The Columbia University Medical Center and New York-Presbyterian Hospital and
The University of Texas Medical Branch (UTMB)

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Title:

Comparison of Misoprostol Ripening Efficacy With Dilapan

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Signature and Approval Section:

Reviewer	**Signature and Date of last review & Approval**
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Regulatory Notice:
This clinical study protocol is prepared in accordance with Helsinki Declaration and MEDDEV2.12 / 2 rev 2 January 2012 - Post Market Clinical Follow-up studies. This clinical study protocol and subsequent study report will become the part of technical product documentation and serves as proof of compliance with the requirements of the Directive and other related regulations.

Investigator´s Signature Section:

I hereby declare that I have read this Clinical Investigational Plan and I understand the information. With my signature, I agree to conduct this clinical investigation in accordance with the Clinical Investigational Plan, applicable Helsinki Declaration and MEDDEV2.12 / 2 rev 2 January 2012 - Post Market Clinical Follow-up studies, applicable local laws and regulatory requirements. Moreover, I will keep all information obtained from the participation in this clinical investigation confidential unless otherwise agreed in writing.

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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PROTOCOL SYNOPSIS PAGE

Background - In developed nations 25 % of pregnant women undergo induction of labor (IOL) for various indications. Likelihood of vaginal delivery depends on the degree of ripeness of cervix. Majority of women undergoing induction of labor are candidates for cervical ripening. Dilapan-S® is an osmotic hygroscopic dilator of cervix commonly used for cervical preparation for mid trimester abortions. It has been proven safe for use for IOL at term. Misoprostol is a synthetic prostaglandin E1 analogue, widely used for cervical ripening and IOL in United States and is considered as standard of care.

Objective - To assess the efficacy of Dilapan-S® for cervical ripening compared to Misoprostol in women undergoing IOL at or more than 37 weeks gestation.

Primary outcome - Proportion of women randomized to receive Dilapan-S® and Misoprostol for cervical ripening achieving vaginal delivery within 36 hours of intervention.

Secondary outcomes - A composite of maternal and fetal outcomes including overall vaginal delivery rate, cesarean section rate, Bishop score after cervical ripening, infections, postpartum hemorrhage. Neonatal outcomes include Apgar scores, NICU admission and sepsis.

Study design - Non Inferiority, unblinded randomized, controlled trial where 322 eligible participants undergoing IOL at >37 weeks gestation at CUMC and admitted to labor and delivery unit will be enrolled and randomly assigned in a ratio 1:1 to either receive Dilapan-S® or Misoprostol for cervical ripening. The study is powered at 85% for detecting the primary outcome with a type 1 error at 2.5% for one-sided test.

Procedures - After randomization all participants will undergo assessment as per the floor protocol including Bishop Score. Patients will have either Dilapan-S® rods inserted into their cervix by the providers or receive 25 mcg of misoprostol orally every 2 hours to a maximum of 6 doses over 12 hours. Patients will be examined after 12 hours, Dilapan-S® rods will be removed and Bishop Score will be reassessed. There will be a ±30 minute window for the removal of the Dilapan-S® rods and ±15 minutes for Misoprostol administration. Patients in both groups will be evaluated for artificial rupture of membranes and initiation of oxytocin for inducing uterine contraction. A diagnosis of failed IOL will be made if patient does not go into active labor within 24 hours after initiation of Oxytocin and AROM. Intrapartum management will be according to institutional guidelines. All study participants will be contacted by phone 2 weeks after delivery to find out if they needed any additional treatment following discharge. All study patients will be asked to fill out a questionnaire regarding their experience with the method of induction. Data will be collected by chart review and analyzed based on the outlined statistical plan.

Title
Dilapan vs Misoprostol for cervical ripening
[COMRED – comparison of Misoprostol ripening efficacy with Dilapan]

Trial Objective
To assess efficacy of Dilapan-S® [osmotic hygroscopic dilator] for cervical ripening compared to 25mcg of oral Misoprostol

Background
In developed countries about 25% of the pregnant women are delivered by induction of labor annually [1]. A decision to proceed with induction of labor is made when continuation of pregnancy may worsen the condition of mother or her fetus. This number is expected to go up in the future as our understanding of pathophysiology of pregnancy improves. A recent landmark randomized controlled trial involving more than 6000 nulliparous women has proved that induction of labor at 39 weeks improves perinatal outcomes without increasing the cesarean section rate compared to expectant management [2].
Induction of labor is one of the most common obstetric procedure [1]. Current practice in United States is to admit the patients to labor and delivery floor once a decision to proceed with induction of labor has been made. Majority of these women are candidates for cervical ripening as their cervix is found to be unfavorable for initiation of oxytocin based on the assessment of Bishop Score at the time of admission. Bishop score of 6 or more is a good predictor of likelihood of achieving vaginal delivery within 24 hours after initiation of labor induction. Cervical ripening is a process by which cervix undergoes enzymatic dissolution of collagen fibrils and changes in intercellular matrix, leading to increase in water content and softening [1]. These changes transform cervix to a soft, pliable structure that undergoes dilatation and effacement in response to uterine contractions. Two commonly methods used for cervical ripening are prostaglandins and mechanical devices.

Misoprostol
Misoprostol is a prostaglandin E1 analog approved for treatment and prevention of gastric ulcers. Misoprostol acts on the intracellular matrix of the cervix, causes breakdown of the collagen fibrils leading to cervical softening. It also induces uterine contractions. ACOG has indicated that use of Misoprostol appears to be safe and effective for induction of labor when used in low dose [2]. Despite a large number of trials of Misoprostol for cervical ripening there is no clear consensus as to the optimal oral dose, dosing interval and the maximum number of doses that can be given. In PROBAAT II, a non-inferiority trial comparing oral Misoprostol to Foley catheter for cervical ripening, Eikelder, Jozwiak et al. [3] used 50mcg of Misoprostol orally, dosed every 4 hours with a maximum of three times per day. Ibraheemi et al. [4] in their recent RCT - Misoprostol with Foley bulb compared with Misoprostol alone for cervical ripening, used 25 mcg of Misoprostol vaginally every 4 hours to a maximum 6 doses. Levine et al. [5] in their randomized clinical trial - Foley or Misoprostol for management of induction used 25 mcg of Misoprostol every 3 hours with a maximum of 6 doses over 24 hours. WHO [10] has suggested using Misoprostol 25 mcg orally every 2 hours.

Weeks et al. [7] recommend use of oral misoprostol every 2 hours. This is supported by the pharmacokinetic studies that show that oral Misoprostol reaches its peak serum level in 30 minutes and its half-life is only 90 minutes. Misoprostol is rapidly metabolized by the liver and excreted by kidneys. This is also supported by a recent randomized trial of oxytocin versus oral misoprostol given every 2 hours which found no differences in major outcomes but reduced rates of hyperstimulation with Misoprostol.

Dilapan-S®

Dilapan-S® is a mechanical method for cervical ripening using rods made of a patented hydrogel Aquacryl, it is marketed in form of rods of 3 and 4 mm diameter. The rods are inserted into the cervical canal just above the internal os (see APPENDIX 1: Instructions for Use). Within 6-8 hours these rods expand up to 4 times of their original diameter and create a radial force inside the cervical canal causing it to dilate. In addition, an inflammatory process begins which activates endogenous prostaglandins leading to cervical softening and shortening. This response occurs at a predictable rate. Studies done in 1990s and recent ongoing, national and international trials [11, 12] have established safety of Dilapan-S® for use in pregnant women.

Rationale for randomized clinical trial

Misoprostol is one of the most commonly used methods for cervical ripening and labor induction in United States. It is safe and cost effective and shortens induction to delivery interval compared to other pharmacological and mechanical methods [5]. Dilapan-S® is a device that is FDA approved for cervical ripening. It has predictable response over time and lower risk of uterine tachysystole and hyperstimulation. Dilapan-S® has potential for use in outpatient setting among low risk patients due to its efficacy and predictable response. There are no studies comparing efficacy and safety of Dilapan-S® to Misoprostol. We propose to do a well-designed randomized trial to assess if Dilapan-S® has a similar safety and efficacy profile compared to 25 mcg of oral Misoprostol.

Study Design

Non-inferiority unblinded randomized controlled trial where subjects will be randomized in a ratio of 1:1 to Dilapan-S® and misoprostol groups. We decided to use the non-inferiority design as Misoprostol is considered as one of the accepted and standard treatments for induction of labor in United States. Our assumptions for the trial are based on results of PROBAAT-II trial, a large well designed randomized trial conducted in EU for studying efficacy of mechanical and pharmacological methods for labor induction. Assuming a rate of vaginal delivery within 36 hours to be 65% for Misoprostol and 71% for mechanical method (based on data on transcervical Foley catheter in PROBAAT-II [3] and a recent trial comparing Foley catheter to Dilapan-S® for cervical ripening done by Saad et al. [12]), with a non-inferiority margin of 10 % and an expected screen failures rate of 5%, a total of 322 subjects will need to be randomized in ratio 1:1 to Dilapan-S® vs Misoprostol group. 153 eligible and assessable subjects are needed in Dilapan-S® group and 153 in Misoprostol group for analysis. The study is powered at 85% for detecting the primary outcome with a type 1 error at 2.5% for one-sided test.

Objective for the trial
To assess efficacy of cervical ripening with Dilapan-S® or Misoprostol in women undergoing induction of labor.

Primary research question (primary endpoint)
Proportion of subjects achieving vaginal delivery within 36 hours after the initiation of the cervical ripening in Misoprostol and Dilapan-S® group.

Rationale: The authors of PROBAAT-II study make the valid point that as an outcome of labor induction, giving birth vaginally is more important than how quickly it happens; therefore 24 hours may not be a long enough time for appropriate assessment. Indeed, the effect found in the PROBAAT-II study would have been reversed had the outcome been measured by assessing vaginal delivery within 36 hours. There is therefore a call to standardize the outcome measure in IOL trials to a vaginal delivery within 36 hours [6], particularly when mechanical methods are employed.

Secondary research questions (secondary endpoints)
- Bishop score at 12 hours after the intervention
- Percentage of subjects delivering vaginally in 24 hours after the initiation of intervention
- Overall vaginal delivery rate in each group
- Rate of operative deliveries
- Rate of cesarean deliveries in each group.
- Total length of hospital stay

Maternal outcomes:
- Chorioamnionitis
- Endometritis within 2 weeks after delivery ,
- Postpartum hemorrhage (EBL>1000cc /and or drop in HCT by 10 points)

Neonatal outcomes:
- Apgar score <7 at 5 min
- Cord Arterial blood pH <7
- Base excess >12mmol/l
- NICU admission within 2 weeks after delivery
- Antibiotic use within 2 weeks after delivery

Exploratory research questions (exploratory endpoints)
There is paucity of clinical data in the literature obtained through well designed clinical trials for Dilapan-S® use for cervical ripening in women undergoing induction of labor. We would like to collect following information for assessing safety of Dilapan-S® use when compared to Misoprostol. Similar information was collected by Saad et al. [12] in their recent randomized trial comparing efficacy of Dilapan-S® to Foley catheter for cervical ripening. These are known potential complications of planned interventions and include (but are not limited to) the following:

Undesirable side effects

- Fever, nausea, vomiting and diarrhea
- Uterine tachysystole
- Hyperstimulation
- Uterine hypertonus
- Failed induction of labor, arrest of first and second stage of labor

Complications specific to dilator insertion

- Vaginal bleeding
- Rupture of membranes
- Cervical laceration
- Excessive pain causing need for analgesia during cervical ripening
- Vasovagal reaction during insertion of the device
- Entrapment of the device
- Fragmentation of device during removal or insertion
- Retraction of device into uterine cavity.

Study subjects inclusion criteria

1. Women undergoing labor induction with a gestation of ≥37 weeks determined by best clinical and/or ultrasound estimation
2. Live fetus with in cephalic presentation
3. Singleton pregnancy
4. Able to provide informed consent for participation in the study.

Study subjects exclusion criteria

1. Contraindication for vaginal delivery
2. Age less than 18 years
3. Prior uterine scar from a cesarean section or myomectomy
4. Patients who have HELLP syndrome or eclampsia
5. Active genital herpes at the time of labor induction
6. Complex medical problems that may require assistance with second stage of labor
7. Bishop score ≥ 6
8. Major fetal congenital anomalies (as assessed by investigator)
9. Premature rupture of membranes

Pre-randomization training

Participating providers at Columbia University Medical Center will watch a video tutorial on insertion as part of their training and perform at least one Dilapan-S® insertion for patients undergoing induction of labor, prior to initiation of the trial. These will not be study participants and no data will be collected in these women. This will be done in the presence of the PI or other trained providers. The purpose of this training is to ensure that all participating providers follow the Dilapan-S® Instructions for use as per the manufacturer's recommendation based on FDA approval for its use for cervical ripening. This will be documented in Training Log placed in Regulatory binder.

Participating providers at UTMB regularly perform Dilapan-S® insertion for patients undergoing induction of labor per standard of care, however any provider that has not previously performed Dilapan-S® insertion will watch a video tutorial on insertion as part of their training and perform at least one Dilapan-S® insertion for patients undergoing induction of labor, prior to placing Dilapan-S® for research study purposes. These will not be study participants and no data will be collected in these women. This will be done in the presence of the PI or other trained providers. The purpose of this training is to ensure that all participating providers follow the Dilapan-S® Instructions for use as per the manufacturer's recommendation based on FDA approval for its use for cervical ripening. This will be documented in Training Log placed in Regulatory binder

Study Procedures

Screening for Eligibility and Consent

All women admitted to labor and delivery at initiated sites within Columbia University Medical Center and at UTMB for induction of labor will be screened for eligibility for participation by trained research staff. Women who meet the criteria for inclusion in the trial will be assessed by the Attending physician, Resident or Midwife providing care to the patient and informed about the trial and they are candidates for cervical ripening. Patients who agree to participate in the trial will be required to sign and date an Informed Consent Form (ICF).

Randomization

Participants will be randomized in a ratio of 1:1 for Dilapan-S® insertion or oral Misoprostol, using stratification for:

(A) parity (nulliparous vs. parous women) and
(B) gestational age (≤39 weeks vs. >39 weeks).

Due to the nature of intervention blinding of subjects or providers is not possible.
Randomization plan will be generated based on computer program. Subjects will either undergo Dilapan-S® insertion or receive up to 6 oral doses of 25 mcg of Misoprostol based on their allocation to treatment groups.

Baseline procedures

Subject enrolled in the study will be evaluated by a care provider and a history and physical examination including a sterile speculum and digital vaginal exam will be done. Provider will also review maternal vital signs and indication for induction of labor. All enrolled subjects will have CTG monitoring for at least 20 minutes prior to the planned intervention and IV access and Type and Screen as per the labor and delivery standard procedure.

Pre-induction

Arm A: Dilapan-S® group
Patients who are randomized to receive Dilapan-S®, will have rods of Dilapan-S® inserted in their cervix by the supervising provider, under aseptic precautions with a speculum exam, either digitally or using a sponge forceps, as per manufacturer's recommendations [Appendix 1]. The Bishop score at the time of eligibility assessment and number of rods inserted will be recorded. Dilapan-S® will be left in cervix for 12 hours (±30 minutes). Patients will be allowed to ambulate, shower and have light meals as long as they meet the criteria based on institutional guidelines for intermittent fetal heart monitoring. “Nothing per vagina” including douching and no bathing is allowed.

Arm B: Misoprostol group
For subjects randomized to Misoprostol group, after the baseline assessment and a reassuring CTG monitoring for 20 minutes, 25mcg of Misoprostol will be administered orally every 2 hours (±15 minutes) to a maximum of 6 doses. All subjects will have continuous fetal monitoring. A dose will be held if patient is noted to have uterine tachysystole, hyperstimulation, fetal heart tracing abnormalities or 3 or more painful uterine contractions over a period of 10 minutes (indicating onset of labor). Administration of Misoprostol will be done by the nurse assigned to the patient.

Subjects in both groups will remain on labor and delivery (L&D) floor and will have continuous fetal monitoring as per the institutional guidelines.
All study participants will be examined after 12 hours of receiving intervention unless there is an indication for an exam prior to this period. Reasons for an exam earlier than 12 hours after the initiation of cervical ripening intervention include:

1. Onset of spontaneous labor
   (defined as regular painful uterine contractions with a dilation of ≥ 4 cm and effacement of 75% or more)
2. Vaginal bleeding
3. Persistent Category 2 or Category 3 fetal heart tracing
4. Spontaneous rupture of membranes
5. Spontaneous expulsion of Dilapan-S® rods
   (if Bishop score is still <6, another set of rods may be placed and allowed to remain in situ for a maximum of 12 hours cumulative based on clinical assessment made by the supervising provider)
6. AROM is indicated

Labor Induction
Subjects in both groups will have an assessment of Bishop score 12 hours after the study intervention and evaluated for amniotomy and Oxytocin infusion. Oxytocin will be initiated as per the institutional guidelines. Amniotomy will be undertaken as soon as clinically feasible. If after 24 hours of amniotomy with Oxytocin the patient is not in active labor [cervical dilatation<6 cm], a diagnosis of failed induction will be made [Appendix 2] and a decision will be made to proceed with cesarean section. During labor, decision to proceed with operative delivery or cesarean section will be made by the attending physician supervising the care of the patient. All subjects will have the option to receive epidural during labor for pain management.

Oxytocin administration

CUMC:

Oxytocin will be administered for labor induction and augmentation as per the institutional guidelines [Appendix 2]. Oxytocin is supplied to L&D unit in prepared bags with 30 units of Oxytocin in 500 cc of Normal Saline. Oxytocin will be initiated at 1 milliunit/minute and increased every 15 minutes, till an optimal response is obtained.
The maximum dose is limited to 40 milliunits/minute.

UTMB:

Oxytocin will be administered for labor induction and augmentation as per the institutional guidelines [Appendix 3]. Oxytocin is supplied to L&D unit in prepared bags with 20 units of Oxytocin in 1000 cc of Lactated Ringers. Oxytocin will be initiated at 2 milliunit/minute and increased every 20 minutes, till an optimal response is obtained.
The maximum dose is limited to 40 milliunits/minute.

Delivery period

Data for date, time and mode of delivery and intra-partum complications (incl. those found during induction period) will be collected. The complications will include, but are not limited to following:

- Uterine tachysystole
  (defined as > 5 contractions per 10 minutes averaged over 30 minutes.
- Hyperstimulation
  (defined as > 5 contractions averaged over 20 min with abnormal fetal heart changes)[3]
- Uterine hypertonus
  (defined as a single contraction lasting at least 2 minutes.
- Failed induction of labor, arrest of first and second stage of labor (see Appendix 2)
  (defined according to the US NICHD, ACOG and SMFM workgroup guidelines [9]
- Intrapartum fever
  (defined as body temperature (skin or oral) of 39°C at one reading or as body temperature of 38-38.9°C which persists when retaken after 30 minutes) [13]
  Intrapartum fever when present with any of the following indicates infection may be present.
  1. Purulent discharge on speculum exam from the cervical canal
  2. Fetal tachycardia lasting more than 10 minutes
  3. Maternal WBC count of more than 15 K
  4. Amniotic fluid analysis results indicative of an infection

Postpartum and FU procedures

All participants will receive routine postpartum care. They will be asked to fill out a questionnaire (Appendix 4) in the postpartum period regarding their experience with the cervical ripening method.
All study participants will be contacted via phone two weeks after delivery to find out if they or their baby had any postpartum complication and received treatment at any health care entity other than the hospital where they were admitted for delivery.

Safety reporting

Scope

In relation to the **Dilapan-S®**, the Clinical Trial is a post-market clinical follow-up study (PMCF) conducted using CE marked device within its intended use. The provisions of Directive 93/42/EEC concerning information and notification of incidents occurring following placing devices on the market are fully applicable. Medical Device Reporting regulation (21 CFR 803) will be followed to report certain device related adverse events and product problems to the FDA.

The Investigator shall ensure that Funder will be informed about any SAE that would be related to study device according to the definitions given below. Complaints about any Product Problem are within the scope of obligatory notification too, incl. product defects, malfunctions or user errors.

AEs not related to the study device are not to be reported to Funder. Borderline events should be handled conservatively and the Funder should be notified in case of any doubt.

Definitions

Adverse Event (AE) is any untoward medical occurrence in a subject and that does not necessarily have a causal relationship to the study device and study procedure.

Serious Adverse Event (SAE) is any AE that:

- Results in death;
- Is Life-threatening;
- Leads to Hospitalization
- Causes Disability and/or Permanent impairment of a body function or structure;
- Requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
- Leads to fetal demise, a congenital abnormality, or birth defect.

Product Problem includes:

- Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. It also includes inadequate labelling.
- Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan.
- User error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Evaluation of an AE

When evaluating AEs, the Investigator must determine:

- if the event is serious. Seriousness criteria are based on definition of an SAE (above).
- if the event is related to the study device. The following rules are to be applied:
  a) **Not Related**: AE which are clearly and unquestionably due to causes other than the study device (e.g., concomitant disease).
  b) **Related**: AE which are felt with a reasonable degree of certainty to be related to the study device.

c) **Unknown**: AEs for which a connection with the study device cannot be ruled-out with certainty, or not enough information is available to assess the relationship.

Confidentiality of Study Data

Data and research records will primarily be stored electronically in a study database. This study database will be developed and maintained with support from Columbia University's Department of Obstetrics and Gynecology CORE Data Team. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies [8]. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self- documenting process by all members of the research team with planning assistance from the OB/GYN Division of Research Informatics Support Team. The iterative development and testing process results in a well-planned data collection strategy for individual studies. With the assistance of the OB/GYN Division of Research Informatics, the research team work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap servers are securely housed in an onsite limited access data center and is managed by the OB/GYN IT Division. The data is all stored on a private, protected university managed server. All users are authenticated via the CU and NYP LDAP servers and their access is restricted on a role-specific basis. Access can only be granted by administrators of the system.

REDCap@OBGYN was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Columbia University and New York Presbyterian guidelines. All collected data are backed up daily. REDCap@OBGYN system ID is 4283. Source data will be stored on encrypted, password protected servers maintained by OBGYN IT at the CUMC server farm; system id is 3959. Some data may be collected on paper case report forms, which will be stored in a locked file cabinet in the Study Investigators' office and will be accessible only to named research personnel. Privacy Protections Patient information will be collected by trained research personnel in a private setting. Patient confidentiality will be maintained following HIPAA rules and regulations.

Data Safety and Monitoring

To ensure safety of the subjects, local monitoring will be completed by the Quality Assurance Monitor for the Department of Obstetrics and Gynecology for this Investigator/Peer study. At each scheduled monitoring visit, the QA will randomly select a representative number of study subject charts to be reviewed. Additional monitoring will be based on the initial monitoring review. An independent monitor appointed by the Funder {Medicem} will review the data periodically throughout the duration of trial to ensure the subject safety, data quality and protocol compliance.

Biostatistics

Primary/Null Hypothesis, to be rejected is as follows:
Dilapan is inferior to Misoprostol in efficacy for cervical ripening for induction of labor.

Basic principles for an evaluation of the study are presented in this section. It is concerned mostly about the study populations and evaluation of the study endpoints, more detailed

description of how to analyze collected data will be specified in statistical analysis plan (SAP) which will be written and approved before the database lock.

Additionally, the primary outcome will be analyzed on each stratification factor. Mantel-Haenzsel test will be used to test the difference between the subgroups. This testing will be done for exploratory purposes only.

Study populations

Safety Population
The Safety population will be comprised of all subjects to whom Dilapan-S® was inserted or who received at least one dose of misoprostol. This population will be based on the actual treatment received if this differs from that to which the subject was randomized. This population will be used for the analysis of safety data.

Intent-to-treat Population (ITT)
ITT includes all patients that were randomized into the study. ITT subjects will be analyzed in accordance with their randomized study treatment (i.e. in the treatment group they were originally allocated, regardless of treatment actually received). ITT will be used for evaluation of the baseline characteristics and as the primary population for efficacy assessments.

Per Protocol Population (PP)
PP is a subset of ITT patients who received study treatment. Following patients will be excluded from the PP population:

1. Patients with major protocol violation affecting the efficacy endpoints. Major protocol violations include (but are not limited to): a. Treatment assignment error
   b. Violation of one or more inclusion/exclusion criteria
   c. Use of forbidden medication
2. Patients who were prematurely withdrawn
3. Patients with missing data for the evaluation of the primary endpoint

This list can be extended based on a knowledge of other serious issues appearing in the data. PP population will be used for evaluation of efficacy endpoints as a sensitivity analysis.

Evaluation of the primary variable

The primary endpoint of this study is:
Proportion of subjects achieving vaginal delivery within 36 hours after the initiation of the cervical ripening in Misoprostol and Dilapan-S® group.

Proportion of patients in each group and their difference will be calculated. 97.5% one-sided confidence interval adjusted for the stratification factors (parity and gestational age) will be calculated for the difference in the proportions and conclusion about non-inferiority will be drawn from it taking into consideration 10% non-inferiority margin. Unadjusted confidence interval will be calculated as well.

Evaluation of the secondary variables
Bishop score at 12 hours after the intervention and total length of hospital stay will be summarized separately for each arm. Means of the two treatment arms will be compared by two-sample t-test.
All secondary variables considering rates and percentages of patients will be calculated for both arms. Difference in proportions will be derived together with a 95% two-sided confidence interval. The difference between treatment groups will be concluded if the confidence interval does not include zero.
Maternal and neonatal outcomes will be summarized as reported in the CRF.

Exploratory variables
Exploratory variables will be evaluated from the adverse event and device deficiency reports. Number of cases and proportion of patients will be presented.

Potential Risks
The potential foreseeable risks to the subjects are:

- pain and discomfort during insertion of Dilapan-S®
- vaginal bleeding
- rupture of membranes and cervical lacerations.
- entrapment of Dilapan-S® rods inside cervix
- retraction into uterine cavity necessitating additional procedures for removal.
- infection leading to chorioamnionitis/endometritis
- allergic reaction to the hydrogel
- risk of improper release or misuse of personal information or specimens. *(the chance of this happening is very small; the research team has many protections in place to lessen this risk)*
- unexpected unknown risk to mother and fetus *(very unlikely)*

Potential Benefits
This trial may show that Dilapan-S® is a safe and effective method for cervical ripening and may increase the likelihood of vaginal delivery. If subjects decide to participate in this research study, they (and/or their newborn) may or may not directly benefit from their participation. The data gathered on maternal and neonatal outcomes will serve to increase the general knowledge regarding safe and effective methods for cervical ripening in women undergoing induction of labor. The study may also provide information if Dilapan-S® is cost effective for cervical ripening in terms of impact on length of stay and has a satisfactory safety profile for use in outpatient setting.

Alternatives
The alternative to this study is not to participate and to continue receiving standard care during delivery and postpartum period.

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