Title: Early amniotomy following transcervical Foley balloon in the induction of labor: a randomized clinical trial

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The University of Texas Medical Branch at Galveston

Research Protocol IRB #20-0163

Title: Early amniotomy following transcervical Foley balloon in the induction of labor: a randomized clinical trial

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1. Introduction and Purpose:

Amniotomy is a common practice in the management of labor induction. It is performed using a plastic hooked device to rupture the amniotic membranes. Currently at UTMB, it is left to the discretion of the provider to determine when amniotomy is performed during labor. There is little data to guide the timing of amniotomy. A recent meta-analysis suggests that amniotomy performed earlier in the labor course is associated with a decreased time from induction to delivery, with no change in rates of cesarean section[1]. However, one study showed longer labors with an increase in rates of cesarean section with early amniotomy[2]. Additionally, this meta-analysis was limited by the small number of trials included with varying methods of cervical ripening used prior to amniotomy, including Foley balloon, prostaglandins, or a combination[2,3,4,5]. Lastly, in two of the studies included, spontaneous rupture of membranes was used as the control group, which does not provide clear guidance regarding the timing of amniotomy during labor, as in many cases amniotomy was not performed[4,5]. Further data is needed to sufficiently evaluate the timing of amniotomy during induction, controlling for the method of cervical ripening.

The purpose of this study is to evaluate the impact of early versus delayed amniotomy on time from induction to the active phase of labor, as well on total time to delivery and maternal and neonatal outcomes in women undergoing cervical ripening with the Foley balloon.

2. Background:

Amniotomy, i.e. artificial rupture of amniotic membranes, has become a common method used in management of both induction and augmentation of labor. It has been shown to shorten the duration of labor[6]. Risks associated with amniotomy include ascending infection, fetal heart rate decelerations, umbilical cord prolapse, and rupture of vasa previa[6]. While there are risks associated with amniotomy, there are also risks associated with prolonged labor, including an association with cesarean delivery and decreased fetal cord pH[6].

Timing of amniotomy in the management of induction of labor has not been widely studied. The limited studies have mixed results, but a recent meta-analysis suggests that early amniotomy shortens the length

of labor and has no effect on rates of cesarean section[1,3,4,5]. However, these studies use a variety of methods for cervical ripening prior to amniotomy, which may affect the outcome as well. Additionally, the studies differed in whether they compared early amniotomy to delayed amniotomy or spontaneous rupture of membranes. Levy et al. showed longer labors with increased cesarean section rates in those receiving early amniotomy after cervical ripening with a Foley balloon[2]. These results may be in part due to the fact that oxytocin infusion was not initiated in these subjects until the labor progress was deemed to be inadequate.

With the limited amount of published research, and conflicting results, more data is needed to be able to determine the ideal time for amniotomy during the management of the induction of labor, specifically when using a Foley balloon for cervical ripening.

The primary objectives of this study are to evaluate time to reach active phase of labor (defined as 6 cm or more of cervical dilation). The secondary objectives of this study are to evaluate in these subjects 1) cesarean section rates and indications, 2) occurrence of maternal complications including isolated maternal fever, chorioamnionitis, postpartum hemorrhage, endometritis, wound infection, and 3) occurrence of neonatal complications including umbilical cord prolapse, Apgar score <7 at 1 and 5 minutes, cord pH <7.0, NICU admission, neonatal infection. We will also be looking at time to vaginal delivery and vaginal deliveries within 24, 36 and 48 hours.

3. Concise Summary of Project:

- The target population for our study is both nulliparous and parous women who present for induction of labor. If there is a decision by the obstetric team to place a transcervical Foley balloon for cervical ripening, the obstetric team will notify the research team so that the patient may be screened for the study. If the subject consents to participation, written informed consent will be obtained by person-to-person contact. The PI or a collaborator will be responsible for the informed consent. After informed consent is obtained, the transcervical Foley balloon will be placed. The method of placement will be left to the discretion of the provider. After placement of the Foley balloon, the subject will be randomized to the study group (early amniotomy) or the control group (delayed amniotomy).

  The control group will undergo amniotomy at least four hours after expulsion of the Foley balloon.

  The study group will undergo amniotomy as soon as possible after Foley balloon expulsion or within two hours of expulsion.

  At any point, if the treating provider determines amniotomy is unsafe, amniotomy may be delayed and performed as soon as the provider deems safe.

  This will be an unblinded randomized clinical trial.

  No significant adverse effects are expected with the use of amniotomy. The most significant risks associated with amniotomy are fetal heart rate decelerations, ascending infection, umbilical cord prolapse (<1%), rupture of vasa previa (<1%). The subject will undergo inpatient induction of labor, so any adverse reaction would be promptly detected and addressed.

- The number of subjects studied will be 174 subjects at UTMB.
  The subjects will be withdrawn from the study if she wishes to discontinue participation. If any of the exclusion criteria listed above are met, or there is a change in condition that leads to inclusion

criteria no longer being met, data collection will be terminated and the subject will be withdrawn from the study.

4. Study Procedures

The decision to place a transcervical Foley balloon as a means of mechanical dilation will be made by the managing clinical team independent of the trial. After a subject who meets inclusion criteria agrees to be screened for participation in our study, the obstetric team will contact one of the investigators. Signed informed consent will be obtained by the PI or collaborator. Intrapartum management will be performed by the obstetric team. Providers will only be performing activities that are standard of care, but will receive protocol training. Documentation of provider training will be maintained with the research records as a training log dated and signed. The total participation time in the study will be considered terminated at time of delivery.

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 subject by the subject's MRN number. This identifier is needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted.

4.1 Screening, Recruitment, and Consenting:

- Under the direction of the PI, trained research staff will be available 24/7 to **screen** and **consent** subjects according to study protocol. Subjects will be enrolled at the time a decision to place a transcervical Foley balloon for purposes of mechanical dilation is made in labor and delivery. Potential subjects will be approached for recruitment at least 30 minutes prior to Foley balloon placement in order to ensure adequate time to make an informed decision regarding their participation.
- After informed consent is obtained, the subject will be randomized to the study group or the control group. A screening log will be used to track all subjects approached for the study. Subjects will only be randomized on L&D after the transcervical Foley balloon has been placed AND they continue to be eligible.
- Recruitment: We will recruit all pregnant patients admitted to L&D for induction of labor who have had a decision made by their managing clinical team to place a transcervical Foley balloon for purposes of mechanical dilation who do not meet any of the exclusion criteria listed above. Once the inclusion criteria for our study are met, the primary team will inform the patient about the study and ask her authorization to contact one of the study personnel. Eligible subjects may not be patients of the study providers; hence, in these cases, the managing clinical providers will inform eligible subjects for permission to research staff approach for potential recruitment. All clinical providers (residents, midwife and obstetricians) that work in the L&D unit will be educated by email and in person of the trial's eligibility and purpose before initiation of the trial.
- Consenting process: Written consent will be obtained by direct person-to-person contact. The principal investigator or a collaborator will be responsible for the informed consent. The consent form will be thoroughly reviewed with the subjects prior to signing. Questions will be invited and just prior to signing, the research staff will ask questions of the subject to ensure her complete understanding of the study and her voluntary willing participation.
  Subjects will be informed that their decision about participating in the study will in no way affect the care they will receive. Consent will be obtained prior to placement of the Foley balloon. Non-English-speaking subjects are anticipated to be part of the study population and informed consent will be provided in their primary language. For non-English speaking subjects, a certified translator will review the consent with them. Additionally, the consent will be translated in Spanish.

Privacy will be maintained by approaching and consenting subjects in their private room in L&D.

The data collected will not be used for clinical diagnosis or treatment purposes.

Subjects will be reassured that participation in the study is voluntary and will not interfere with the diagnosis or treatment of her condition.

The subjects will receive the same care and expertise as any other patient treated in our unit.

Placement of the Foley balloon and amniotomy will be performed by the managing obstetrical team, that are trained physicians that perform these procedures in a daily schedule as part of their routine clinical skills and duties.

4.2. Randomization and Masking

A confidential computer-generated simple randomization scheme (using STATA 16, Dallas, TX) has been prepared. A randomization log with group assignment, subject name, and medical record number will be used to track the randomization process.

Subjects will be randomized in a ratio of 1:1 for delayed or early amniotomy.

Due to the nature of the intervention, blinding of subjects or providers will not be possible.

The subject will be included in the analysis by intent-to-treat once the randomization assignment has been made.

4.3. Amniotomy

The control group will undergo delayed amniotomy. At least four hours after Foley balloon expulsion, the provider will perform amniotomy using a plastic amniotomy hook. After amniotomy, standard intrapartum management of the subject will ensue.

The study group will undergo early amniotomy. The provider will perform amniotomy as soon as possible after Foley balloon expulsion or within two hours of expulsion. After amniotomy, standard intrapartum management of the subject will ensue.

If the provider feels the amniotomy is unsafe (floating or ballotable presenting part, head not engaged in the pelvis), amniotomy will be performed as soon as it is deemed safe. If amniotomy is performed outside of the time limits outlined, the subject will remain in the study since we will perform an intent-to-treat analysis.

Foley balloon placement is standard of care in our facility for cervical ripening. Decision for its placement will be solely left to provider's discretion. Both groups will have a foley balloon placed as per standard protocol in our institution.

Oxytocin infusion will be left to provider's discretion based on our unit's standard of practice.

4.4. Baseline Procedures

Routine intrapartum care will be provided by the subject's managing obstetric team.

Trained and experienced research staff will be responsible for all research data abstraction.

The PI and collaborators will review and validate the diagnosis for all subjects identified to have the primary outcomes.

Maternal and neonatal outcomes will be assessed following delivery.

Subjects will be encouraged to call the principal investigator with any concerns.

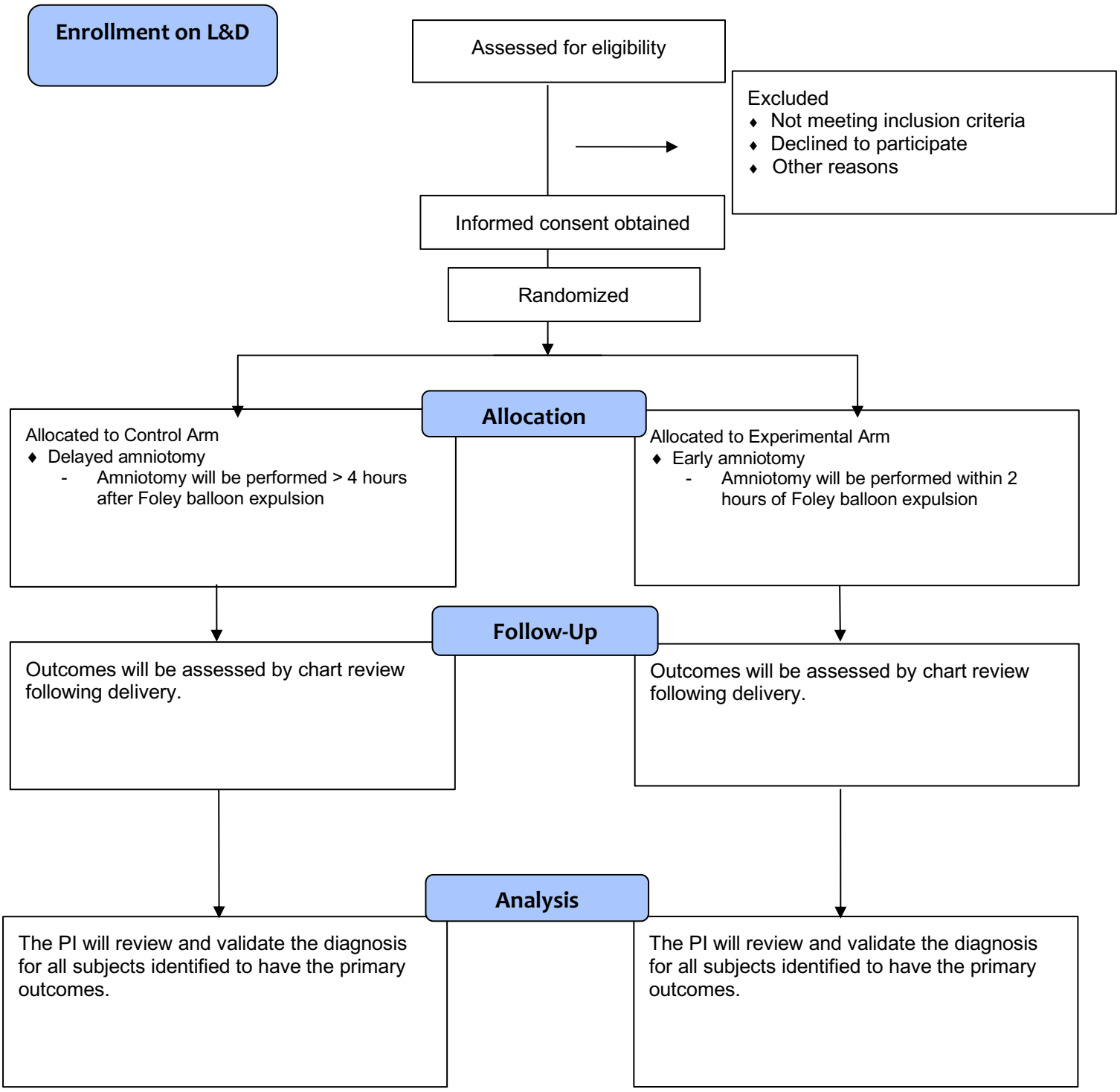
Data collection forms will be used during these processes and charts will be reviewed up to 30 days postpartum. We will collect demographic data, as well as data related to the subject's intrapartum course, delivery, and immediate postpartum period while inpatient. Data on newborn status, including those admitted to the NICU, will be obtained from the infants' charts.

Subjects' participation will end after being discharged home from the hospital.

4.5. Study visits / Follow-up
No additional postpartum follow-up visits will be performed.

4.6. Withdrawals
Subjects who withdraw from the study after randomization will be excluded from further follow-up. Outcomes ascertained up until the time of withdrawal will be reported in intent-to-treat fashion.

Study Summary Flow Diagram



4.9. Primary Outcomes

- Time interval from Foley balloon placement to reaching the active phase of labor (6 cm cervical dilation)

4.10 Secondary Outcomes

- Induction to delivery time in minutes
- Time interval from completion of cervical ripening to delivery in minutes
- Vaginal delivery within 24, 36 and 48 hours of induction
- Cesarean section rates and indications
- Operative delivery rates
- Total length of hospital stay
- Maternal outcomes
    - Isolated maternal fever
    - Chorioamnionitis (also known at "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 [1]:
            - 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
        - Subject 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
    - Postpartum hemorrhage
        - EBL >1000 cc
    - Wound infection
    - Umbilical cord prolapse

- Neonatal outcomes
    - Apgar score <7 at 1 and 5 minutes
    - Cord arterial pH <7.0
    - NICU admission
    - Neonatal infection, defined as sepsis, fever, positive cultures, or a suspicious clinical course that warranted treatment with antibiotics

5. Sub-Study Procedures: No sub-studies will be performed

6. Criteria for Inclusion of Subjects

- Age ≥ 18
- Singleton pregnancy
- Term gestation (≥37 weeks gestation)
- Cephalic presentation
- Undergoing labor induction with transcervical Foley balloon

7. Criteria for Exclusion of Subjects

- Previous uterine surgery
- Prelabor rupture of membranes
- Severe pre-eclampsia, HELLP, or eclampsia
- HIV, HCV, or HBV
- Heart disease
- Fever (≥38 ^{0}C) at admission
- Category II or III fetal heart rate tracing prior to randomization
- Polyhydramnios
- Fetal growth restriction <3%
- EFW > 4200 g
- Fetal demise or major congenital anomaly
- Prisoners

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

9. Potential Risks:

9.1. Amniotomy & Randomization Risk

Since the timing of amniotomy will be randomized, it is possible that the subject may be in a group with higher adverse outcomes, such as early amniotomy. Risks with amniotomy including fetal heart rate decelerations, ascending infection, umbilical cord prolapse, and bleeding due to vasa previa, and it is possible to see a difference in the rates of these complications with earlier amniotomy.

9.2. Loss of Confidentiality

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

10. Subject Safety, Data Monitoring and Protocol deviations

Subjects will be continuously monitored throughout their labor course for the development of any adverse events. If a complication is identified, immediate treatment will ensure per standard of care. Study collaborators will be responsible for notifying the principal investigator of any adverse events. The PI and research collaborators will be responsible for monitoring the safety of this study. The PI will notify the faculty sponsor of the occurrence of any adverse events. The yearly report, submitted at time of continuing review, will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues.

The PI 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 faculty sponsor will be notified by the PI if any issues are identified regarding data quality during the monitoring process.

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 PI will be available to monitor the data and correct any discrepancies based on source documents if needed.

For each patient enrolled in the study, their primary obstetric care providers and team currently taking care of the patient will be notified of their participation in person after randomization. For any deviations from study group assignment that may arise, providers will be asked to notify the study team or if missed, the deviation will be identified chart review. The study team will then complete documentation which will be submitted to the IRB as a protocol deviation via InfoEd; according to IRB policies.

11. Procedures to Maintain Confidentiality

- The data collected will be indirectly linked to the subject by subject's MRN number.
- When the subject accepts to participate in the study, a number will be attributed to the subject, 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 subject'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.

12. Potential Benefits

Subjects who undergo either early or delayed amniotomy may be at decreased risk for adverse perinatal outcomes. If this is the case, our study stands to benefit women who have amniotomy in future cases of labor induction.

13. Statistical Approach

Analysis will be performed by intent to treat. Univariable and multivariable analysis will be used to describe the population in the study and to identify potential confounding variable. For this analysis normality will be tested using Shapiro-Wilk method. Demographics and descriptive statistics such as t test, Pearson's chi square, and Mann-Whitney tests will be used as indicated. Data will be either shown as median +/- Range or mean +/- SDEV. Statistical analyses of primary and secondary outcomes between two groups will be performed by multivariate logistic regression analysis accounting for confounding variables if indicated.

Based on our prior results (DILAFOL Trial), women who received Foley balloon and delayed amniotomy reached active phase of labor in 1111 mins with a standard deviation of 525 mins[8]. Using difference rate of 25%, power of 90% and 2-sided alpha of 0.05, we estimate that we will need 150 with complete ascertainment. This difference of 278 or ~4hours was decided after consulting clinical experts in the field of obstetrics, supporting clinical reasoning that a difference between both methods is clinically significant. Detailed from stata 16 : Estimated sample sizes for a two-sample means test (z test) ;Study parameters: alpha = 0.0500; power = 0.9000; delta = -278.0000; mean1 = 1111.0000; mean2 = 833.0000 sd = 525.0000 Estimated sample sizes: N = 150
N per group = 75. Assuming a 13% loss to follow, we propose to enroll a total of 174 subjects. Analyses will be performed by intent to treat. We will be using STATA 16 (Dallas, TX) for statistical computations
This trial will be registered with Clinical Trials Register (Clinicaltrials.gov), before recruitment is initiated and after IRB approval.

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