University of Texas Medical Branch at Galveston

Research Protocol IRB #21-0327

Title: (Free Foley Trial) Tension versus Tension-Free Foley Balloon for Cervical Ripening in Nulliparous Women Undergoing Induction of Labor: A Cluster Randomized Controlled Trial
Principal Investigator: Meagan Benson, DO
Faculty supervisor: Antonio Saad, MD
Funding: Departmental

1. Introduction and Purpose:

Foley balloons are commonly used as a mechanical method of cervical ripening for induction of labor. Foley balloons may be placed either under tension or without tension (tension-free). Currently at UTMB, it is left to the provider to decide which technique is utilized. The purpose of our study is to examine time to delivery in nulliparous women undergoing induction of labor who have a Foley balloon placed as a mechanical cervical dilator, assigned to either tension or without tension. The goal is to determine if there is a potential added benefit to placing the Foley balloon on tension as compared to no tension, both are considered standard of care at our institution. Our hypothesis is that Foley balloon under tension for cervical ripening results in shorter time to vaginal delivery compared to Foley balloon placed without tension.

2. Background:

The rate of induction of labor has increased significantly in the United States. The US National Vital Statistics Report birth data for 2018 reported an induction of labor rate of 27.1% compared to 23% in 2013.[14,15] The rate of induction of labor will likely continue to increase as studies are published demonstrating maternal and neonatal benefits associated with elective 39-week induction of labor.[10] The rate of induction of labor is likely to also continue to increase as the incidence in medical comorbidities continue to increase in the United States. Even though induction of labor occurs in greater than a quarter of births in the United States, significant variation in clinical practice exists in the management of induction of labor. There is significant need to research methods for induction of labor given these shifts in clinical practice and the lack of an accepted standard of care.

Placement of a mechanical dilator is a common method of labor induction.[2,3,5,7,8,11,13,16, 17,18] Advantages of mechanical dilators over pharmacologic methods include typically lower cost and the ability to discontinue the induction agent in case of fetal distress. The first use of a Foley balloon for cervical dilation was described by Krauss in 1853. The use of a transcervical Foley balloon for labor induction was initially described by Embrey and Mollison.[6] The transcervical Foley balloon is the most common method of mechanical dilation utilized at our institution, placed either with or without tension based on provider and nursing practices and preferences. There is not an evidenced-based standard of care protocol for mechanical cervical ripening with a Foley balloon; therefore, significant variation in clinical practice exists between individual providers and institutions. Variations exist in type of balloon (Foley balloon verses double balloon), placement (manual verses visual placement with sterile speculum), the use of concomitant ripening agents, and the use of tension on the balloon.

The use of tension placed on a Foley balloon has been previously examined. Fruhman, G. et al., examined Foley balloon with tension verses Foley balloon without tension with the use of concomitant Pitocin.[7] In addition, an extensive search on clinicaltrials.gov revealed another study that is currently recruiting to assess Foley balloon placement with tension verses no tension with the use of concomitant vaginal misoprostol for cervical ripening (NCT03588585). No studies were found that examined the use of a foley balloon with or without tension without the use of concomitant cervical ripening agents for term induction of labor in nulliparous subjects. Both methods are currently being used inconsistently in our labor and delivery unit at UTMB and both are standard of care in our institution. In addition, prior trials examined were not powered for parity.

3. Concise Summary of Project:

This will be a pragmatic cluster randomized clinical trial. The study period will be between February 2022 and February 2023. The number of subjects studied will be 405 subjects at UTMB. The target population for our study is nulliparous women who present for induction of labor at term. If there is a decision by the obstetric team to place a transcervical foley dilator for cervical ripening in a prospective subject meeting inclusion criteria for the study, the obstetric provider will follow the weekly randomization sequence for study group (No Tension) or the control group (Tension) based on the assigned cluster for the entire unit for that week. Both study groups will receive standardized labor management as currently performed at UTMB as Foley balloon placed with tension and without tension are both considered standard of care at our institution. The subjects will receive the same care and expertise as any other patient treated in our unit. See below for more details on study procedures and consenting process.

The Tension standard of care (control group) will undergo induction of labor by placement of a transcervical Foley balloon, which is standard of care at our institution. A Foley balloon will be introduced into the cervix either manually or under direct visualization based on provider preference and training. The balloon tubing will be pulled to create tension and will then be taped to the patient's inner thigh. Balloon tension will be periodically assessed, and tension reapplied if needed as per the unit's standard protocol.

The No Tension standard of care (study group) will undergo induction of labor by placement of a transcervical Foley balloon. A Foley balloon will be introduced into the cervix either manually or under direct visualization as the control group but the foley will not be taped or under tension. The balloon tubing will be left free of tension and will hang freely.

Subjects in the control and study group will then undergo standard intrapartum care. The total participation time in the study will be considered terminated following delivery. Details of the procedure for the control group and study group can be found below.

4. Study Procedures:

Visit#1

4.1 Recruitment, Screening and Consenting:

Recruitment: Subjects will not be recruited, however, we will include records of all nulliparous pregnant subjects admitted to L&D for scheduled induction of labor at term who have had a decision made by their managing clinical team to place a transcervical foley balloon for purposes of mechanical dilation who met inclusion and exclusion criteria listed below.

Screening: Subject records will be screened and included if they met inclusion and exclusion criteria at the time a decision to place a transcervical foley balloon with or without tension under the randomized sequence for purposes of mechanical dilation was made in labor and delivery.

Consenting process: Subjects will not be consented; we are requesting a waiver of patient consent. However, we will be obtaining written consent from all faculty providers that practice in our unit, relinquishing the standard of care method for placement of Foley balloon with tension versus no tension to a controlled randomized process before initiation of the trial. The provider consent form is attached in the application. Subjects will not be consented for the study; however, subjects will be verbally informed about the methods used for induction of labor. Providers placing the Foley balloon will obtain verbal consent for labor induction with Foley balloon with tension or without tension, which is the current standard of care. Written consent to participate in this study will be obtained from the faculty who agree to allow their patients to participate in this research protocol. Providers may withdraw individual patients from the study if the provider no longer deems that participation is in the best interest of the individual.

Justification of waiver:
Consent for research will not be obtained as this study involves two standards of care that are currently being performed at UTMB. A waver of informed consent will be submitted with the IRB application. However, we will be obtaining written consent from all providers (see attached document and more information below).

The primary risk of participation in the study is breach of confidentiality. The waiver of consent for research is appropriate because no contact between the study team and subjects will take place outside of standard clinical care. All subjects will receive one of two standards of care, which are currently selected per providers choice for placing the Foley balloon either under tension (tubing taped to thigh) or without tension (tubing hangs free). We feel this study is of minimal risk, as subjects would normally receive this standard of care through an uncontrolled randomized process of provider's choice, which inconsistently varies between tension vs. no tension. Randomizing the method of tension versus no tension in a controlled process, will allow data to be effectively analyzed to assess if one method is best for subjects. Both methods of induction utilized are approved by the American College of Obstetricians and Gynecologists, and it is not currently known if one method is inferior to the other.

Additionally, we will be obtaining written consent from all providers that practice in our unit, relinquishing the standard of care method of Foley balloon placement with tension or no tension to a controlled randomized process before initiation of the trial. The provider consent document is attached in the IRB application.

The cluster randomized trial design is such that each week, the chosen method of induction of labor in subjects meeting inclusion criteria is randomized to either:

- Foley balloon with tension which is current standard of care (control group)
- Foley balloon without tension (tension free) which is also a current standard of care (study group).
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To summarize:

- A waiver of patient consent for research is requested
- No subjects will be consented for research

- Written medical consent for delivery will be obtained from all subjects per standard of care
- The risks and benefits of induction of labor will be discussed with each patient prior to obtaining medical consent for delivery, which is consistent with the current standard of care.
- In addition subjects will be verbally informed the type of labor induction they will receive, (which is also consistent with current standard of care):
    - Foley balloon with tension (tubing taped to thigh)
    - Foley balloon without tension (tubing hangs free)
- Written research consent will be obtained from all providers to follow weekly randomization of tension vs. no tension
- The two methods of induction being compared (tension vs. no tension) are currently accepted and considered standard of practice for women with an unfavorable cervix who require induction of labor.

4.2. Operationalization

Randomization

This study will use cluster randomization, with each week group described as a cluster. Prior studies have investigated induction of labor methods utilizing cluster randomization.[1] Cluster randomization will be computer generated and will assign each cluster (weeks) to the control or study group. Both the study group and the control group are considered part of the standard of care for induction of labor at UTMB. Clusters will be block randomized in groups (weekly).

Labor and Delivery Unit/Staff

Several training sessions will occur to notify all staff of the trial and the protocol. Training sessions will include a copy of the protocol to review as well as follow-up email communication. The PI will also be available for questions. All operations will be also reviewed with all staff.

At shift change 0630-0700 am and pm every Monday to Friday, randomization assignments will be announced to all nurses and providers on the Labor and Delivery unit. All staff caring for subjects during the week of randomization will be notified of the cluster randomized for that week for all labor inductions. Notifications and plastic tags will be placed in the workstations for the providers and at all nursing stations on labor and delivery and at the patient's room door stating Tension or No Tension. A notification will also be placed at the work station of the study team. All study team in the Perinatal Research Department will also be notified via email at the beginning of each week.
An Epic order will be placed by provider specifying "Foley balloon under tension" or "Foley balloon No Tension" according to the randomization assignment.
Subjects under treatment conditions before this time will be included as part of the treatment block assignment at the time of inclusion and will not be allowed to cross over. The subject will be included in the analysis by intention-to-treat once the randomization assignment has been made.

The cluster randomized trial design is such that each week, the chosen method of induction of labor in subjects meeting inclusion criteria is randomized to either the Tension standard of care (control group) or No Tension standard of care (study group). All subjects who would meet inclusion criteria for foley balloon induction of labor will be participants in the study. The two methods of induction being compared are currently accepted and practiced standards used for women with an unfavorable cervix who

require induction of labor. The risks and benefits of induction of labor will be discussed with each patient prior to administration and consent for delivery obtained, consistent with the current standard of care on Labor and Delivery at ***UTMB***.

4.3. Placement of Foley Balloon

The control group will undergo induction of labor by placement of a transcervical Foley balloon, which is standard of care at our institution. A Foley balloon will be introduced into the cervix either manually or under direct visualization with a sterile speculum exam based on provider preference and training. The balloon will be filled with 60 ml of sterile 0.9% NaCl. Proper placement will be confirmed manually. The balloon tubing will be pulled to create tension and will then be taped to the patient's inner thigh. The foley balloon will be left in place on tension for at least 12 hours, and no longer than 24 hours. Balloon tension will be periodically assessed, and tension reapplied if needed.

The study group will undergo induction of labor by placement of a transcervical Foley balloon as the control group. A Foley balloon is introduced into the cervix either manually or under direct visualization as the control group but the foley **will not be taped or under tension**. The balloon tubing will be left free of tension and will hang freely.

Additional information regarding management of the foley balloon in both the study and control group:

- Placement of the Foley balloon will be performed by the managing obstetrical team.
- The Foley balloon will be left in place for at least 12 hours, and no longer than 24 hours.
- Balloon will be assessed close to 12 hours following placement in all participants.
- The balloon may be assessed prior to the 12 hours for a variety of reasons including, for example, patient request, changes in fetal heart tracing, increased reported pain, and spontaneous rupture of membranes. The reason for checking prior to twelve hours will be documented.
- Following expulsion or removal at 12 hours, sterile vaginal exam will be performed. Patient will then undergo standard intrapartum care.
- If cervix remains unfavorable after extraction of the foley balloon at 12 hours (< 3cm and at most 60% effaced), a second Foley balloon will be used in this case for a maximum of 12 hrs. No crossover will be allowed. In other words, a second Foley balloon will be placed in the same manner as the first assignment arm.
- If the Foley balloon is unable to be placed in either insertion technique, a prostaglandin agent for cervical ripening may be used and insertion of the mechanical dilator can be re-attempted at a later time, as is the standard of care at our institution. No cross over will be allowed.

Visit#2

4.4. Additional Baseline Procedures

- Routine intrapartum care will be provided by the patient's managing obstetric team.
- Trained and experienced study team will be responsible for all research data abstraction.
- The PI and faculty sponsor will review and validate the diagnosis for all subjects identified to have the primary outcomes. If there is uncertainty, a faculty sponsor will review the chart, discuss with the study team as needed, and make a final determination regarding the outcome.

- Maternal outcomes will be assessed following delivery.
- Data collection forms will be used during these processes and charts will be reviewed up to 30 days postpartum. We will collect demographic data, as well as data related to the patient's intrapartum course, delivery, and immediate postpartum period while inpatient.
- Subjects' participation will end following delivery.

4.5. Study visits / Follow-up

No extra postpartum follow-up visits will be performed.

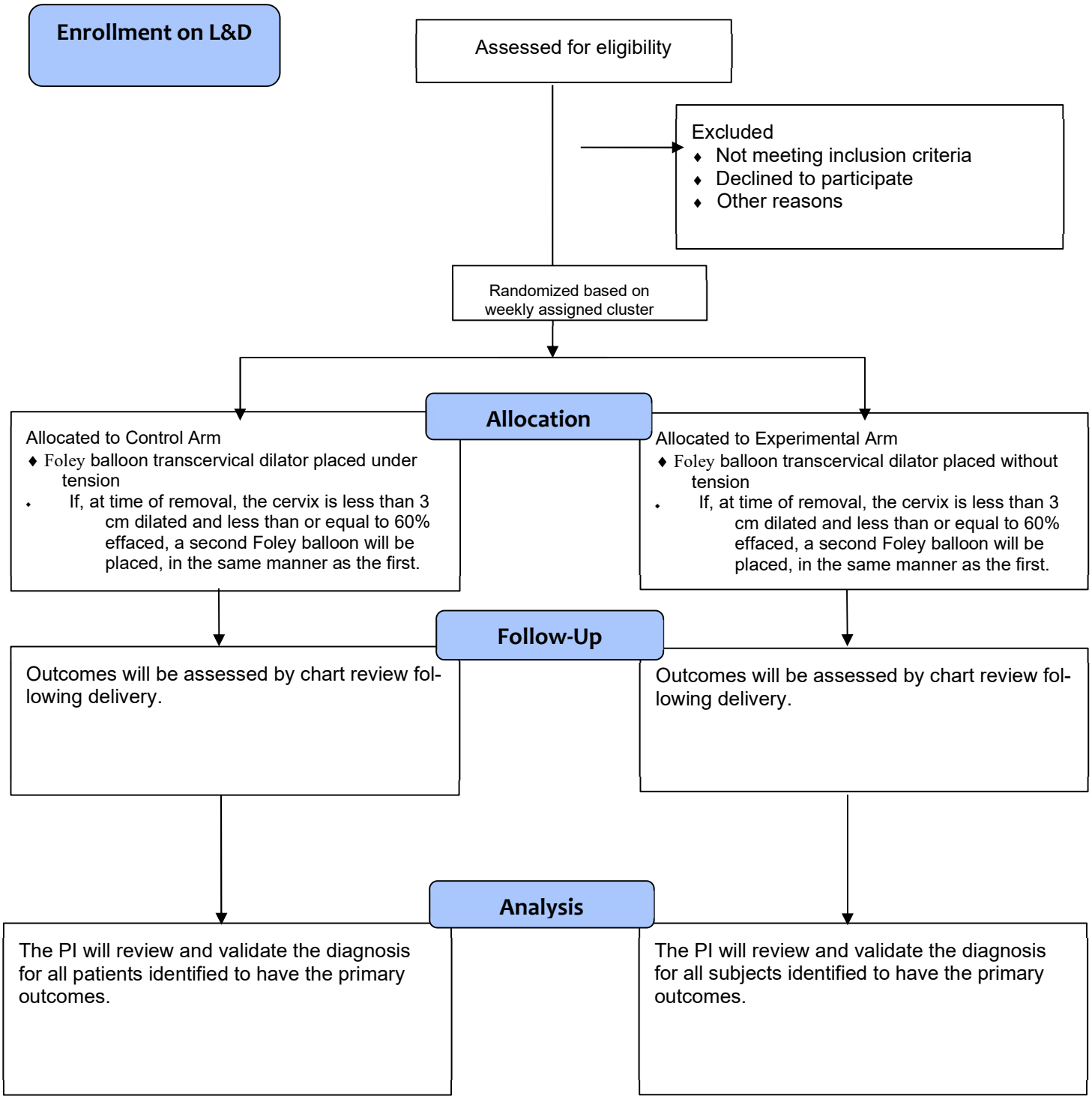
4.6. Withdrawals

Subjects who withdraw from the study will be excluded from further follow-up. Outcomes ascertained up until the time of withdrawal will be reported in intention-to-treat fashion. The patient will be withdrawn from the study if she wishes to discontinue participation. If any of the exclusion criteria listed above are met, or condition changes that leads to inclusion criteria not being met anymore, data collection will be terminated, and the patient will be withdrawn from the study.

4.7. Data Collection

The data collected will not be used for clinical diagnosis or treatment purposes. The data collected will be kept on a password-secured UTMB computer. An encrypted USB flash drive will be used to transfer data. The data will be linked to the patient by the patient's MRN number. This identifier is needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted. Data will be collected from the patient's chart and the chart of the neonate. The data collected will include demographics and data needed to assess the primary and secondary outcomes listed below. The data collection sheet is uploaded for review by the IRB. It is imperative that studies involving induction of labor and intrapartum care assess the outcomes of the neonate.

Study Summary Flow Diagram



4.8. Primary Outcomes

- Time to vaginal delivery measured from time of initial foley balloon placement to delivery

4.9 Secondary Outcomes

- Request for IV/PO pain medications or epidural placement following placement of Foley balloon transcervical dilator during cervical ripening period
- Time of artificial rupture of membranes
- Incidence of malpresentation following removal of foley balloon
- Incidence of primary cesarean delivery
- Incidence of postpartum hemorrhage
- Chorioamnionitis (also known as "IAI," or "triple I"):
    - A **presumptive diagnosis** of IAI (suspected triple I) can be made in women with:
        - **Fever** – ≥39.0°C [102.2°F] **or** 38.0°C [100.4°F] to 38.9°C [102.02°F] on two occasions 30 minutes apart, without another clear source **PLUS** one or more of the following:
        - Baseline fetal heart rate >160 beats/min for ≥10 minutes, excluding accelerations, decelerations, and periods of marked variability
        - Maternal white cell count >15,000/mm3 in the absence of corticosteroids and ideally showing a left shift (bandemia)
        - Purulent-appearing fluid coming from the cervical os visualized by speculum examination
    - A **confirmed diagnosis** of IAI can be made in women with:
        - **All of the above PLUS** one or more of the following objective laboratory findings:
            - Positive Gram stain of amniotic fluid
            - Low glucose level in amniotic fluid
            - Positive amniotic fluid culture
            - High white cell (WBC) count in amniotic fluid in the absence of a bloody tap
            - Histopathologic evidence of infection or inflammation or both in the placenta, fetal membranes, or the umbilical cord vessels (funisitis)
- Endometritis - must meet the following criteria:
    - Infection occurs within 30 days after the operative procedure AND
    - Infection presumed to involve the uterus AND
    - Patient has at least one of the following:
        - Purulent drainage from a drain that is placed through a stab wound into the abdomen or pelvis
        - Organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ / space
        - An abscess or other evidence of infection involving the abdomen or pelvis that is found on direct examination, during re-operation, or by histopathologic or radiologic examination
- Neonatal infection, defined as sepsis, fever, positive cultures, or a suspicious clinical course that warranted treatment with antibiotics

- APGAR scores
- NICU admission rates
- Neonatal hospital length of stay

5. Criteria for Inclusion of Subjects:
- Women ≥18 and ≤50
- Term induction of labor
- Nulliparous
- Vertex
- Singleton
- Plan for Foley balloon placement by the managing obstetrics team
- Cervical exam less than 3 cm dilated and less than or equal to 60% effaced

6. Criteria for Exclusion of Subjects:
- Patient unwilling or unable to provide verbal consent
- Fetal demise or major congenital anomaly
- Preterm (<37 0/7weeks)
- Multiple gestation
- Previous uterine surgery
- Abnormal placentation
- Malpresentation
- Magnesium infusion for preeclampsia with severe features
- Prelabor rupture of membranes
- Fetal growth restriction
- Non-reassuring fetal heart rate tracing prior to inclusion

7. Sources of Research Material: Electronic medical chart / records

8. Potential Risks:
No significant adverse effects are expected with the use of transcervical Foley balloons for mechanical dilation. Foley balloons are the standard of care for induction of labor at UTMB. The most significant risks are vaginal bleeding due to cervical trauma and incidental rupture of membranes, as well as pain or discomfort with placement. The patient will undergo inpatient induction of labor, so any adverse reaction would be promptly detected and addressed.

8.1. Randomization risk
There are no foreseen randomization risks as both the study and control group are currently methods utilized for induction of labor at UTMB.

8.2. Loss of Confidentiality
Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep patient's information confidential; however, this cannot be guaranteed.

8.3 Mechanical dilator (Foley balloon):
1. No tension has no adverse effects except possibly a longer cervical ripening time. A foley balloon placed without tension is currently used as an accepted form of induction of labor at UTMB and is not thought to have any increased risks. Foley balloons placed with and without

tension are both considered standard of care at our institution, with one not thought to have any more risk.

9. Subject Safety and Data Monitoring

The PI and research collaborators will be responsible for monitoring the safety of this study. The report will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AE's) or serious adverse events (SAE's) which may have occurred, and any changes in the protocol because of these issues.

The PI's and collaborators will ensure all aspects of data quality, including monitoring for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness, and responsiveness to data queries. The team will be meeting every quarter to review procedures and resolve any issues that need to be addressed.

A final report will be submitted yearly with every continuation review IRB application.

Data will be collected and stored with the participant ID code only. The master enrollment log linking patient identifiers with study ID numbers will be kept in a password-protected database on the OB/GYN department's internal server separate from the data. Data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The principal investigator or approved research staff will be available to monitor the data and correct any discrepancies based on source documents if needed.

10. Procedures to Maintain Confidentiality

- The data collected will be indirectly linked to the subject by patient's MRN number.
- When the subject accepts to participate in the study, a number will be attributed to the patient, and this number will be entered on the data collection sheet.
- The data collected will be transferred to the PI's password-secured UTMB computer that is stored in a locked room using an USB flash drive.
- The study PI will be the only person to have a list with the number designated to each subject and the corresponding patient's MRN number. This list will be kept in a locked cabinet of the PI's locked UTMB office. This identifier is needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted.
- Data will not be disclosed to outside persons or entities.

11. Potential Benefits

Subjects who undergo Foley balloon placement with tension may be at decreased risk for protracted labor. If this is the case, our study stands to benefit women who have a Foley balloon or other mechanical dilator placed in future cases of labor induction.

12. Statistical Approach

Analysis will be performed by intention-to-treat. Univariable and multivariable analysis will be used to describe the population in the study and to identify potential confounding variables. For this analysis, normality will be tested using Shapiro-Wilk method. Demographics and descriptive statistics will be used to provide a profile of the study sample. Data will be either shown as median +/- IQR or mean +/- SDEV. Bivariate tests such as t test, Pearson's chi square, and Mann-Whitney tests will be used as indicated to identify any key differences in the profiles of subjects across study conditions. Statistical

analyses of primary and secondary outcomes between study groups will be performed by multilevel regression analysis accounting for both confounding variables as well as adjusting for any potential intra class correlation that may arise from the cluster study design.

Sample size was calculated based on the determination of superiority. The primary outcome is time in minutes from Foley balloon placement to delivery. For the sample size calculation, based on our prior published data[10], the primary outcome in control arm would be 1053.4 ± 535.73 mins. Using difference rate of 25% (No tension group: 1316.748 mins), power of 80% and 2-sided alpha of 0.05, and the assumption that 10 eligible subjects are induced per week, we previously estimate that we will need 13 clusters (10/cluster) with complete ascertainment. Currently, we have recruited approximately 15 subjects per cluster. For the previously planned 13 clusters in each group (26 clusters total), we estimate a final total number of 405 subjects. Final sample size: 405 (minimum of 130/group). This difference between both methods is clinically significant. Detailed : Estimated sample sizes for a two-sample means test (z test) ;Study parameters: alpha Since this is a single center study in one same location the intra-cluster correlation coefficient of variance (rho) should be close to 0 and would give us a sample size of 140, but we chose the worst-case scenario of a rho of 0.1 (graph).[4,9]

This trial will be registered with Clinical Trials Register (Clinicaltrials.gov), before recruitment is initiated and after IRB approval.

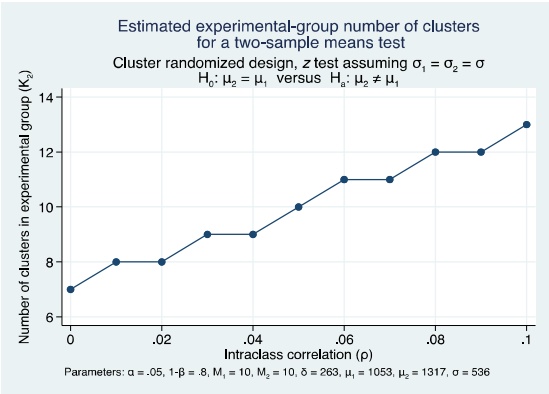
SAMPLE SIZE COMPUTATION
power twomeans 1053.399 1316.74, sd(535.73) m1(10) m2(10) rho(0.1)

Performing iteration ...

Estimated numbers of clusters for a two-sample means test
Cluster randomized design, z test assuming sd1 = sd2 = sd
Ho: m2 = m1 versus Ha: m2 != m1

Study parameters:

alpha = 0.0500
power = 0.8000
delta = 263.3410
m1 = 1053.3990
m2 = 1316.7400
sd = 535.7300



Cluster design:

M1 = 10
M2 = 10
rho = 0.1000

Estimated numbers of clusters and sample sizes:

K1 = 13
K2 = 13
N1 = minimum 130

N2 = minimum 130

Addendum 10/3/2022

Since we started recruitment on June 6th, 2022, we have completed 17 clusters (N total of 265 subjects), averaging 15 subjects per week. To preserve power in a cluster design trial, our statistician recommended completing the original plan of 26 clusters (13 clusters per group). Therefore, we anticipate that 405 patients will be enrolled in total. In addition, the trial will be considered completed whenever the final cluster number is reached. If we need more than 405 subjects to be enrolled, the trial will be paused, and an addendum will be submitted to the IRB.

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