The University of Texas Medical Branch Galveston
Research protocol

TREAT: **T**reatment of pp**R**OM with **E**rythromycin vs. **A**zithromycin **T**rial

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Funding: Departmental.

1- **Introduction/Background/Purpose:**

In the United States, preterm premature rupture of membranes (PPROM) complicates 4% of pregnancies annually. This pregnancy complication is a major contributor to preterm births and results in neonatal morbidity and mortality. Without treatment, 70-80% of women deliver within the 1st week following membrane rupture. Multiple trials have proven that antibiotics given to this population prolong the latency from time of PPROM to delivery, hence reducing maternal and neonatal morbidities.

According to the American College of Obstetrics and Gynecology, the current standard of care for PPROM subjects between the gestational age of 24 weeks and 0 days and 33 weeks and 6 days, is to administer ampicillin 2 gm IV every 6 hours for 48 hours followed by amoxicillin 250 mg orally every 8 hours for 5 days, with erythromycin 250 mg IV every 6 hours for 48 hours followed by 500 mg orally every 8 hours for 5 days. In this regimen, multiple doses of intravenous (IV) and oral (PO) doses of erythromycin are needed to achieve the desired outcome. Erythromycin can cause GI upset and some subjects do not tolerate this regimen over the course of 7 days. In addition, there is a national shortage of erythromycin, and published expert opinion proposed to use a second-generation macrolide (azithromycin) instead of erythromycin. This strategy was adopted nationwide including our maternal center at UTMB since 2014. Compared to erythromycin, advantages of azithromycin include:

- It is taken once orally (due to its long intracellular half-life).
- The entire regimen is much cheaper than the multiple does of erythromycin (23 doses).
- It has less gastrointestinal adverse effects.

As a result, azithromycin is now commonly being used as a substitute for erythromycin on many labor and delivery units around the country.

Despite its common use, there exists no level 1 evidence that azithromycin is equivalent to erythromycin. Haas and colleagues published a retrospective comparison of the two regimens in 2014 and concluded that the substitution of azithromycin for erythromycin in the recommended antibiotic regimen did not impact latency or any other measured maternal or fetal outcomes. This study, however, was limited by its non-randomized retrospective nature.

Our objective is to compare the effectiveness of the 2 regimens in prolonging pregnancy after PPROM.

2- **Concise summary of project:**

This trial will be a comparative effectiveness pragmatic multi-site randomized trial performed in singleton pregnancies with the diagnosis of PPROM between 24 weeks and 0 days - 32 weeks and 6 days. It will be comparing two well-accepted standardized treatments of care in this subject population: Erythromycin (FDA Category B) versus Azithromycin (FDA Category B). Our primary outcome will be the proportion of women still pregnant by day 7 after the diagnosis of PPROM is made. Our working hypothesis is that there is no measurable difference in the primary outcome between the group randomized to the azithromycin regimen versus the group randomized to the erythromycin regimen. Our secondary outcome will be latency defined as interval from PPROM to delivery. We propose a total of 324 subjects will be needed to complete the study.

3- **Participating sites:**

The following sites are participating in this trial:

United States, UTAH

Obstectrics & Gynecology Research Network **Recruiting**
30 North 1900 East Suit 2B119
Contact: Dr. Torri Metz (PI)801-587-3069 Torri.metz@hsc.utah.edu

United States, Texas

St. David's North Austin Medical Center **Recruiting**
Austin, Texas, United States, 78758
Contact: Richard T Hale, PhD 512-821-2540 Richard.Hale@stdavids.com
PI : Sina Haeri Sina.Haeri@hcahealthcare.com

Each center had the protocol reviewed and approved independently by their local IRB before participating in this trial or recruiting.

UTMB is the leading site for this trial. There is no specific accrual number per site. Across multi-sites, randomization is centralized. UTMB perinatal research division coordinates randomization assignment schedule by increments of blocks of 10 as enrollment is ongoing. Each block has 10 subjects randomized to either intervention A or B which is independent and does not affect the remaining sequence. For example, Block #1 has the first 10 subjects, within the block we will have 5 in intervention A and 5 in intervention B randomization independent of the remaining sequence or Block. Each site will be given 1-3 blocks of 10 increments for randomization. . This approach is independent of the remaining sequence or blocks, thus not affecting the remaining randomization sequence.

4- **Study procedures:**

Eligible subjects will be approached, and those who consent will be randomized to one of the two groups below in a 1-to-1 allocation.

- Erythromycin group: Ampicillin 2 gm IV every 6 hours first 2 days followed by amoxicillin 250 mg PO every 8 hours for next 5 days with erythromycin 250 mg IV every 6 hours for first 2 days followed by 500 mg PO every 8 hours for next 5 days (standard of care at UTMB).
- Azithromycin group: Ampicillin 2 gm IV every 6 hours first 2 days followed by amoxicillin 500 mg PO every 8 hours for next 5 days with azithromycin 1 gm PO once at randomization (Standard of care at UTMB).
  Both groups receive a total of 7 days of antibiotics as per standard of care at UTMB.

The remaining standard of care will be the same for both groups concerning the management of PPROM according to NICHD/ACOG guidelines including GBS prophylaxis.
GBS chemoprophylaxis is beyond the scope of this trial, since we are randomizing the portion of macrolides only and not the Ampicillin portion that actually covers GBS. As noted, this regimen of intravenous ampicillin/ amoxicillin, is standard on both interventions and covers GBS. GBS cultures and GBS treatment is left per providers' discretion beyond our intervention period (7 days of latency antibiotics).
In addition, drug adverse effects profiles between the two will be assessed in a post treatment subject survey. Subjects will complete a survey before being discharged from the hospital after receiving the assigned antibiotic regimen. Any questions will be answered and sufficient time will be given for the subject to fill the survey.
Data will be collected retrospectively from EPIC EMR:

- Time of initiation of antibiotics to delivery.
- Maternal outcomes: chorioamnionitis, postpartum infectious morbidity, placental abruption
- Route of delivery
- Gestational age at delivery
- Adverse events: Allergic reactions (anaphylaxis, angioedema, skin rashes including Stevens Johnson and Toxic Epidermal necrolysis), GI symptoms (vomiting, diarrhea, constipation, ileus)
- Neonatal outcomes: perinatal death, need for oxygen supplementation (not intubated), ventilation support (intubated), necrotizing enterocolitis (NEC) stage 2 or 3, duration of ventilator support (intubated), NICU days and neonatal infection/sepsis, individually and as a composite.

Both survey forms and data forms are attached with protocol application.

3.1 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. Medical records of all potential subjects with a diagnosis of PPROM will be reviewed and those who satisfy inclusion and exclusion criteria will be approached and a written informed consent will be obtained. A screening log will be used to track all subjects approached for the study. Potential subjects may be patients of the investigators.
Subjects will be enrolled at the time of admission to labor and delivery (L&D) or thereafter. Subjects will be recruited, enrolled and consented in a private room in labor and delivery or antepartum units in order to respect the privacy of potential subjects. Subjects will be given all the time needed in order to fully understand and read the consent forms. All questions will be fully answered. If needed, a certified language interpreter will be available and Spanish consents will be used as appropriate. Women will only be randomized on our labor and delivery or antepartum units when the decision to initiate antibiotics is made, AND they continue to be eligible (using a randomization screen).

3.2 Randomization

A confidential computer-generated simple randomization scheme (using STATA 14, Dallas, Tx) will be prepared and provided on an ongoing basis to our study coordinator. A randomization log with group assignment, subject name and medical record number will be used to track the randomization process.
Across multi-sites, randomization is centralized. UTMB perinatal research division synchronizes randomization assignment schedule by increments of blocks of 10 as enrollment is ongoing.

3.3. Antibiotics Disposal and Administration

Once a subject is consented and randomized, the appropriate antibiotics according to group assignment will be dispensed by the regular hospital pharmacists after order is placed in EPIC (as part of standard procedure at UTMB). Both drugs are standard of care at UTMB. This is a pragmatic/comparative effectiveness of two standard of care therapies. Regular hospital pharmacy currently stores and disposes the drugs and subject's insurance will be responsible for paying for either antibiotic, as any other subject not in the study. Floor nurses will be administering antibiotics. Research staff will be checking medication administration record (MAR) in EPiC for compliance to the research protocol; if an antibiotic is withheld for any reason the staff will inform the PI and report it as a protocol deviation which may potentially affect the integrity of the data for that subject.

The subject will be included in the analysis by intent-to-treat once the assigned antibiotics are dispensed from inpatient pharmacy and sequential number posted on the subject specific randomization form.

3.4. Baseline Procedures

Routine PPROM care will be provided by the subjects' clinical providers.

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

The PI will review and validate the diagnosis for all subjects identified to have the primary outcomes. These reviews will be conducted masked to treatment group. If there is uncertainty, a will review the chart, discuss with the co-investigators as needed and make a final determination regarding the outcome.

Maternal and neonatal outcomes will be assessed in the hospital following the delivery (on an ongoing basis until discharge).

Several data collection forms will be used during these processes. Data on these forms, devoid of personal identifiers, will be securely stored at our perinatal research division.

3.5. Study visits/Follow-up

No study visits or follow up will be needed for this study. The subject participation will be considered complete when the subject and her child are discharged from the hospital.

3.6. 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 an intent to treat fashion. Those who withdraw prior to determining the primary outcome will be accounted for by randomizing an equal number of additional subjects.

3.7 Outcomes

Primary outcome:

- Proportion of undelivered subjects at day 7 from the diagnosis of PPROM

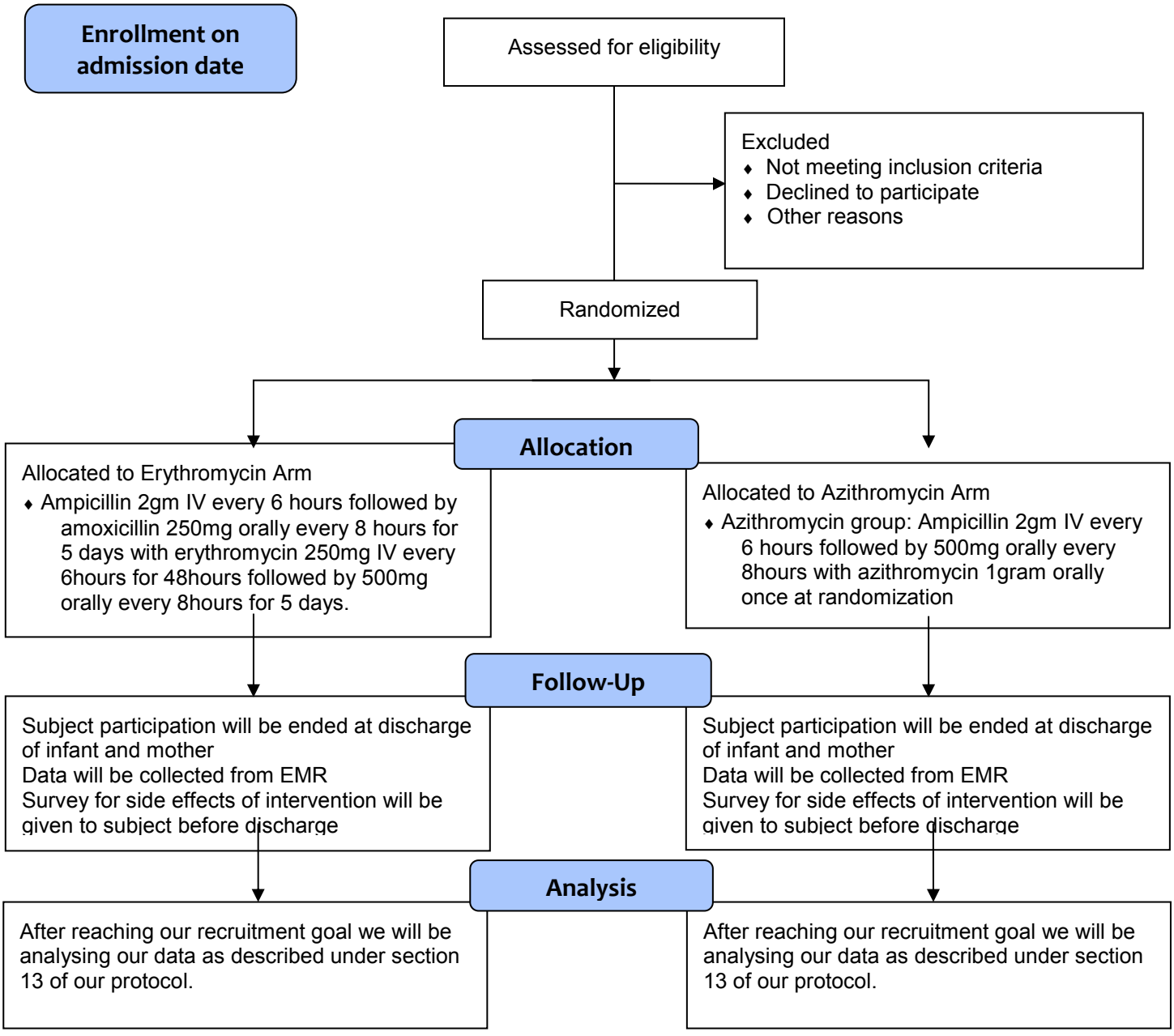
Secondary outcomes:

- Latency defined as time interval from PPROM to delivery

Data to be collected will consist of demographics, obstetrical history, relevant vital signs and laboratories. Examples of data to be collected but not limited to include: age, ethnicity/race, gravida, para, received tocolytics, received antenatal steroids, gestational age at rupture of membranes, reason for delivery, mode of delivery, gestational age at delivery, chorioamniotis, date & time of initiation of antibiotics, date & time of delivery, placental abruption, hospital length of stay, number of women undelivered at day 7 of admission, NICU admission, infant intubation days, neonatal NEC and neonatal sepsis.

In addition, drug adverse effects profiles between the two will be assessed in a post treatment patient survey. The latter will be assessing the severity and incidence of diarrhea and other symptoms such as nausea and vomiting and their severity.

Study Summary Flow Diagram



5- **Criteria for inclusion of subjects:**

- Maternal age ≥ 18 years and <50 years
- Pregnant women between the gestational age 23 6/7 and 32 6/7 weeks
- Singleton pregnancy
- Preterm premature rupture of membranes, determined clinically
- Cervical dilation visually ≤ 5cm on sterile speculum exam.

6- **Criteria for exclusion of subjects:**

- Intrauterine fetal demise (no fetal heart beat identified and documented by two physicians)
- Any contraindication to expectant management (e.g. fetal compromise, chorioamnionitis, placental abruption)
- Cervical cerclage in place
- Placenta previa or other known placental anomalies
- Contraindication to any of the antibiotics used (allergy to macrolides).
- Enrolled in another trial that may affect outcome.
- Clinical chorioamnionitis or any other active bacterial infection (e.g. pyelonephritis, pneumonia, abscess) at time of randomization: because standard antibiotic therapy for these conditions may confound trial intervention.
- No prenatal care (less than 2 prenatal visits)
- Non-resident subject who is unlikely to be followed-up after delivery
- Any fetal congenital anomaly.
- Significant liver disease defined as known cirrhosis or elevated transaminases of at least 3-fold upper limit of normal
- Significant renal disease defined as serum creatinine known to be >2.0 mg/dl or on dialysis.
- Active congestive heart failure (EF<45%) or pulmonary edema.
- Immunosuppressed subjects: i.e., taking systemic immunosupressants or steroids (e.g. transplant subjects; not including steroids for lung maturity), HIV with CD4<200, or other.

7- **Sources of research material**: Electronic medical records and subject survey.

8- **Recruitment Methods and Consenting Process:**

Please refer to section 3.1 above.

9- **Potential risks:**

7.1. Randomization Risk
Since the antibiotic regimen type will be randomized, it is possible that one or more of the other treatment groups will have more benefit or lower side effects than the group to which subject is assigned.

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

7.3 Drug Adverse Affects
According to the FDA, Azithromycin is a macrolide and a derivative of erythromycin. Its mechanism of action is mediated by binding to the 50S ribosomal subunit of susceptible bacteria, and inhibiting protein synthesis. Azithromycin targets ureaplasma, aerobic and facultative gram-negative and gram-positive organisms, and some anaerobes. Azithromycin is classified as a pregnancy category B drug – animal studies using maternally toxic doses showed no fetal harm. However, there are no adequate well-controlled studies in pregnant women. It is not known whether azithromycin is excreted in human milk. The only absolute contraindication to its use is a known hypersensitivity reaction to azithromycin, erythromycin or other macrolide antibiotic (quite rare). There are no specific drug-drug interactions warranting dose adjustments when given with other medications. Elimination is by both renal and hepatic route, and no specific adjustments are mandated for subjects with renal or hepatic insufficiency. The long elimination 1/2-life of 68 hours is due to extensive uptake and subsequent release of drugs from tissues.
The FDA does not raise any suspicion that prenatal exposure to azithromycin is associated with long-term adverse outcomes. Animal studies showed that azithromycin did not have mutagenic potential.
Subjects receiving azithromycin may have the following adverse effects:

a. Rash, increase liver enzymes, kidney dysfunction, neutropenia and thrombocytopenia (rare)
b. Nausea and vomiting (3%)
c. Diarrhea (5%)

Subjects receiving erythromycin may have the following adverse effects:

a. C difficile colitis, increase liver enzymes, confusion, headache (rare)
b. Nausea and vomiting (25%)

c. Diarrhea (8%)

If any of these risks occur, subjects will be managed according to standard of care based on the symptoms and signs/complaints.

10- **Subject Safety and Data Monitoring:**
The collaborators and research coordinator 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 (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues. This report will be prepared yearly and be sent to the PI's. The collaborators and research coordinator will monitor for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness and responsiveness to data queries. Data collection will be identified with a participant ID number. Data will be collected and stored with the participant ID code only. The master enrollment log linking subject identifiers with study ID numbers will be kept in a password-protected database. Several data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The research coordinator and PIs will be available to monitor the data and correct any discrepancies based on source documents if needed.

11- **Procedures to Maintain Confidentiality**:
Each subject will be assigned a study number with personally identifiable information deleted or removed. If needed, charts will be reviewed in the medical records area. Subjects' information will be de-identified and tagged with a number. Data will be collected and stored on a UTMB password-protected computer in a locked room.

12- **Potential benefits:**
In the background of erythromycin nationwide shortage, this will be the first level 1 trial to show that azithromycin may be equivalent to erythromycin in delaying delivery in patients with PPROM. This study may show for the first time that current alternative practice with azithromycin is as effective as erythromycin but with less adverse effects, less costly and easy administration.

13- **Statistical approach:** Analysis will be performed by intent to treat. Univariable analysis (such as t-test, Mann-Whitney or Chi-square) will be used for descriptive statistics such as patient demographics and assessment of primary outcome. Multivariable logistic analysis will be used to account for potential confounding variables. Sample size was calculated using a non-inferiority trial design. Azithromycin will be tested against erythromycin for PPROM. The primary outcome will be the proportion of subjects undelivered

by day 7. For the sample size calculation, it is assumed the proportion undelivered in the erythromycin group would be 70% (pi = 0.7) based on Haas et al study. We considered that a difference in undelivered rate as large as 15% in favor of erythromycin would allow azithromycin to be non-inferior (delta = 0.15). This study will use 80% power to confirm non-inferiority and a one-sided confidence level of 97.5%.

Estimated sample size for two-sample comparison of proportions (non-inferiority)

Null hypothesis: p2 - p1 ≥ delta (inferior), where:
pi (entered in command) is the overall proportion of participants expected to experience the outcome if the treatments are non-inferior, and delta is the smallest change in proportions between groups (p2 - p1) which would still be clinically important.
Alternative hypothesis: p2 - p1 < delta (non-inferior)

Note: a non-inferiority analysis is one-sided.

Assumptions:
power = 0.8000
alpha = 0.0250 (one-sided)
pi = 0.7000
delta = 0.1500
estimated required sample size (per group) = 147

The total estimated sample size is 294. Assuming 10% loss to follow, this study proposes a total of 324 subjects will be needed to complete the study. The STAT 14 (Dallas, Tx) will be used for statistical computations. This trial will be registered with Clinical Trials Register (Clinicaltrials.gov), before recruitment is initiated and after IRB approval."

References

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