for cervical ripening:

- From the time of admission ("outpatient in a bed" status by iCentra, our EMR), patients in the outpatient cervical ripening arm will progress to complete cervical dilation in less time.
- The total overall cost of care for the encounter will be reduced for the group in the outpatient cervical ripening arm.
- Patients in the outpatient cervical ripening arm will have more overall satisfaction.

1.3 Purpose of the Protocol

This protocol describes the background, design and organization of the clinical trial and may be viewed as a written agreement among the study investigators. Before recruitment begins, the protocol will be approved by the Institutional Review Board (IRB). Any changes to the protocol during the study period require the approval of the Principal Investigator and the IRB.

The trial will be conducted in accordance with this written protocol, referenced documents, Good Clinical Practice guidelines, and all applicable regulatory requirements.

A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 - BACKGROUND

2.1 Introduction

The rate of induction of labor for singleton pregnancies was 23.3% in 2013 according to the CDC(Osterman & Martin, 2014). For women with an unfavorable cervix (bishop score <6) the risk of cesarean section and labor lasting over 24 hours is increased.(Chen, Xue, Gaudet, Walker, & Wen, 2015;

Chen et al., 2016) Decreasing healthcare costs while maintaining or improving outcomes is a major focus at local and national levels. Being able to do this with improved patient satisfaction is also a goal as demonstrated by Hospital Consumer Assessment of Healthcare Scores (HCAHPS).

Multiple trials have shown that cervical ripening decreases the 24 hour delivery rate and decreases primary C-Section rates. This however has not been demonstrated for all methods of cervical ripening or even consistently enough to recommend a specific method or process(Chen et al., 2016).

Pre-induction cervical ripening is not new. Use of Cervidil for use in initiation of labor has been used for over 40 years. (Elias, 1972; A. C. Turnbull, 1973). It has been reported that outpatient pre-induction cervical ripening may increase patient satisfaction. (Amorosa & Stone, 2015; D. Turnbull et al., 2013). Published studies demonstrate cost benefit and increased patient satisfaction from medical healthcare systems outside of the United States. Studies from facilities within the United States are needed to determine if these findings extend to our healthcare system. With the extensive documentation of use of the efficacy of pre-induction cervical ripening, the long history of outpatient cervical ripening, reports of possible cost saving, and increased patient satisfaction. (Howard et al., 2014) a comparison of outpatient cervical ripening methods along with a specific process including standardization of patients appropriate for the procedure, education of patients and hospital staff is needed.

Use of Cervidil is a mechanism that has been shown to be effective and safe for pre-induction cervical ripening is an option for outpatient cervical ripening. (Dowswell, Kelly, Livio, Norman, & Alfirevic, 2010; Kelly, Alfirevic, & Ghosh, 2013; Wang, Hong, Liu, Duan, & Yin, 2016)

2.2 Purpose and Rationale for Study

This trial is looking at patient satisfaction and cost comparison between inpatient and outpatient pre-induction cervical ripening. The method will be compared with inpatient pre-induction cervical ripening and patients admitted to the hospital in labor. Time from initiation of method, time in labor and delivery and time from onset of labor to delivery, and rate of achieving a vaginal delivery within 24 hours will be evaluated.

This protocol outlines a randomized trial of 200 women evaluating placement of Cervidil to the posterior vaginal fornix to soften the cervix in preparation for induction of labor. 100 patients will be randomized into the inpatient cervical ripening arm, and 100 to the outpatient cervical ripening arm. The study will not be powered for fetal or newborn mortality.

Increasing patient comfort, patient satisfaction, and inpatient costs will benefit future patients and healthcare for women who require/desire induction of labor.

2.3 Product being investigated:

Cervidil (outpatient cervical ripening) – Cervidil

2.4 Risks and Benefits to Participants

2.4.1 Risks to Participants

Cervical ripening has been studied extensively using Cervidil.

Risks as described in the product insert as revised February 2016 include:

1) Uterine hyperstimulation with fetal distress.
2) Uterine hyperstimulation without fetal distress
3) Fetal distress without uterine hyperstimulation

Several studies have shown that there have been no cases of fetal distress occurring after 2 hours of placement of dinoprostone. (Kamerling et al., 2003), (O'Brien, Mercer, Cleary, & Sibai, 1995), (Salvador, Simpson, & Cundiff, 2009). Salvador et. al. show that hyperstimulation resolved within 15 minutes after removal of Cervidil. There were no serious complications when patients were sent home after 1 hour of monitoring. (add (Salvador et al., 2009). Most of the patients in this study would otherwise have inpatient cervical ripening with Cervidil, or a different mechanism with similar risk. Thus there would be minimal additional increased risk to the study participants. The risk of hyperstimulation is decreased because the participants and healthcare personnel would both be trained to remove the insert with any sign of hyperstimulation. The term hyperstimulation is no longer used in most clinical settings and has been supplanted with the term uterine tachsystole. (Macones, Hankins, Spong, Hauth, & Moore, 2008) Tachysystole is when there are more than five contractions in 10 minutes, averaged over 30 minutes. Hyperstimulation is used here as that was the term used in the original documents.

2.4.2 Benefits to Participants

- Increased patient satisfaction by allowing them to be in their home environment;
    - There is more patient satisfaction if the patient can stay at home for the early part of labor. ("Committee Opinion No. 687: Approaches to Limit Intervention During Labor and Birth," 2017), this has also been shown to be true in some studies evaluating cervical ripening.
    - The patient has a scheduled time for initiation of the process of cervical ripening and for admission for induction. The current process is that the patient is scheduled for induction, and then must be available for up to several days to come to the hospital.
- Avoid the cost of the Cervidil insert. The Cervidil insert will be supplied to the patient free of charge. Other than the cost of the Cervidil and involvement of the study investigators the hospital and provider charges will not differ from those of patients not involved with the study.
- Focused patient education on labor, induction of labor, and cervical ripening.
- The patient will have the same or greater access to her OB provider, the OB Hospitalist, Labor and Delivery Staff or the study investigators than if she did not participate in the study.

3 – STUDY DESIGN

3.1 Primary Objectives

To show that when compared to patients admitted to the hospital for cervical ripening:

a. From the time of admission, patients in the outpatient cervical ripening arm will progress to the second stage of labor in less time.
b. Patients in the outpatient cervical ripening arm will have more overall satisfaction.
c. The total overall cost of care for the encounter will be reduced for the group in the outpatient cervical ripening arm.
d. Patients in the outpatient cervical ripening arm will spend less total time in the hospital.
e. Cesarean section rates will be similar.

3.2 Study Design Summary

This study is a prospective observational study.

3.3 Primary and Secondary Endpoints

3.3.1 Primary endpoints

- Time of complete dilation
- Date/time of hospital discharge

3.3.2 Secondary endpoints

- Time of delivery
  - Vaginal Delivery
  - Assisted Vaginal Delivery
  - Cesarean Delivery

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

1. Accurate gestational dating by Intermountain dating criteria placing the patient between 39 0/7 and 41 6/7 weeks gestation at the time of cervical ripening.
2. Planning to undergo cervical ripening for induction of labor
3. Participants must live <20 minutes away from the enrolling facility, or must stay < 20 minutes away.
4. Pregnant women
5. Over the age of 18 and less than age 41 at the time of enrollment
6. Fetal vertex position

Table 1. Guidelines for Re-dating Based on Ultrasonography		
Gestational Age Range*	**Method of Measurement**	**Discrepancy Between Ultrasound Dating and LMP Dating That Supports Re-dating**
≤13 6/7 wk ≤ 8 6/7 wk 9 0/7 wk to 13 6/7 wk	CRL	 More than 5 d More than 7 d
14 0/7 wk to 15 6/7 wk	BPD, HC, AC, FL	More than 7 d
16 0/7 wk to 21 6/7 wk	BPD, HC, AC, FL	More than 10 d
22 0/7 wk to 27 6/7 wk	BPD, HC, AC, FL	More than 14 d
†28 0/7 wk and beyond	BPD, HC, AC, FL	More than 21 d
Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CRL, crown-rump length; FL, femur length; HC, head circumference; LMP, last menstrual period. *Based on LMP †Because of the risk of re-dating a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone are especially problematic and need to be guided by careful consideration of the entire clinical picture and close surveillance.		

3.4.2 Gestational Age Determination

Gestational age will be determined by use of LMP, dating by ART, and obstetric ultrasound findings. Ultrasound dating will be used if LMP is uncertain. LMP will be used unless it is uncertain or the LMP – Ultrasound discrepancy is as shown in table 1. ACOG Committee Opinion 611 2014 reaffirmed 2016 ("Committee opinion no 611: method for estimating due date," 2014)

3.4.3 Exclusion Criteria

1) Gestational age <39 weeks or >41 weeks and 6 days
2) Hypertension (chronic, transitional, gestational, preeclampsia).
3) Multiple Gestation
4) IUGR
5) Anticoagulant therapy or at high risk for thromboembolism
6) Cardiac disease other than class I AHA
7) Prior incision in the contractile portion of the uterus
8) Placenta Previa
9) Documentation of Oligohydramnios per ACOG criteria: AFI ≤5 or deepest vertical pocket ≤2
10) Documentation of Polyhydramnios per ACOG criteria: AFI ≥24
11) Cervical dilation ≥ 3cm
12) Known fetal anomaly that would require advanced neonatal care

13) Pitocin-induction of labor is otherwise contraindicated
14) Patient is currently receiving other uterotonics (e.g., oxytocin, Cytotec, etc.)
15) Fetal distress
16) Unexplained vaginal bleeding during the pregnancy
17) Sensitivity to prostaglandin
18) Evidence of or suspicion of marked cephalo-pelvic disproportion (per the Cervidil package insert revision 02/2016, Ferring Pharmaceuticals INC. Parsippany NJ)

3.5 Informed Consent

Written informed consent will be obtained from patients prior to any research-related procedures. Full disclosure of the nature and potential risks of participating in the trial is to be made.

3.6 Randomization Method

Women will be randomized to either an inpatient or outpatient cervical ripening procedure using a computer generated randomization scheme through REDCap.

3.7 Investigational Drugs

Cervidil has FDA approval for hospital cervical ripening.

3.7.1 Investigational New Drug Application/Exemption

3.7.1.a

This protocol may need an Investigational New Drug Application (IND) as Cervidil has approval for inpatient use, and this study will evaluate the use of Cervidil in both inpatient and outpatient settings.

3.7.1.b

The risks to the participant is minimal, as the product is lawfully marketed as a prescription drug product, and this study does not utilize a route of administration or dosage level different than the current approved use of the product.

3.7.1.c

Even though published research indicates minimal risk for outpatient use, because outpatient use is not an indication listed on the package insert an IND will be obtained.

3.7.2 Drug Administration

Participant will come to labor and delivery prior to her induction. Cervidil 10mg timed release insert will be placed in the posterior vaginal fornix. The Cervidil will remain in place until the participant returns to continue the induction procedure (12 hours maximum.)

3.7.3 Concomitant Medications

1. Excluded medications include other uterotonics (example: oxytocin) – while Cervidil remains in place.
2. Known hypersensitivity to prostaglandins.

3.7.4 Drug Compliance

1. Participants will call Labor & Delivery if the insert does not stay in place prior to returning to L&D.
2. Upon admission to Labor and Delivery for induction, the RN will check for and remove the Cervidil and will notify study staff if any problems were noted with participant compliance.
3. Patient will call L&D immediately for any other study related concerns.

3.7.5 Drug Accountability

Drug accountability, including inventory, will be recorded using a drug accountability log.

4 – STUDY PROCEDURES

4.1 Screening for Eligibility and Recruitment

All women scheduling an induction with cervical ripening are potentially eligible for the study. Inclusion/exclusion criteria will be reviewed with the patient's chart.

The following methods of recruitment may be used:

- Participants will be referred to study personnel personally or by the offices of their Obstetric providers.
- Participants will be screened for eligibility by one of the investigators by review of submitted study participation form/prenatal record and electronic medical records.
- Study recruitment materials such as brochures and fliers may be used throughout the studies. As they are developed, these will be submitted to the IRB for approval.

If a patient appears to meet the criteria for the trial, she will be told about the study and asked for written informed consent to participate in the trial. Consent may be obtained any time after her induction is scheduled.

4.2 Study Procedures

Eligible and consenting patients will be randomized by a certified research staff member using an internet based randomization system maintained by the Women and Newborn Research department. The patient will be assigned to either the inpatient or outpatient cervical ripening group. Patients will be consented and randomized at the time the patient is being scheduled for their induction. If for any reason a research staff member is unavailable to consent the patient at the time the induction is being scheduled, a time will be set for the Cervidil placement as well as a time for the induction and consent/randomization will be scheduled prior to Cervidil placement. If they are randomized to the "inpatient group" then the following induction appointment will be cancelled.

When the participant comes in for their scheduled induction, eligibility criteria will be verified again.

4.2.1 For participants randomized to the Outpatient cervical ripening arm:

1) The patient will be an outpatient in L&D ("place in observation" status in iCentra) and placed on the fetal monitor. The clinician or hospitalist will perform an ultrasound for assessment of amniotic fluid volume by deepest vertical pocket (DVP) and review the fetal heart tracing. If the fetal heart rate is reactive (Category I) and the DVP is > 2cm the procedure may proceed once ordered by the attending obstetric provider or OB hospitalist.
2) Nursing or research staff member completes the outpatient cervical ripening case report form (CRF).
3) The cervix is examined and Bishop score is documented: Requirements of exam to do cervical ripening
    a. Cervix is dilated less than 3cm
    b. Presenting part is vertex
    c. The provider places the Cervidil into the posterior vaginal fornix with the string at the introitus.

   d. The provider is available for immediate phone consultation by the patient or nursing staff and is readily available to L&D.
4) The patient is watched with continuous fetal monitoring for 2 hours.
5) The patient is discharged to home if all of the following are present:
   a. Category 1 tracing X2 hours.
   b. No vaginal bleeding
   c. Normal maternal vital signs.
   d. Intact BOW
   e. Less than 1 contraction every 10 minutes at the time of discharge.
6) The patient remains for further evaluation if any of the following are noted. (If the patient must remain for any of these reasons, she will need an evaluation by her attending MD or the Hospitalist prior to discharge.):
   a. Category 2 or 3 tracing
   b. Vaginal bleeding (beyond spotting from placement of Cervidil insert)
   c. Any abnormal maternal vital signs (as defined in Intermountain Healthcare Standard Practice Guidelines)
   d. ROM
   e. More than 1 contraction every 10 minutes is noted in the last 30 minutes of monitoring.
   f. If the insert is inadvertently dispelled from the vagina, a new insert should be placed within 15 minutes and the participant may still be discharged if she meets criteria. (The vaginal insert releases prostaglandin at a rate of 0.3 mg/hr so replacing the insert within 15 minutes will not change the overall effect of the medication)
7) Patient will remove the insert and return to the hospital:
   a. For spontaneous rupture of membranes
   b. For vaginal bleeding
   c. Consistent contractions closer than every 10 minutes
   d. Severe pain
   e. Decreased fetal movement
   f. Temperature over 100.5 degrees F.
8) When admitted to L&D for induction as outpatient in a bed:
   a. Admission history and physical is done by labor nurse
   b. Cervidil is removed and Bishop score is documented.
   c. Results of exam are given to the attending provider.
   d. If appropriate, Pitocin induction of labor is started per Intermountain Healthcare Standard Practice Guidelines.
9) Cervidil placement should not exceed 12 hours.
   a. Management of induction per Intermountain Healthcare Standard Practice Guidelines continued at the discretion of the admitting provider.
   b.

4.2.2 For participants randomized to the inpatient cervical ripening arm:

The patient is scheduled in L&D for:

1) Admission as “outpatient in a bed” in iCentra for hospital placement of Cervidil.

   a. The patient's priority is based on the maternal and fetal condition compared to other scheduled inductions.
2) Induction of labor.

Preadmission:

The patient will have education and consent to the procedure prior to admission.

1) The patient will be admitted to L&D ("outpatient in a bed" status in iCentra) and placed on the fetal monitor. The clinician or hospitalist will perform an ultrasound for assessment of amniotic fluid volume by deepest vertical pocket (DVP) and review the fetal heart tracing. If the fetal heart rate is reactive (Category I) and the DVP is > 2cm the procedure may proceed once ordered by the attending obstetric provider or OB hospitalist.
2) Nursing or research staff member completes the outpatient cervical ripening CRF.
3) If the fetal heart rate is reactive (Cat I) and the DVP is >2cm the procedure may proceed once ordered by attending obstetric provider or OB Hospitalist.
4) The cervix is examined: Requirements of exam to do cervical ripening
   a. Cervix is dilated less than 3cm
   b. Presenting part is vertex
   c. The provider places the Cervidil into the posterior vaginal fornix with the string at the introitus.
   d. The provider is available for immediate phone consultation by the patient or nursing staff and is readily available to L&D.
5) The patient is watched with continuous fetal monitoring for 2 hours.
6) The patient remains hospitalized
   a. If the insert is inadvertently dispelled from the vagina, a new insert should be placed within 15 minutes and the participant may still be discharged if she meets criteria. (The vaginal insert releases prostaglandin at a rate of 0.3 mg/hr so replacing the insert within 15 minutes will not change the overall effect of the medication)
7) The Cervidil may be removed and induction of labor per Intermountain Healthcare Standard Practice Guidelines may be started per discretion of the admitting provider for any of the following:
   a. For spontaneous rupture of membranes
   b. For vaginal bleeding
   c. Consistent contractions closer than every 10 minutes
   d. Severe pain
   e. Decreased fetal movement
   f. Temperature over 100.5 degrees F.
   g. Document dat/time of Cervidil removal
   h. Document Bishop score
8) Cervidil placement should not exceed 12 hours.
   a. Management of induction per Intermountain Healthcare Standard Practice Guidelines continued at the discretion of the admitting provider.

4.3 Event Reporting

Adverse events, unanticipated problems and intercurrent illnesses will be documented in REDCap when reported by the participant or the RN caring for the patient during labor. Follow up by her physician will continue throughout the duration of her hospital stay. Serious Adverse Events (SAE's) will be reported to both the FDA and to Ferring's safety mailbox Safety.MailboxUS@ferring.com within 24 hrs. Non-serious adverse events will be reported to Ferring cumulatively on a quarterly basis.

4.3.1 Adverse Events/Unanticipated Problems

Adverse events will be reported by submitting a completed adverse events form to the Principal Investigator.

The Investigator is responsible for identifying adverse events that occur to each subject during their participation in the study. An adverse event or unanticipated problem can occur at any time during the conduct of the study. An adverse event can be identified by the Investigator or reported by the subject.

Protocol deviations/violations may occur throughout the study. These must be recorded and evaluated for IRB reporting.

Definitions

- Adverse Event: An adverse event is any undesirable experience associated with the use of a medical product in a patient.
- Serious Adverse Event: An adverse event is serious when it involves a death, is life-threatening, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage, any other serious event that may jeopardize the patient and may require medical or surgical intervention/treatment to prevent other outcomes.
- Unanticipated Problem: unforeseen event in terms of nature, severity, or frequency, given the research procedures and the subject population being studied

Reporting Requirements

Events must be reported to the IRB or sponsoring agency, per policy. All events are reported in the Event Reporting Portal in the Intermountain Healthcare Women and Newborn Research Department.

Unanticipated Problems: Reporting is required if the following criteria are met.

a) unexpected -considering the research procedures described in the protocol, investigator's brochures and informed consent documents, and in consideration of the characteristics of the study population;

b) is related or possibly related to the subject's participation in the research; and

c) Suggests that the research places subjects or others at greater risk of harm than was previously known or recognized.

Unanticipated problems will be recorded in the Event Reporting Portal that will be evaluated by the principal investigator or designee. This will include a summary of the event, correction of the deviation/violation, and a corrective action plan. The PI/designee will indicate if it is reportable to the IRB, per current IRB policy.

4.3.2 Protocol Deviations/Violations

Protocol Deviation/Violation: Accidental or unintentional changes to, or non-compliance with, the IRB approved protocol without prior IRB review and approval that could affect the subject's rights, safety, welfare, and/or the integrity of the resultant data, regardless of whether there was actual harm.

All events are reported in the Event Reporting Portal in the Intermountain Healthcare Women and Newborn Research Department. The Protocol Deviation Form that will be evaluated by the principal investigator or designee. This will include a summary of the event, correction of the deviation/violation, and a corrective action plan. The PI/designee will indicate if it is reportable to the IRB.

4.4 Study Outcome Measures and Ascertainment

4.4.1 Primary Outcome

- Time of admission for induction (as recorded in iCentra) to complete dilation
- Total hospital costs charged to patient, as obtained by Intermountain Healthcare billing services.

4.4.2 Maternal Secondary Outcomes

- Patient satisfaction as measured by patient satisfaction/pain/anxiety surveys.
- Vaginal delivery rate
- Operative Vaginal delivery rate.
- Cesarean delivery rate.
- Start of oxytocin until delivery
- Time of delivery until discharge
- Time of admission until discharge

4.4.3 Fetal and Neonatal Secondary Outcomes

- 5 minute APGAR score
- Time of admission to Mom/Baby
- NICU Admission/Length of stay

4.4.4 Hospital System Outcomes

- Cost of hospitalization to the system

5 – STATISTICAL CONSIDERATIONS

5.1 Data Relevant to the Primary Outcome

5.1.1 Sample Size and Power

1. 200 women randomized to two groups for comparison will be enrolled in the study to participate in the research group (receiving Cervidil insert). Data will be collected on the comparison group (all patients admitted cervical ripening and induction of labor) during the same time period.
2. With 200 patients in each group a standard two sample t test has 95% power to detect a difference of 0.36 times the standard deviation and 80% power to detect differences of 0.28 times the standard deviation. For example, if the mean time from admitting to delivery is 10 hours with a standard deviation of 2 hours (meaning that most (95%) times are in the range from 6 to 14 hours) then with this sample size we would have 95% power to detect a reduction of 43.2 minutes in the treatment group and a 80% power to detect a difference of 33.6 minutes. These numbers will differ if the true standard deviation is different from 2 hours.

5.2 Withdrawal of Participants

Withdrawal per patient choice

Patient will be withdrawn if she goes into spontaneous labor prior to the date of planned cervical ripening.

5.2.1 Feasibility

It is estimated that it may take up to 3 years to complete the study.

5.3 Analysis Plan

Primary analysis will be done using 2 sample t-tests on the numeric outcomes with the possibility of using the log of the outcome when the outcome is skewed (as is common for waiting times and cost variables). If the data is not sufficiently normal after logging, then a 2 sample permutation test on the means will be used instead. For categorical outcomes (e.g. delivery type) a chi-squared test will be used to compare the proportion in each category between the treatment and control groups. All tests will be performed at a 5% significance level. The p-values will be reported both unadjusted for multiple outcomes and also adjusted using the False Discovery Rate method. Conclusions will be made using the unadjusted values since each outcome is of interest by itself and they are predetermined.

Additional exploratory data analysis will be done using linear model including regression and logistic regression to adjust for other variables of interest. Any interesting results will be reported as exploratory with need for confirmation since the potential results are not on a predetermined list.

5.4 Interim Analysis

Each adverse outcome will be reviewed within 24 hours of report by the PI. In the event that the PI is unavailable, the adverse outcome may be reviewed by any of the other physician investigators.

Interim analysis will be done every 6 months until completion of the study. The study investigators may perform an interim analysis at any time if they suspect a higher adverse outcome than anticipated.

6 – DATA COLLECTION

6.1 Data Collection Forms

The data collection forms will include a 24 item study specific survey consisting of questions from the previously validated DoD/VA pain Supplemental Questions scale, study specific questions, and a 32 item survey to be completed by all patients seen at Intermountain.

- DoD/VA Pain Supplemental Questions (Cleeland & Ryan, 1994)
- HCAHPS (HCAHPS Fact Sheet. June, 2015, http://www.hcahpsonline.org/Facts.aspx)

6.2 Web Data Entry System

This study will utilize the REDCap data management system. This system will reside behind Intermountain Healthcare firewalls and is CFR Part 11 compliant.

6.3 Performance Monitoring

The following data elements will be collected.

- Participant ID
- Age
- EDC
- Method of Dating
- G/TPAL
- Date/Time
    - Hospital evaluation
        - Bishop score prior to placement of cervidil insert
        - Bishop score on admission upon removal of Cervidil insert
    - Time of insertion
    - Time Home
    - Time of readmit
    - Reason for readmit (see above reasons to return to L&D)
    - Time of removal of Cervidil insert
    - Time Pitocin started
    - Epidural- if placed and if so when
    - Delivery time
- Method of delivery
    - Spontaneous vaginal
    - Operative vaginal
    - C-Section
    - Indication if other than spontaneous vaginal delivery
- Apgar, weight, cord pH if done

6.4 Confidentiality and Data Protection

Confidentiality

Information is kept with study identification numbers to protect the identity of participants. Electronic data are protected on encrypted drives and databases (REDCap) that are only accessible to authorized research staff.

Paper documents are locked in research offices, accessible only to the study team.

Data Protection

REDCap and Intermountain servers are maintained by the Intermountain IS team. These are regularly backed up to ensure data integrity.

7 – STUDY ADMINISTRATION

7.1 Organization and Funding

Intermountain Healthcare. See attached budget requested from Ferring Pharmaceuticals.

7.1.1 Participating Clinical Centers

Dixie Regional Medical Center, labor and delivery unit, and Utah Valley Hospital, labor and delivery unit will conduct this study.

7.1.2 Funding

Funding will be provided by Ferring Pharmaceuticals

7.2 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) will be compromised of at least 3 members who are not affiliated with the trial to monitor the maternal and fetal outcomes in the study. The DSMC will evaluate study data from the first five participants, including any reported adverse events. Thereafter, they will meet on a quarterly basis throughout the remainder of the study enrollment period of the study.

7.2.1 Stopping Rules/Discontinuation Criteria

As per interim analysis above (5.4). The study can be discontinued at any time by the investigators or the DSMC if any of outcomes are less than anticipated and there is documented or a concern for patient harm.

7.2.2 Data Monitoring

The overall responsibility of data monitoring for the study is with the principal investigator. This includes ensuring that data are collected accurately, timely, and retained throughout the study on all participants. A member the Women and Newborn Research department will perform periodic reviews of the data to provide feedback to the investigator and research team. These reviews will be scheduled with the study team in advance.

<u>Monitored Events</u>

- Informed consent documents
- Inclusion/exclusion criteria
- Potential adverse events
- IRB reports and documentation
- Regulatory Documentation

<u>Monitoring Intervals</u>

- After the first five patients are enrolled, an initial review will be conducted to ensure that consent documents are appropriately reviewed and participants are appropriately enrolled.

Monitoring will occur at least quarterly of the events listed above under “Monitored Events.”

Quality Assurance

Monitoring will occur at least quarterly to review data as described above. As often as possible the information listed above will be reviewed for all participants. If unable, a random selection of participants will be monitored.

To ensure appropriate consent, a Consent Documentation Form will be utilized for this study. This will document the informed consent process, review of required elements of consent, and allow for a double-check for staff to ensure that the proper document is used.

8 – STUDY TIMETABLE

8.1 Training and Certification

All investigators will be certified by Intermountain Healthcare standard by CITI.

Staff at the hospital (DRMC) and participating provider's offices will be trained prior to initiation of the study. Training will be done by the study investigators and include reviewing the protocol, and the process.

8.2 Recruitment and Data Collection Period

The study sign-up period is anticipated to be up to 3 years and the participants will be followed from sign up until 3 months after delivery.

8.3 Final Analysis

After a two-month period for completion of data entry for the trial and close-out of the delivery and primary outcome, the data set will be locked and available for the primary and other main analyses.

9 – REFERENCES

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