

Prevention of maternal and neonatal death/infections with a single oral dose of azithromycin in women in labor (in low- and middle-income countries): A randomized controlled trial

ClinicalTrials.gov number: NCT03871491

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This document contains the following items:

- 1. Final study protocol (V.1.6, dated 15 July 2022)-- See *Appendix 2 for model informed consent form***
- 2. Final Statistical Analysis Plan (V.2.0, dated 13 October 2022)**

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Version Tracking

Version	Date	Authors	Comments
1.0	Sep 27, 2018	A-PLUS WG	This version will be used for IRB/ERC submissions.
1.1	Dec 19, 2018	A-PLUS WG	Internal version to document and review proposed revisions from GN investigators.
1.2	Dec 20, 2018	A-PLUS WG and GN Investigators	At request of GN investigators, revisions made to the following sections: Inclusion and exclusion criteria (Section 2.2); Consent procedures (Section 2.4); Description of data forms (Section 4.1); Sample informed consent form (Appendix 2); and in-text references. This version will be used for IRB/ERC submissions after December 20, 2018.
1.3	January 24, 2020	A-PLUS WG	Revisions made based on feedback from pilot study and requests from GN investigators. The following sections have been revised: <ul style="list-style-type: none"> Section 1 (Statement of Problem), including 1.2 and 1.3 (Primary and Secondary Specific Aims) and 1.5 (Rationale/Justification) Section 2 (Methods), including 2.1 (Inclusion Criteria); 2.4.7 (Monitoring after Discharge); 2.5 (Primary Outcomes); 2.6 (Other Maternal Outcomes); 2.7 (Other Neonatal Outcomes) and 2.8 (Safety Monitoring) Section 3 (Analytical Plan) Section 4.1 (Data Forms) Section 5 (References) Figure 1. Flowchart of Study Activities Appendix 2. Sample Informed Consent Appendix 3. Schedule of Study Procedures
1.4	January 29, 2020	A-PLUS WG	<u>Additional revisions made to:</u> <ul style="list-style-type: none"> Section 1.3 (Secondary Specific Aims) Section 2.5 (Primary outcomes) Section 2 (Methods), including 2.6 (Other Maternal Outcomes) and 2.7 (Other Neonatal Outcomes) Section 3 (Analytical Plan, including 1.2 (Secondary Analysis-Women at High Risk for Infection Cohort) 3.2.1 (Sample Size for Primary Outcome) and 3.2.2 (Sample Size for High-risk Women) This version will be submitted to IRBs/ERCs at all GN sites.
1.5	February 09, 2021	A-PLUS WG	<u>Updates made based on recommendations from the Data Monitoring Committee:</u> <ul style="list-style-type: none"> In Section 2.5 (Primary Outcome), removed urinary tract infection, omphalitis, eye infection, and skin infection from neonatal sepsis definition, removed fast breathing from the pSBI definition, and changed the pSBI fever criteria to 38 C/100.4 F. In Section 2.7 (Other Neonatal Outcomes), added urinary tract infection, omphalitis, and fast breathing to the “other neonatal infection” outcome. <u>Other updates:</u> <ul style="list-style-type: none"> In Section 3.5.1 (Reporting Adverse Events), made minor text changes to align with revised AE reporting procedures. [Refer to A-PLUS Technical Memo #2] In Section 3.5.4 (Interim/Adverse Event Monitoring Plan), made minor text revisions to clarify that the interim analysis will be conducted in both the all-comers and high-risk cohort. This revision was made at the request of the Boston University IRB. In list of Azithromycin Investigators, updated SFI for GN06-Guatemala to Manolo Mazariegos. This version will be submitted to IRBs/ERCs at all GN sites.
1.6	12 July, 2022	A-PLUS WG	High-risk definition updated to “Prolonged labor [≥18 hours] and/or prolonged membrane rupture [≥8 hours]”. The following sections have been updated to reflect this change: <ul style="list-style-type: none"> Abstract-<i>Secondary Outcomes</i> Section 1.3 (Secondary Specific Aims) Section 1.5 (Rationale/Justification) Section 1.6.1 (The Gambian and Cameroon Trials) <i>[Note: new reference added to this section, with full citation in reference list; as a result, all subsequent references have been renumbered]</i> Section 2.2.2 (Exclusion Criteria) Section 3 (Analytical Plan) Section 3.1.2 (Secondary Analysis-Women at High Risk for Infection Cohort) Section 3.2.2 (Sample Size for High-risk Women) Appendix 2 (Sample Consent) Other minor updates were made to the list of “Azithromycin Investigators” to reflect staffing changes since protocol V. 1.5 was released. This version will be submitted to IRBs/ERCs at all GN sites.

Table of Contents

Azithromycin Investigators	6
ACRONYMS	9
Abstract	10
1 Statement of Problem	11
1.1 Primary Hypotheses	11
1.2 Primary Specific Aims	11
1.3 Secondary Specific Aims	11
1.4 Background	12
1.4.1 Prevention of Maternal and Neonatal Deaths from Infections.....	12
1.4.2 Risks for Maternal and Neonatal Infections	12
1.4.3 Intrapartum Azithromycin to Prevent Maternal and Neonatal Infection	13
1.5 Rationale/Justification.....	13
1.6 Previous Studies	14
1.6.1 The Gambian and Cameroon Trials.....	14
1.6.2 The US Trial and Cost Analysis.....	14
1.6.3 Other Important Considerations	15
2 Methods	16
2.1 Study Design	17
2.2 Study Population/Location	17
2.2.1 Inclusion Criteria	17
2.2.2 Exclusion Criteria	17
2.3 Study Intervention and Comparison	18
2.4 Detailed Study Procedures	18
2.4.1 Community Sensitization.....	18
2.4.2 Screening.....	18

2.4.3	Consent	18
2.4.4	Masking	19
2.4.5	Randomization Procedures	20
2.4.6	Monitoring before Discharge	20
2.4.7	Monitoring after Discharge	20
2.4.8	Sequence of Study Activities	21
2.5	Primary Outcomes.....	22
2.6	Other Maternal Outcomes	22
2.7	Other Neonatal Outcomes.....	23
2.8	Safety Monitoring	23
2.9	Site Preparation	24
2.10	Potential Risks and Benefits to Participants	24
3	Analytical plan.....	25
3.1	Statistical Analysis Plan.....	25
3.1.1	Primary Analyses.....	25
3.1.2	Secondary Analyses – Women at High Risk for Infection Cohort	26
3.1.3	Secondary Analyses – Other Secondary Outcomes	26
3.2	Sample Size	27
3.2.1	Sample Size for Primary Outcome	27
3.2.2	Sample Size for High-Risk Women	28
3.3	Available Population.....	29
3.4	Projected Recruitment Time	29
3.5	Study Monitoring Plan.....	29
3.5.1	Reporting Serious Adverse Events	29
3.5.2	Method and Timing for Reporting Serious Adverse Events	30
3.5.3	Data Monitoring Plan and Stopping Rules	30
3.5.4	Interim/Adverse Event Monitoring Plan	31
3.5.5	Risks/Benefits	32
3.6	Quality Control.....	32

3.6.1	Training.....	32
3.6.2	Study Monitoring	32
3.6.3	Drug Quality Assurance and Monitoring	32
3.6.4	Plan for Sustaining Intervention	33
4	Data Management Procedures	33
4.1	Data Forms.....	33
5	References	35
	Appendix 1. Description of Participating Global Network Sites.....	38
	Appendix 2. Sample Informed Consent	40
	Appendix 3. Schedule of Study Procedures	44

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ACRONYMS

AC	All-comers
ACOG	American Congress of Obstetricians and Gynecologists
ANC	Antenatal Care
BP	Blood pressure
DCC	Data Coordinating Center
DMC	Data monitoring committee
DMS	Data Management System
DRC	Democratic Republic of Congo
ERC	Ethical review Committee
FIGO	International Federation of Gynecology and Obstetrics
FDA	Food and Drug Administration
GA	Gestational age
GI	Gastrointestinal
GN	Global Network for Women's and Children's Health Research
HR	High-risk
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association
ITT	Intention to treat
LIC	Low-income country
LMIC	Low- and middle-income countries
LMP	Last menstrual period
MNH	Maternal and Newborn Health
NEJM	New England Journal of Medicine
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNT	Number needed to treat
OHRP	U.S. Office of Research Protections
PI	Principal Investigator
pSBI	possible serious bacterial infection
RCT	Randomized controlled trial
RTI	Research Triangle Institute International
SAE	Serious adverse event
SC	Steering Committee
SFI	Senior Foreign Investigator
SMFM	Society for Maternal-Fetal Medicine
UAB	University of Alabama at Birmingham
WHO	World Health Organization

ABSTRACT

Background: Maternal and neonatal infections are among the most frequent causes of maternal and neonatal deaths, and current antibiotic strategies have not been effective in preventing many of these deaths. Recently, a randomized clinical trial conducted in a single site in The Gambia showed that treatment with oral dose of 2 g azithromycin vs. placebo for all women in labor reduced certain maternal and neonatal infections. However, it is unknown if this therapy reduces maternal and neonatal sepsis and mortality.

Hypotheses: The trial includes two primary hypotheses, a maternal hypothesis and a neonatal hypothesis. First, a single, prophylactic intrapartum oral dose of 2 g azithromycin given to women in labor will reduce maternal death or sepsis. Second, a single, prophylactic intrapartum oral dose of 2 g azithromycin given to women in labor will reduce intrapartum/neonatal death or sepsis.

Study Design Type: Randomized, placebo-controlled, parallel multicenter clinical trial. Women in labor will be randomized with one-to-one ratio to intervention/placebo.

Population: Pregnant women in labor at ≥ 28 weeks gestational age with a live fetus pregnancy who plan to deliver vaginally in a facility. Women with evidence of chorioamnionitis or other infection requiring antibiotic therapy (not prophylaxis) at time of eligibility, allergy to azithromycin, use of azithromycin, erythromycin or other macrolide within 3 days of enrollment, known arrhythmia or cardiomyopathy, or plan for cesarean section delivery prior to enrollment will be excluded.

Intervention: A single, prophylactic intrapartum oral dose of 2 g azithromycin.

Comparison: A single intrapartum oral dose of an identical appearing placebo

Outcomes:

Primary outcomes: 1) Incidence of maternal death or sepsis and 2) incidence of intrapartum/neonatal death or sepsis.

Secondary outcomes: Individual components of the primary outcomes (maternal death, maternal sepsis, intrapartum/neonatal death, neonatal sepsis), neonatal death/sepsis, neonatal deaths due to sepsis, and all-cause neonatal death; the primary maternal and neonatal outcome in a high-risk for infection population; specific maternal infections; use of subsequent maternal antibiotic therapy; pyloric stenosis; health care resource utilization; culture-positive infections and resistance; in an ancillary surveillance study, incidence of antimicrobial resistance and microbiome diversity.

1 STATEMENT OF PROBLEM

1.1 Primary Hypotheses

This study will have two primary hypotheses, one with a maternal focus and one with a neonatal focus. First, a single, prophylactic intrapartum oral dose of 2 g azithromycin given to women in labor in low and middle-income settings will reduce maternal death or sepsis. Second, a single, prophylactic intrapartum oral dose of 2 g azithromycin given to women in labor in low and middle-income settings will reduce intrapartum/neonatal death or sepsis.

1.2 Primary Specific Aims

To test the effectiveness of a single dose of prophylactic intrapartum azithromycin compared to placebo in reducing the risk of the composite outcome of maternal death or sepsis. To separately test the effectiveness of a single oral dose of intrapartum azithromycin prophylaxis (2 g) compared to placebo in reducing the risk of the composite outcome of intrapartum/neonatal death or sepsis. Both groups will receive the routine or usual care provided at the facility during and after labor.

1.3 Secondary Specific Aims

The single dose of intrapartum azithromycin prophylaxis (2 g) will be compared to placebo to accomplish the following secondary aims:

- Main Secondary Aim for Women at High-Risk for Infection Cohort:
 - a. To evaluate whether the risk of maternal death or sepsis differs among laboring women with and without high-risk for infection (high risk is defined as women with prolonged labor [≥ 18 hours] and/or prolonged membrane rupture [≥ 8 hours] at time of randomization).
- Other secondary specific Aims:
 - b. To evaluate the effectiveness in reducing the risk of individual components of the primary composite endpoints (i.e., maternal death, maternal sepsis, intrapartum/neonatal death, neonatal sepsis including specifically all-cause neonatal deaths and neonatal deaths due to sepsis).
 - c. To evaluate the effectiveness on the risk of intrapartum/neonatal death or sepsis in infants of laboring women at high-risk for infection because of prolonged labor (≥ 18 hours) and/or prolonged membrane rupture (≥ 8 hours).
 - d. To evaluate the effectiveness on the risk of maternal infections including clinical chorioamnionitis, endometritis, wound infections (perineal or Cesarean), abdominal or pelvic abscess, mastitis/breast abscess or infection, pyelonephritis, pneumonia and other bacterial infections in all laboring women as well as in those at high-risk for infection.
 - e. To evaluate the effectiveness in reducing the use of subsequent maternal antibiotic therapy from randomization to 42 days postpartum for any reason in all laboring women as well as in those at high-risk for infection.
 - f. To compare the use of health care resources. Use of health care resources will be measured in terms of maternal and neonatal duration of hospital stay, unscheduled visits, readmission, and admission to special care units/intensive care units in all laboring women and newborns as well as in those at high-risk for infection.
 - g. To assess maternal GI symptoms (e.g., nausea, vomiting, and diarrhea) and other reported side effects, as well as infant pyloric stenosis and type of culture positive infections

(antimicrobial resistance and maternal and infant microbiome diversity are compared in an ancillary study).

- h. To determine whether the effect on each of the primary outcomes differs by region (Africa, Latin America or Asia), any other antibiotic use during labor, and mode of delivery (cesarean or vaginal). Note that antibiotic use will not include use to treat any infections diagnosed after randomization as those will be outcomes.

1.4 Background

Maternal and neonatal infections are among the most frequent causes of maternal and neonatal death. Maternal infection during pregnancy and the puerperium account for approximately 10% of the global burden of maternal deaths. This places maternal infection among the top five causes of maternal mortality worldwide.¹ Neonatal infection is the third most common cause of neonatal mortality and accounts for about 16% of neonatal mortality worldwide.² Furthermore, maternal and neonatal deaths from infections are not decreasing compared with deaths from other frequent causes of mortality.^{1,2} There is a need for innovative simple effective interventions that can be scaled up to reduce the burden of both maternal and neonatal mortality due to infections.

1.4.1 Prevention of Maternal and Neonatal Deaths from Infections

Current strategies to prevent maternal and neonatal deaths from infections are insufficient. Current approaches to prevention, identification, and treatment of neonatal sepsis have had limited impact. According to the WHO, maternal deaths from infection have remained unchanged or increased in some instances, whereas deaths from other causes have reduced. The evidence backing current WHO guidelines for prevention and treatment of peripartum infections is generally graded as low or very low quality.¹ Efforts for early identification and treatment of neonatal infection are important but neonatal deaths due to infection continue to be very prevalent. Recent studies of alternative antibiotic regimens that do not require a full course of intravenous antimicrobial therapy have shown comparable effectiveness but have not reduced deaths from infections.³⁻⁶ Among research priorities, a WHO guideline panel identified the evaluation of the role of routine prophylactic antibiotics in women who undergo a normal vaginal birth as well as in those at high risk for infection due to prolonged labor or membrane rupture.¹

1.4.2 Risks for Maternal and Neonatal Infections

Maternal and neonatal infections by maternal risk including cesarean delivery. While the role of antibiotic prophylaxis for cesarean delivery is well-established, in many low-resource settings, many maternal infections occur after vaginal deliveries with high-risk for infections. Cesarean delivery especially after labor or membrane rupture is the strongest risk factor for maternal peripartum infection including endometritis, wound infection and sepsis (increasing risk by up to 5 to 10 times compared to vaginal delivery).⁷ The fraction of maternal infection attributable to cesarean delivery is rather low because of the low cesarean delivery rate of 5-10% or lower, especially in the Africa region, compared with 20-30% or higher in the US and many high income countries.⁸ Therefore, strategies that address maternal peripartum infection and sepsis in the developing world should focus as well on identifying and preventing (as well as treating) infection in women who have a vaginal birth, particularly those who are at high-risk. There is an increased risk of infection in women who undergo prolonged labor ≥ 18 hours (at least 2 fold) or membrane rupture ≥ 6 hours (at least 2-3 fold) compared to women who do not experience these risk factors.¹ These risk factors identify a large group of women who are at the highest

risk for maternal peripartum infections (including chorioamnionitis, endometritis, perineal wound infection and post-cesarean surgical site infections) and sepsis after a vaginal or cesarean delivery and also place newborns at increased risk for sepsis. However, even though 80-90% of pregnancies in labor are not at this highest-risk for infection depending on criteria used, they may account for about 50% of maternal and neonatal infections in LMICs. Thus, testing antibiotic strategies during labor in LMICs should include both the high-risk and lower risk women as highlighted in research priorities from the WHO guideline panel.¹

Antibiotic Prophylaxis for Women who deliver by Cesarean section. The appropriate use of antibiotic prophylaxis for cesarean delivery and antiseptic agents are among the most effective preventive interventions as highlighted by the WHO guidelines for maternal peripartum infections.¹ Antibiotic prophylaxis, preferably prior to incision, in particular, among several strategies, effectively reduces the risk of infection and the associated high health care and personal costs.^{1,9-11} However, the prevalence of cesarean sections is low, in many low-resource settings, particularly in sub-Saharan Africa, and thus, do not account for the large burden of the maternal and neonatal infections worldwide.

1.4.3 Intrapartum Azithromycin to Prevent Maternal and Neonatal Infection

Azithromycin: a novel approach to maternal and neonatal infections. A novel approach to maternal and neonatal infection is to target organisms that may be very frequent pathogens but that historically have not been the target of antimicrobial treatment.¹² A multicenter randomized clinical trial (RCT) of azithromycin prophylaxis added to the standard prophylactic regimen (cephalosporin) in women who underwent cesarean delivery following labor or membrane rupture for at least 4 hours in the US showed that maternal infection was reduced by about 50%.¹³ A single center RCT in a low-income country (LIC) setting suggested that azithromycin prophylaxis may improve maternal and neonatal outcomes. In an RCT in The Gambia that included all women in labor, treatment with 2 g of azithromycin vs. placebo before delivery reduced maternal and neonatal infections.¹⁴ Therefore, we propose to evaluate the effectiveness of a single oral dose of azithromycin as an intrapartum prophylactic agent for maternal and neonatal infection and death. We will also monitor the potential side effects of this intervention.

1.5 Rationale/Justification

Maternal infection and sepsis is a priority to reduce maternal and neonatal deaths. Compared to postpartum hemorrhage and preeclampsia/eclampsia, maternal infection has received less attention as a major cause of maternal death; proportionally it accounts for increasing deaths.¹ The WHO and other global health authorities identified maternal infection/sepsis as a priority problem to reduce maternal deaths. In addition, maternal infection significantly increases the risk of neonatal sepsis which is one of the leading causes of neonatal death in LICs.¹⁵ Most recently, a NEJM perspective article highlighted the WHO resolution issuing a clarion call recognizing “Sepsis” as a global health priority.¹⁶ Drawing from our findings on azithromycin prophylaxis for cesarean delivery in the US¹³ and data from another preliminary trial in The Gambia, Africa,¹⁴ we propose to evaluate the role of a single oral dose of azithromycin (plus usual care) to prevent maternal death or peripartum sepsis and intrapartum/neonatal death or sepsis in laboring women as well as the targeted sub-population of those at the highest risk for infection because they have prolonged labor (≥ 18 hours) and/or prolonged membrane rupture (≥ 8 hours).

Azithromycin is available as a generic agent with easy storage requirements. It has a bimodal half-life of up to 70 hours in the non-pregnant population. Although its pharmacokinetic characteristics are not as

well studied in the pregnant population, it is commonly used during pregnancy for treatment of chlamydia and other infections. Azithromycin covers a broad spectrum of bacteria (including gram-positive cocci, genital ureaplasmas and mycoplasmas, and certain gram-negative bacilli and anaerobes) that are associated with maternal infections which are often polymicrobial (chorioamnionitis, endometritis, and perineal/cesarean wound infection) and sepsis. In addition to the aforementioned organisms which may play a role in neonatal infection, azithromycin also has activity against Group B streptococcus which is a major cause of neonatal sepsis in developed countries and may be implicated in LICs and low-resources settings as well. Therefore, a successful prophylaxis intervention is likely to reduce infections and death and may also reduce health care costs and need for prolonged antibiotic therapy to treat infections which may be associated with resistance. Indeed, the recent WHO Guidelines on peripartum infection articulated the following among research priorities: what are the benefits of initiating prophylactic antibiotics among women undergoing uncomplicated vaginal birth and among those at high risk such as after prolonged rupture of membranes?¹ A JHPIEGO consultative meeting on enhancing the focus on maternal infections suggested that "Attention to identification and prompt management of prolonged labor and prolonged rupture of membranes is critical to reduce disease and death due to maternal sepsis."^{15,16,17}

1.6 Previous Studies

1.6.1 The Gambian and Cameroon Trials

Data from a single center trial in a LIC setting suggest the potential for azithromycin prophylaxis to improve maternal and neonatal outcomes. Among 829 Gambian mothers (randomized to 2 g of azithromycin vs. placebo before delivery) and their 830 newborns, maternal infections were lower in the azithromycin group (3.6% vs 9.2%; relative risk [RR], 0.40; 95% confidence interval [CI], 0.22-0.71; P = 0.002).¹⁴ Among newborns, the overall prevalence of infections was also lower in the azithromycin group (18.1% vs 23.8%; RR, 0.76; 95% CI, 0.58-0.99; P = 0.052).¹⁴ Maternal and neonatal carriage of infectious organisms was lower in the azithromycin group.¹⁸ A test of concept trial focusing on high-risk women in Cameroon (labor ≥18 hours or membrane rupture ≥8 hours at randomization) was underpowered by suggested lower maternal infection in women who received azithromycin.¹⁹

1.6.2 The US Trial and Cost Analysis

In a multicenter US RCT, it was demonstrated a further 50% reduction in the risk of maternal peripartum infection by adding a single 500 mg intravenous dose of azithromycin to the standard prophylactic regimen (a single intravenous dose of cefazolin 1-2 g or ampicillin) in the highest-risk group of women who undergo cesarean delivery following labor or membrane rupture for at least 4 hours.¹³ These results were observed despite universal use of other antibiotics in both arms of the trial. Specifically, the 95% without penicillin allergy had a cephalosporin (mainly cefazolin) for usual cesarean prophylaxis; the remainder that gentamicin and clindamycin. In addition, 25-30% received a penicillin for GBS prophylaxis. Infection was significantly lower in the azithromycin group compared to the placebo group; 6.1% vs. 12%; RR = 0.51 (95 % CI 0.38 to 0.68); p<0.001. Specifically, adjunctive azithromycin use was associated with significant reductions in the risks of endometritis (3.8% vs. 6.1%, RR=0.62, 95% CI: 0.42-0.92; p=0.02) and wound infections (2.4% vs. 6.6%, RR=0.35, 95% CI: 0.22-0.56; p<0.001). The number needed to treat (NNT) to prevent one infection was 17 for any infection, 43 for endometritis and 24 for wound infection. Other maternal outcomes including need for readmission or unscheduled visits for any reason or specifically for infection (decreased by up to 50%), serious adverse events, postpartum fever,

or subsequent treatment with antibiotics were also significantly less common with azithromycin prophylaxis. Short-term perinatal/infant outcomes including deaths, sepsis, and other serious neonatal morbidities were rare in this developed country population and did not differ between groups.¹³ In a related cost-analysis report, it was estimated that use of adjunctive azithromycin saves approximately \$360 for each use in unscheduled (high-risk) cesarean deliveries such as those studied in the RCT and \$143 per use in scheduled or pre-labor cesarean delivery.²⁰ The results suggesting cost-savings were robust across wide ranges of baseline risk of infection and treatment effect size.²⁰ Thus, in the US alone, adjunctive azithromycin prophylaxis for cesarean delivery could lead to \$350M in cost-savings/year due to avoided infection. These works built upon, and are supported by, over 20 years of research on maternal infections at UAB and elsewhere.²¹⁻³¹ Azithromycin provides coverage against the most common pathogens identified in association with peripartum infections including genital mycoplasmas and ureaplasmas (when specific methods are utilized to identify them).

1.6.3 Other Important Considerations

A recurrent concern regarding the potential routine use of azithromycin in a large population is antibiotic resistance. Monitoring for characteristics suggestive of resistant infection will be important to incorporate in the protocol. However, a number of factors mitigate concerns about antibiotic resistance: (a) the design of the trial using a single prophylactic dose (as opposed to recurrent treatment doses) of antibiotic, (b) surveillance of maternal clinical cultures up to 6 weeks in the trial in cesareans in the US revealed that positive wound cultures overall and those positive for resistant organisms were significantly less frequent in the azithromycin group;¹³ (c) if successful, prophylaxis will reduce the risk of infection and actually reduce the overall frequency of use of antibiotics to treat infection (a result in the US trial as stated above). It is estimated that women in the high-risk for infection group as defined will account for about 10-20% of laboring women. In principle, the use of single prophylactic dose (as opposed to multiple) minimizes the likelihood of antimicrobial resistance but samples will be taken to determine antimicrobial resistance.³²

Azithromycin is currently recommended to treat or prevent several infections in pregnancy including gonorrhea (1 g po), chlamydia (1 g po), and *Mycobacterium avium* complex prophylaxis (600 mg twice/week or 1.2 g weekly po). Azithromycin is sometimes used for perioperative prophylaxis in patients at risk for endocarditis (500 mg po). Considering the success with a single dose of 2 g in the Gambian trial, our success with 500 mg IV for cesarean prophylaxis, and the 40% bioavailability of oral azithromycin, we propose to use 2 g po of azithromycin for the proposed intervention. The best approach to this evaluation in order to influence future uptake into clinical practice is an RCT. The primary maternal outcome will be maternal death or sepsis within 42 days after delivery. The primary neonatal outcome will be intrapartum/neonatal death or sepsis within 28 days after birth (defined by WHO criteria).³³

Azithromycin is *pregnancy category B* – animal studies using maternally toxic doses showed no fetal harm. Limited studies suggest azithromycin is excreted in human milk in a sustained fashion.³⁴ There are no specific drug-drug interactions warranting dose adjustments when given with other medications. Elimination is by both hepatic and renal route, and no specific adjustments are mandated for patients 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 only absolute contraindications are rare: known hypersensitivity reaction to azithromycin, erythromycin or other macrolide antibiotic or history of

cholestatic jaundice due to azithromycin. Potential adverse events include very rare (<1%) allergic hypersensitivity (mild and severe skin reactions – Stevens Johnson Syndrome and toxic epidermal necrolysis, angioedema and anaphylaxis) and clostridium difficile-associated diarrhea. With multi-day azithromycin therapy, 0.6% of patients discontinued azithromycin due to side effects. With single 1-2 gram doses, gastrointestinal symptoms (nausea 5-18%, diarrhea/loose stools 7-14%, abdominal pain 5-7%, vomiting 2-7%, and dyspepsia 1%) as well as vaginitis 2% and dizziness (1%) were the most commonly reported side effects. No other side effect occurred with a frequency greater than 1%.

Azithromycin has been associated with hypertrophic pyloric stenosis in some observational studies. In a retrospective study, oral azithromycin exposure during the first 14 days after birth was associated with an increased incidence of pyloric stenosis.³⁵ However, an increased risk of pyloric stenosis was not reported in infants following a single dose of azithromycin to women in labor in randomized trials in the US and Gambia.^{13-14, 16} The much larger sample size of the proposed study affords the opportunity to further explore this question.

The FDA in 2013 issued an advisory regarding concerns about potential for rare life-threatening arrhythmias with azithromycin use particularly among those with preexisting cardiovascular risk. The information was based on an observational study of older, ill patients who received multiple courses of oral azithromycin over 5 days.³⁶ The findings are not applicable to our current study population for several reasons: the population is much younger, generally without cardiac co-morbidities, a single dose rather than cumulative doses of oral azithromycin over 5 days is being studied, additional studies of younger, healthy patients did not suggest an increased cardiovascular risk³⁷; and patients with arrhythmia or known history of cardiomyopathy will be excluded. In addition, the prior study of 2013 women in the US did not suggest a cardiovascular safety signal, and the potential reduction in severe infection may exceed the excess risk of severe arrhythmia with a single dose of azithromycin.¹³

2 METHODS

Pregnant women in labor at study health facilities who appear to be ≥28 weeks gestational age by best clinical estimate with a live fetus pregnancy will be screened for eligibility (see **Section 2.2**) by research staff starting at the time of admission and continuously during the hospitalization. Gestational age will be determined using the “best estimate” algorithm that is currently used in the GN MNH registry. Those eligible will be consented. Those consented will be randomized to receive a single dose of azithromycin 2 g or identical placebo to be given and directly observed during labor. Because of the ease of storage of azithromycin, sequentially prepared medications in identical packages following the randomization sequence will be available and dispensed by the study staff. The rest of the care will be provided according to the local standard of care. Women will be followed up until discharge and surveillance maintained (in-person), with visits at 3 days, 7 days, and 42 days after delivery as has generally been done in the Global Network to ascertain study outcomes.

We will apply the recently recommended “simple and actionable” WHO definition of sepsis in a 2017 statement endorsed by multiple international organizations. The definition of sepsis includes a suspicion of infection and the presence of organ dysfunction based on clinical findings.¹⁵

To further ensure more objective ascertainment of the sepsis outcome, we propose that the DCC will prospectively define a process for defining criteria for a masked centralized review and adjudication of all

cases of infection to ensure conformity with the proposed definition. This approach of adjudication is applied to validate infection in many trials including our recently completed ASPIRIN trial.³⁸ This approach to adjudication has some similarities to the near-miss classification for adjudication in women delivering in the Global Network sites that was done recently.³⁹

2.1 Study Design

This study is a masked, placebo-controlled RCT. The investigational regimen is 2 g of azithromycin and the comparison arm is an identical placebo which is given orally. Both groups will also receive the standard of care during labor, delivery and postpartum per local standards.

2.2 Study Population/Location

Pregnant women laboring in health facilities of the eight Global Network sites/other health facilities will be eligible. The Global Network sites are described in **Appendix 1**. Health facilities may include any hospitals and health centers where women routinely deliver within the study sites.

2.2.1 Inclusion Criteria

- Pregnant women in labor ≥ 28 weeks GA (by best estimate) with a pregnancy with one or more live fetuses who plan to deliver vaginally in a facility.
- Admitted to health facility with clear plan for spontaneous or induced delivery.
- Live fetus must be confirmed via presence of a fetal heart rate prior to randomization.
- ≥ 18 years of age or minors 14-17 years of age in countries where married or pregnant minors (or their authorized representatives) are legally permitted to give consent.
- Have provided written informed consent [Note: written informed consent may be obtained during antenatal care, but verbal re-confirmation may be needed (per local regulations) at the time of randomization].

2.2.2 Exclusion Criteria

- Non-emancipated minors (as per local regulations)
- Evidence of chorioamnionitis or other infection requiring antibiotic therapy at time of eligibility (however, women given single prophylactic antibiotics with no plans to continue after delivery should not be excluded).
- Arrhythmia or known history of cardiomyopathy.
- Allergy to azithromycin or other macrolides that is self-reported or documented in the medical record.
- Any use of azithromycin, erythromycin, or other macrolide in the 3 days or less prior to randomization.
- Plan for cesarean delivery prior to randomization.
- Preterm labor undergoing management with no immediate plan to proceed to delivery.
- Advanced stage of labor (>6 cm or 10 cm cervical dilation per local standards) and pushing **or** too distressed to understand, confirm, or give informed consent **regardless** of cervical dilation.
- Are not capable of giving consent due to other health problems such as obstetric emergencies (for example, antepartum haemorrhage) or mental disorder.
- Any other medical conditions that may be considered a contraindication per the judgment of the site investigator.
- Previous randomization in the trial.

Sites may choose to obtain written consent during antenatal care from pregnant women of the age of consent who plan to deliver vaginally in a facility and have no known medical exclusions. In this case, study staff must fully assess and confirm eligibility at the time of randomization. It may also be necessary to verbally re-confirm consent at the time of randomization, if required by local regulations. If it is determined that the study needs to be extended to accrue the planned sample size for HR cohort, then women who deliver prior to meeting HR criteria for randomization will be excluded.

2.3 Study Intervention and Comparison

The study intervention is a single 2 g dose of directly observed oral azithromycin, to be administered as four 500 mg pills or tablets directly after randomization. By random allocation, participants will receive 2 g of oral azithromycin vs. placebo. We will design the placebo with the assistance of a reputable pharmacy/pharmaceutical company, using identical capsules or pills containing azithromycin 2 g or a matching placebo (non-antimicrobial agent) to accomplish masking. All of the participants' obstetric care will be similar for all both arms and consist of the routinely available care at each center.

2.4 Detailed Study Procedures

2.4.1 Community Sensitization

Local health providers will receive sensitization about the study to foster communication and collaboration at the facilities where enrollment will take place. In addition, pregnant women and their families in the enrollment area will receive information about the study during antenatal care (ANC) visits to facilitate recruitment and comprehension during the consenting process. Sites may choose to consent women during these sensitization sessions, prior to labor; however, confirmation of eligibility and consent will be required during the screening process described in **Section 2.4.2 and 2.4.3**.

2.4.2 Screening

Women in labor in defined health facilities (both hospitals and health centers) will be identified by research staff. A brief review of eligibility will be made to determine whether the patient is in labor and does not meet any of the exclusion criteria. If a contraindication to participation in the trial is found, the woman will be excluded from the trial at this point.

2.4.3 Consent

Before a woman participates in the trial, the research staff must obtain her informed consent to voluntarily take part in the study. Consent will be obtained from women ≥ 18 years of age or minors 14-17 years of age in countries where married or pregnant minors (or their authorized representatives) are legally permitted to give consent. When enrolling minors, we will follow the in-country policies for human research protection and the guidelines approved by the local ethical review committees (ERCs). In the case of pregnant minors, this may require that written consent is obtained from her parents/guardians or husband, with written assent from the minor.

Potential participants will be screened and enrolled in the study upon admission for delivery; therefore, consent will be obtained during labor. Consent should be obtained as early as possible during the intrapartum period and must be obtained prior to the cervical dilation limit approved by local authorities (e.g. either > 6 cm or 10 cm) and/or pushing, as assessed from clinical exam by health facility staff. It is not feasible to wait because the intervention must be given before delivery. Research sites

may choose to obtain initial consent during ANC; however, in this situation, confirmation of consent will be required during the screening and enrollment process.

If consent is obtained during labor, study staff will make necessary accommodations to ensure that the laboring women can comprehend the information presented during the consent process. Potential participants who present in labor can take as much time as needed to consider participation while in labor and will be able to discuss the study with family/friends if desired before deciding on participation. If the participant cannot read, the form will be read aloud to her by a person unaffiliated with the study. Alternatively, the Research Coordinator or a designate may read the consent, but in the presence of a witness who is unaffiliated with the research study. Potential participants will be given an opportunity to discuss the study procedures and ask questions. Additional details are provided in the study Manual of Procedures.

Fair balance will be maintained while describing the risks and benefits of participation in the study. No undue pressure will be placed on the potential participant to enroll in the trial. It will further be explained that lack of participation will not affect the usual and anticipated standard of care. As the literacy levels will vary and may be a challenge, the consent process will include a verbal review of the consent form.

After the potential participant has read the consent form, but before she signs, the research staff will show her a sample study pill and confirm that she is willing and able to take the study pill as prescribed. Only if she is willing to commit to taking the pill will she be enrolled; otherwise, this will be recorded as a refusal of consent. Following review of the consent, the potential participant (or parent/guardian) will be asked to sign the form. If the potential participant (or parent/guardian) is unable to sign her name, she will be asked to use her thumbprint to indicate written approval. In both cases, the unaffiliated person will also sign the consent form. Both the research staff and the study participant retain signed copies of the form.

An eligible woman may refuse to participate in the trial at the time of recruitment. This will be recorded in the Screening and Recruitment Form. She may also choose to withdraw from the study at any time after enrollment. This will be recorded on the Withdrawal/Termination Form.

All research staff responsible for obtaining consent will be trained and certified in the protection of human subjects and the study-specific consent procedures. A model written informed consent form, developed according to the requirements of the U.S. Office of Research Protections (OHRP), is found in **appendix 2**. Each site may modify the model consent to conform to local standards, but the OHRP required elements must be maintained. The research sites will also be responsible for translating the consent form into the appropriate language(s) for their local context.

Global Network countries with legislation regarding the need to videotape consents will comply with the country regulations; however, this is not part of the consent form requirements. This will not be required by protocol but rather decided by each site so as to comply with local rules and regulations.

2.4.4 Masking

Both the azithromycin and placebo will be procured from the same manufacturer. The packaging will be standardized across sites and will be labeled as: “Azithromycin 2 g or Placebo”, with the expiration data and a unique identifier. A certificate of authenticity will likewise be provided.

Clinical and research staff as well as the women will be masked to treatment status unless there is a serious adverse event potentially related to the treatment modality that requires unmasking for safety reasons. There will be one pharmacist at each site who will monitor randomization, drug supply, and safety. Under the instruction of the DCC, the study pharmacist will be trained and authorized to apply un-masking procedures, if concerns about randomization or participant safety are identified.

2.4.5 Randomization Procedures

Randomization of participants will be carried out to obtain a 1:1 allocation ratio between the treatment and placebo arms. Randomization will be stratified by site. A computer algorithm generated by the data coordinating center (DCC) will create the random assignment to one of the treatment arms based on randomly permuted block design with randomly varied block sizes. The block sizes will be known only by the DCC personnel. Each site will receive a lot of the study drug to be distributed sequentially at the participating health facilities which are randomizing women for the study site.

2.4.6 Monitoring before Discharge

Routine post-delivery care will be provided to participants by their clinical providers who will be masked to the study interventions. Research staff (also masked to study medications) trained in obstetric and perinatal outcomes abstraction will be responsible for collecting research data from participant medical records or directly from participants, as relevant, before discharge. Data needed to determine sepsis will include temperature (fever or hypothermia) essentially, plus one or more of heart rate (tachycardia), blood pressure (hypotension), respiratory rate (tachypnea or distress), clinical exam (jaundice or altered mental status) and urine output (low) and a suspicion of infection by the clinical provider or research team. Maternal and neonatal outcomes will be evaluated in the hospital following the delivery (on an ongoing basis until discharge). All participants will be asked to agree to maternal/infant medical record release to abstract information for outcome assessment as part of the consent form. In addition, participants will be educated about the signs and symptoms of infection and other study outcomes and encouraged to call the research team with any concerns.

2.4.7 Monitoring after Discharge

After discharge, study staff will contact participants at the following timepoints:

- In-person visits will be conducted at 3-day, 7-day, and 42-day postpartum to identify maternal or infant infection, unexpected medical visits, side effects, and other study outcomes. WHO criteria for infections will be used and included in the data collection forms. In the case of suspected infection, research staff will collect specimens (e.g. blood, urine, or pus from wound or drained abscesses), as is feasible, in order to identify individual infectious agents.
- Supplemental phone contacts will be conducted at 14-day and 28-day postpartum to review maternal and neonatal signs of infection using WHO criteria. If signs of infection are identified during the review, participants will be asked to visit a study facility for further assessment. These supplemental contacts will reinforce the participants' ability to self-assess for signs of maternal and neonatal infection and improve identification of infection between the 7-day and 42-day postpartum visits. If phone contact is not feasible, in-person visits may be conducted.

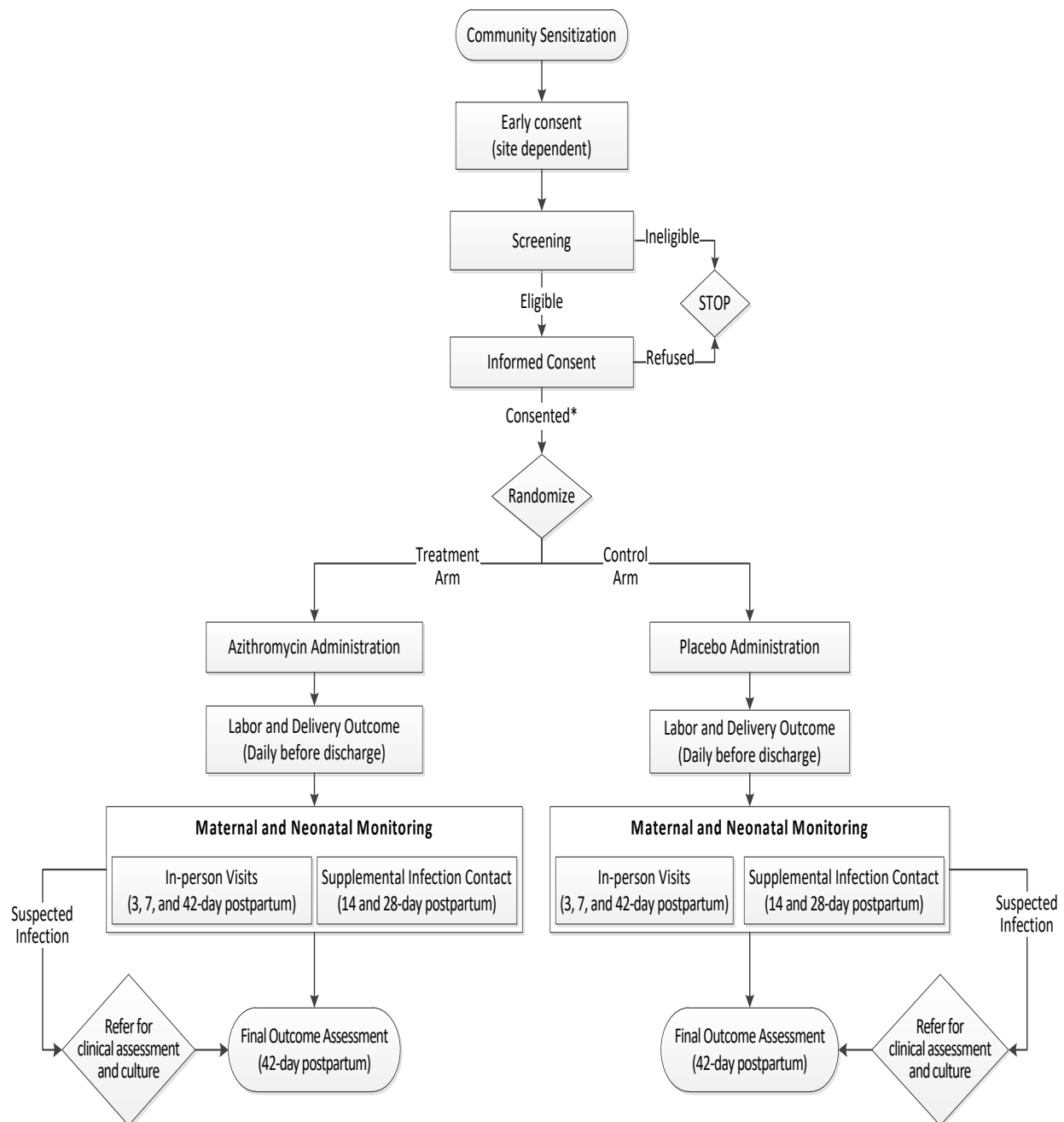
If indicated, records of unscheduled visits to any health facility prior to the routine study visits will be obtained and reviewed to ascertain study outcomes. Treating providers may also be called if clarification is needed. Based on the scheduled visits, study staff will identify any unscheduled visits or readmissions

that occurred in the interim. Readmissions and related diagnoses identified during follow-up visits will be then be validated through medical record review.

2.4.8 Sequence of Study Activities

The sequence of study activities is described in **Figure 1**. A detailed scheduled of study procedures is found in **Appendix 3**.

Figure 1. Flowchart of Study Activities



***If early consent, confirmation of eligibility and reconfirmation of consent required.**

2.5 Primary Outcomes

The primary outcomes are:

- Maternal: Incidence of maternal death or sepsis within 6 weeks (42 days) post-delivery in intervention vs. placebo group.
- Neonatal: Incidence of intrapartum/neonatal death or sepsis within 4 weeks (28 days) post-delivery in intervention vs. placebo group.

Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from suspected or confirmed infection that occurs post-randomization during labor or the postpartum period. This WHO definition, endorsed by multiple global health organizations, will be operationalized as suspected or confirmed infection based on the presence of fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) or hypothermia ($<96.8^{\circ}\text{F}/36^{\circ}\text{C}$) plus one or more signs of mild to moderate organ dysfunction including tachycardia (≥ 120 bpm), low BP (systolic <90 mm Hg), tachypnea (>24 breaths/min), altered mental status/confusion, reduced urinary output (<500 ml over 24 hours), jaundice, or renal failure (>1.2 mg/dl).^{15, 40, 41, 42} Components of peripartum infection which will be considered in making the diagnosis of suspected or confirmed infection include clinical chorioamnionitis, endometritis, wound infections (perineal or Cesarean), abdominal or pelvic abscess, mastitis/breast abscess or infection, pyelonephritis, pneumonia, and other bacterial infection as defined in Section 2.6 below.

Neonatal sepsis is defined as a newborn with proven or possible serious bacterial infection (pSBI) or pneumonia, or meningitis. Possible serious bacterial infection will be determined using WHO criteria of pSBI defined as severe chest in-drawing, fever (temperature $\geq 100.4^{\circ}\text{F}/38.0^{\circ}\text{C}$), hypothermia (temperature $<95.9^{\circ}\text{F}/35.5^{\circ}\text{C}$), no movement at all or movement only on stimulation, feeding poorly or not feeding at all, and/or convulsions.³³ Clinical and laboratory signs of infection will also be considered in making the diagnosis of suspected or confirmed infection.

Centralized masked adjudication of key infection outcomes will be implemented by the DCC and investigators during the trial to standardize and enhance the reproducibility of trial results. In addition to the above specified criteria, reported antibiotic treatment and culture status will also be considered as part of the adjudication process in making the diagnoses for both maternal and neonatal sepsis. Local site investigators will review and validate the diagnosis for all participants identified to have the primary outcomes applying pre-specified criteria. These reviews will be conducted masked to treatment group. A second investigator from a different site will review the participant's information and make a final outcome determination. If this does not agree with the determination of the local site investigator, then the adjudicating investigator will discuss with the local investigator to reach a consensus, failing which the study PIs will make the final call. This process will be coordinated by the DCC.

The individual components of these primary outcomes are also of interest and will be analyzed.

2.6 Other Maternal Outcomes

- a. Chorioamnionitis: Fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) in addition to one or more of the following: fetal tachycardia ≥ 160 bpm, maternal tachycardia >100 bpm, tender uterus between contractions, or purulent/foul smelling discharge from uterus **prior** to delivery.
- b. Endometritis: Fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) in addition to one or more of maternal tachycardia >100 bpm, tender uterine fundus, or purulent/foul smelling discharge from uterus **after** delivery.

- c. Other infections: Wound infection refers to purulent infection (superficial or deep infection including necrotizing fasciitis) of a perineal or Cesarean wound with or without fever. In the absence of purulence, a wound infection requires presence of fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and at least one of the following signs of local infection: pain or tenderness, swelling, heat, or redness around the incision/laceration; abdominopelvic abscess is evidence of pus in the abdomen or pelvis noted during open surgery, interventional aspiration or imaging; pneumonia refers to fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and clinical symptoms suggestive of lung infection including cough and/or tachypnea (>24 breaths/min) or radiological confirmation; pyelonephritis refers to fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and one or more of the following: urinalysis/dip suggestive of infection, costovertebral angle tenderness, or confirmatory urine culture; Mastitis/breast abscess or infection refers to fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and one or more of the following: breast pain, swelling, warmth, redness, or purulent drainage.
- d. Use of subsequent maternal antibiotic therapy after randomization to 42 days postpartum for any reason.
- e. Time from drug administration until initial discharge after delivery (time may vary by site).
- f. Maternal readmission within 42 days of delivery.
- g. Maternal admission to special care units.
- h. Maternal unscheduled visit for care.
- i. Maternal GI symptoms including nausea, vomiting, and diarrhea and other reported side effects.
- j. Maternal death due to sepsis using the Global Network algorithm for cause of death.

2.7 Other Neonatal Outcomes

- a. Other neonatal infections (e.g., eye infection, skin infection, omphalitis, urinary tract infection, respiratory rate ≥ 60 breaths/minute).
- b. Neonatal initial hospital length of stay, defined as time of delivery until initial discharge (time may vary by site).
- c. Neonatal readmission within 42 days of delivery.
- d. Neonatal admission to special care units.
- e. Neonatal unscheduled visit for care.
- f. Neonatal death due to sepsis using the Global Network algorithm for causes of death.
- g. Pyloric stenosis within 42 days of delivery, defined as clinical suspicion based on severe vomiting leading to death, surgical intervention (pyloromyotomy) as verified from medical records, or radiological confirmation.

2.8 Safety Monitoring

Surveillance of maternal side effects including nausea, vomiting, and diarrhea/loose stools, abdominal pain, vaginitis, and dizziness potentially associated with azithromycin will be conducted during labor and postpartum. For infants, findings suggestive of pyloric stenosis will be assessed during the follow up visits. Maternal and neonatal surveillance will also include assessment of unintended medical visits, maternal deaths, stillbirths, neonatal death within 28 days of birth, and infant death after 28 days of birth. Additional maternal and neonatal risks associated with azithromycin use include anaphylaxis, allergic reactions (rash), liver failure, and arrhythmias. Although rare, these side effects will be monitored and reported as a serious adverse event. All safety outcomes will be reviewed at least twice a year by the Data Monitoring Committee (DMC) appointed by NICHD.

2.9 Site Preparation

In preparation for study implementation, the site investigators will meet with local health authorities and conduct community sensitization activities to ensure that study procedures are appropriate for the local context and to encourage commitment and engagement at the facility and community level. Site preparation activities will focus on:

- Disseminating study objectives to local health authorities and other stakeholders
- Identifying and hiring study staff;
- Developing site-specific procedures for safety monitoring procedures;
- Exploring locally-acceptable methods to monitor and improve follow-up visit compliance;
- Identifying potential implementation challenges and developing culturally-appropriate solutions;
- Training research staff in the implementation of the study procedures, follow-up and ascertainment of infections.

2.10 Potential Risks and Benefits to Participants

There are several potential direct and indirect benefits of this trial. In developing countries, including those of GN partners, fetal and neonatal deaths due to infections and maternal and neonatal infections are common. If intrapartum azithromycin reduces maternal and fetal/neonatal mortality or infections, many deaths could be reduced in the GN sites as well as worldwide.

Emerging data suggest that intrapartum azithromycin reduces maternal and neonatal infection. It is not known if deaths could be prevented but as infections are one of the most frequent causes of maternal and neonatal deaths, there is a possibility that mortality could be reduced.

An ongoing concern for peripartum and perinatal antibiotic prophylaxis is the selection of resistant organisms including azithromycin-resistant organisms leading to resistant infections, and there is concern that disruption of gut and other flora (microbiome) in women and particularly in neonates may lead adverse events including increased allergic reactions, rash and childhood asthma.^{12,18,40} In the trial from Gambia of a single oral dose of azithromycin during labor, higher prevalence of colonization with *S. aureus* azithromycin resistance observed among women and their babies four weeks after treatment had waned 12 months later and azithromycin did not induce other antibiotic resistance to *S. pneumoniae* or *S. aureus*; resistance data from actual infections were not available. There was a 7% vs. 21% prevalence of any bacteria in breast milk in those receiving azithromycin vs. placebo [4-5]. In the US trial of 2013 of adjunctive azithromycin in 2013 women who underwent unscheduled cesarean delivery, culture positive maternal infections (1.4% vs. 3.6%) and infections with at least one resistant bacterial species (1% vs. 2.4%) were significantly less frequent in the azithromycin group. Azithromycin-resistant organisms were identified in only 7 (3 vs. 4) participants. There is a paucity of data to address theoretical concerns that disturbances in the establishment of the indigenous intestinal microbiome caused by antibiotic exposure in early life or cesarean delivery, either directly or through modifications of breast microbiome, may increase risk of immune-mediated and inflammatory conditions such as atopic disorders, inflammatory bowel disease and obesity later in life.²⁷⁻³⁰ While the potential for important benefits in both the mother and infant likely outweighs the likelihood and effects of antibiotic resistance and microbiome changes, these should be monitored. In addition to monitoring resistance patterns in isolates from clinical infections, antimicrobial and microbiome surveillance of a subset of enrolled participants are included in an ancillary protocol.

3 ANALYTICAL PLAN

Baseline demographic characteristics and key clinical measures will be compared between the women in the two treatment arms using contingency table approaches for categorical variables and analysis of variance models' continuous variables.

For summaries of study data, categorical measures will be summarized in tables listing the frequency and the percentage of participants; continuous data will be summarized by presenting mean, standard deviation, median and range; and ordinal data will be summarized by only presenting median and range. P-values presented will be based on two-sided tests unless otherwise specified and generally adjusted for randomization factor of site. For most analyses, the interaction between treatment and site will be assessed and if significant, results will also be presented by site. For continuous outcomes, distributional properties will be evaluated and if required, transformations or non-parametric tests will be employed. Additional details for potential covariate adjustments in secondary analyses or handling violations of analytic method assumptions will be detailed in the statistical analysis plan.

Three key populations are of interest for study analyses:

1. The Intention to Treat (ITT) population will include all women randomized and their infants. Analyses of this cohort will be conducted based on randomized treatment.
2. The High-Risk for Infection (HR) sub-group will include all women in the ITT and their infants meeting criteria for being high risk (i.e., prolonged labor [≥ 18 hours] and/or rupture of membranes [≥ 8 hours]) at the time of randomization. Analyses of this cohort will be conducted based on randomized treatment.
3. The As Treated population will include all randomized participants that receive any study drug during the study and their infants. Analyses of this cohort will be conducted based on treatment received.

The final determination of analysis population membership will be via a masked data review prior to final study analyses in order to address any potential anomalous cases that may arise in this large of a study population (e.g., randomization/treatment of a woman who is discharged prior to delivery due to false labor or unresponsiveness to induction).

3.1 Statistical Analysis Plan

3.1.1 Primary Analyses

Incidence of maternal death or sepsis and intrapartum/neonatal death or sepsis will be compared between the two treatment arms using generalized linear models. These generalized linear models will be fit with each binary outcome separately as the outcome measure. Estimates of relative risk and associated 95% confidence intervals will be reported. The model will include terms for treatment and site. As randomization occurs at the pregnancy level and approximately 1-2% of pregnancies are anticipated to be multiple gestations, models for neonatal outcomes will account for correlation among multiples assuming an exchangeable covariance structure. For the two primary outcomes, these analyses will be conducted using the ITT population and the p-values associated with the treatment term will be used to formally test each of the two primary hypotheses at the $\alpha = 0.05$ level.

As secondary analyses of the primary outcomes, assuming an overall treatment effect is observed, the models will be run including region (Africa, Latin America, or Asia) and a treatment by region interaction

term. If the interaction term has a $p < 0.1$, then effects will be reported by region with treatment effect within region tested at the 0.025 level.

Additional exploratory models will also be run including individually: 1) a treatment by site interaction term, 2) any other antibiotic use during labor (yes or no) and its interaction with treatment, and 3) mode of delivery (cesarean or vaginal) and its interaction with treatment. If the interaction term for any of these models has a $p < 0.1$, then effects will also be reported by the relevant subgroups. These exploratory secondary models will also include any demographic or clinical variables found to differ significantly between the treatment arms in the preliminary analyses described above.

From each final model, estimates of relative risk associated with treatment will be obtained including unadjusted estimates of risk from the primary model as well as estimates of risk adjusted for potential confounders from the secondary analyses.

3.1.2 Secondary Analyses – Women at High Risk for Infection Cohort

The major secondary aim is assessing the two primary outcomes (i.e., incidence of maternal death or sepsis and incidence of intrapartum/neonatal death or sepsis) in the women at high risk for infection cohort. These analyses will also assess if the treatment effect differs between the HR cohort vs. non-high-risk women where non-high-risk women comprise all women and their infants in the ITT population that delivered prior to meeting criteria for high-risk (i.e. they delivered after < 18 hours of labor and < 8 hours post-rupture of membranes relative to time of randomization). Specifically, the model for the primary analysis of both the maternal and neonatal primary outcomes will be run including a treatment by risk status interaction term and excluding any data from individuals that meet high-risk criteria after randomization.

The exclusion of data from individuals meeting high risk criteria between randomization and delivery is intended to provide the most distinct groups regarding the HR risk cohort to non-high-risk women comparison. As this exclusion is based on a post-randomization event, sensitivity analyses will be conducted to examine any treatment group differences in meeting high risk criteria post randomization and if there is a difference, to determine the potential magnitude of impact this difference has on treatment effect. An exploratory analysis will also be completed that assesses if there is a difference in treatment effect between women randomized prior to high-risk classification vs. those randomized after high-risk classification. Finally, an exploratory analysis will be conducted that assesses the definition of high-risk to determine if there is a different cut-off that identifies a group of individuals with a greater treatment effect both in relation to randomization and delivery.

3.1.3 Secondary Analyses – Other Secondary Outcomes

Other maternal and neonatal binary outcomes including: the individual components of the primary outcomes, neonatal deaths due to sepsis, maternal infections (clinical chorioamnionitis, endometritis, wound infections (perineal or subsequent cesarean), pyelonephritis and pneumonia), use of subsequent maternal antibiotic therapy, pyloric stenosis and occurrences of maternal or neonatal readmission or admission into special care unit will be analyzed using the approaches detailed in **Section 3.1.1** for the ITT population and approaches detailed in **Section 3.1.2** for the HR cohort. A similar process with generalized linear models employing an appropriate link function will be used to analyze the outcomes of maternal and neonatal initial hospital length of stay.

Binary safety outcomes, e.g., nausea, vomiting, and diarrhea, will also be analyzed using the approaches detailed in **Section 3.1.1**. These analyses will be conducted using the As Treated population.

3.2 Sample Size

3.2.1 Sample Size for Primary Outcome

Sample size estimates were generated to evaluate the potential benefits of peripartum prophylactic azithromycin to reduce the risk of adverse maternal and neonatal outcomes in two population cohorts of women in low and low-middle income settings. The first population of interest comprises all women delivering in facilities (overall).

Power calculations for the study in the overall study population were generated for two primary outcome measures, one being the risk of maternal death or sepsis among women in the target population and the other being intrapartum /neonatal death or sepsis in infants delivered by women in the target population. For each of these outcome measures estimates of the required sample size needed to detect a risk reduction of 20%, 25%, and 30% were generated for power of 0.8, 0.85, and 0.9. The risk of sepsis or maternal death was assumed to be 3%. That number is slightly higher than the current risk in the GN population, which is slightly less than 2%. However, we anticipate that with active surveillance rather than passive reporting based on the new WHO definition of maternal sepsis (designed to catch more cases of sepsis), the risk will be at least 3%. For the neonatal outcome, the underlying risk of the combined outcome of intrapartum stillbirth, neonatal death, or sepsis was assumed to be between approximately 8% and 14%. This estimate was based on recent data from the GN indicating that the risk of intrapartum stillbirth is approximately 1.8% and the risk of neonatal death during the first 28 days after delivery is 2.3%; we assumed that the risk of sepsis not resulting in death is approximately 4% to 10%. The resulting required evaluable sample sizes are shown in **Table 1** below.

Table 1. Sample Sizes for the Overall Population, Alpha=0.05

Baseline Risk	Risk Reduction	Evaluable Sample Size per Arm		
		Power=0.80	Power=0.85	Power=0.90
3%	20%	11455	13103	15334
3%	25%	7133	8159	9548
3%	30%	4815	5508	6446
8%	20%	4096	4686	5483
8%	25%	2554	2921	3419
8%	30%	1727	1975	2311
14%	20%	2204	2521	2950
14%	25%	1377	1575	1842
14%	30%	932	1066	1247

The sample sizes shown above assume that the hypothesis test of interest is for the overall population and that the Type 1 error is controlled at the neonatal and maternal hypothesis level via testing each at an alpha = 0.05 level. Interest has been expressed for the overall study for being able to test the neonatal risk separately in south Asia and sub-Saharan Africa. Controlling the Type I error rate at the 0.025 level for each of those two areas within this sub-analysis of neonatal risk will be conducted to avoid multiple comparison concerns. The resulting sample sizes for that comparison are shown in Table 2 below. Note that this sample size would be the size required separately for the African and Asian sites.

It is planned that each site will enroll approximately equal number of participants. As such, approximately 37.5% of randomized mothers will be from sub-Saharan Africa and 50% will be from Asia. This planned enrollment distribution is approximately equivalent to the rates of in-facility deliveries observed in the GN registry database. Specifically, approximately a third of the facility deliveries are conducted in sub-Saharan Africa and between 45% and 50% of the facility deliveries are conducted in Asia. These estimates are also consistent with the enrollment rates for the ASPIRIN study that is currently being conducted at these sites. Therefore, to get the total study sample size required, the numbers in the table would need to be multiplied by 3 to achieve reasonable power for the African sites.

Table 2. Sample Sizes Within Region, Alpha=0.025

Baseline risk	Risk Reduction	Evaluable Sample Size per Arm		
		Power=0.80	Power=0.85	Power=0.90
8%	20%	4961	5607	6477
8%	25%	3093	3496	4038
8%	30%	2091	2363	2729
14%	20%	2669	3017	3485
14%	25%	1677	1884	2176
14%	30%	1129	1276	1474

Given the above information, we propose a sample size of 34,000 participants for the overall study. For the primary neonatal outcome of interest of intrapartum/neonatal sepsis or death, assuming that the loss to follow-up will be in the 2% to 3% range (consistent with the current ASPIRIN trial and the Global Network Maternal and Newborn Health registry), this sample size will be sufficient to provide 90% power to detect a 25% reduction in neonatal mortality and sepsis in the sub-Saharan African region and will provide 90% power to detect a 20% reduction in Asia assuming the baseline risk is at least 8%. For the primary maternal outcome of maternal death or sepsis, the sample size will provide 90% power to detect a 20% reduction from 3% in the population aggregated across all study sites.

3.2.2 Sample Size for High-Risk Women

The second population of interest comprises the cohort of high-risk population of women delivering in facilities with high risk being defined as term and preterm pregnant women who experience prolonged labor or prolonged membrane rupture. As a major secondary aim, sample size estimates for the high-risk cohort were also obtained to ensure adequate power for this analysis.

The primary objective of the high-risk component of the study is to test the effectiveness of a single oral dose of intrapartum azithromycin prophylaxis compared to placebo (all receive usual care) in reducing the risk of maternal sepsis or death in high-risk laboring women. To estimate the sample size required for this component of the study, we assumed conservatively that the underlying risk of the combined outcome in the target population is 6%. Comparable to the other study estimates of the required sample size needed to detect a risk reduction of 20%, 25%, and 30% were generated for power of 0.8, 0.85, and 0.9. Because the interest for this study is in testing the hypothesis overall rather than by region, the estimates were generated using an alpha of 0.05. The results of these calculations are shown in **Table 3** below.

Table 3. Sample Sizes for the High-Risk Cohort, Alpha=0.05

Baseline risk	Risk Reduction	Evaluable Sample Size per Arm		
		Power=0.80	Power=0.85	Power=0.90
6%	20%	5568	6369	7453
6%	25%	3470	3969	4644
6%	30%	2344	2681	3138

Because a risk reduction of at least 30% is expected in this population, we propose a sample size for this HR cohort of 5,500 women. That sample size will be sufficient to detect a 30% risk reduction with a power of 0.85 with an assumed 2% to 3% loss to follow-up. Assuming that 20% of the women are at high risk, the overall study sample size of 34,000 should allow for sufficient enrollment into the HR cohort.

If the proportion of “high-risk” women is smaller than anticipated, the target enrollment may be modified. A smaller sample size should still provide sufficient power for plausible potential underlying scenarios. For example, a sample size of approximately 4,000 high risk women will be sufficient to detect a 33% risk reduction with a power of 0.82 assuming a baseline risk of at least 6% as well as a 35% risk reduction with a power of 0.80 assuming a baseline risk of at least 5%.

3.3 Available Population

There are no competing protocols ongoing in the GN. Assuming conservatively that 50% of women in labor (30,000 facility births per year) meet eligibility criteria for entry and are enrolled in the trial, approximately 15,000 women/infant dyad will be enrolled per year.

To reach the enrollment target of 34,000, each study site will aim to recruit an equal number of study participants (n=4,250 per site); however, recruitment will be monitored and if a site does not meet targets, adjustments may be made. No site will be permitted to recruit more than 20% of the overall study sample site.

Based on historic GN data, we anticipate that the target of 5,500 high-risk women will be enrolled during the trial. However, through ongoing monitoring, the DCC will assess the number of women enrolled in the “high-risk” group and may modify target enrollment as needed to ensure at least 5,500 high-risk women are enrolled.

3.4 Projected Recruitment Time

The projected study timeline is 36 months or less. This includes the following:

- 0-6 months: Finalize protocol, forms. Obtain approvals, train staff, and obtain/ship study drug/placebo to sites.
- 7-31 months: Enroll participants (exact period of enrollment may vary by site)
- 32-36 months: Complete follow-up; data cleaning and primary analyses.

3.5 Study Monitoring Plan

3.5.1 Reporting Serious Adverse Events

Serious Adverse events (SAEs) will be monitored continuously for any event that meets the following criteria:

- Results in neonatal/fetal or maternal death;
- Is life-threatening;

- Requires hospitalization or prolongs existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Suspicion of pyloric stenosis within 42 days postpartum (prolonged vomiting leading to death or surgery)
- Any other serious or unexpected adverse event that the study investigator(s) feels should be reported.

3.5.2 Method and Timing for Reporting Serious Adverse Events

The Senior Foreign Investigator (SFI) must report the following SAEs by emailing or faxing a copy of the appropriate study form to RTI as follows:

Within 48 hours of SFI's notification of the event:

- All deaths (maternal, intrapartum stillbirths, neonatal)
- All SAEs with a definite or suspected/probable relationship to the intervention

Within 7 days of SFI's notification of the event:

- All life-threatening events;
- All SAEs considered to have a probable or possible relationship to the intervention;
- All emailed or faxed forms should also be entered into the DMS and transmitted within 7 days as a back-up to ensure no SAE is missed.

Additional reporting procedures include:

- RTI will forward all SAEs to the US-based Principal Investigator (PI) and NIH for further assessment of relationship to study intervention. The PI and SFI will be responsible for reporting to their respective IRB and other regulatory authorities per their institutional policy.
- RTI will be responsible for reporting SAEs to the DMC bi-annually at a minimum. The frequency of reporting to the DMC may be increased if the reported events or interim data reviews by the DMC indicate that more frequent safety monitoring is needed.
- Any SAE considered unrelated to the intervention is not required to be reported in an expedited manner. These events should be entered into the data management system and transmitted per routine procedures.

3.5.3 Data Monitoring Plan and Stopping Rules

All the Global Network sites will report data to the Global Network Data Coordinating Center, located at RTI International. The data will be used to evaluate protocol adherence and site performance (e.g., recruitment, loss to follow-up, data quality). The DCC will provide standardized progress reports to NICHD and the site investigators on a monthly basis to monitor outcome variables and adverse events.

Oversight of the trial will be handled by two principal groups with different focuses:

1. **Protocol-focused Steering Committee (SC):** The SC is comprised of the Central Study Team from the University of Alabama at Birmingham and the University of Zambia, NICHD, the DCC, and investigators from each of the participating sites (see Azithromycin Investigators on page 8). The Central Study Team, with assistance from NICHD and the DCC, will have primary responsibility for overall study design, development of study materials and procedures, and oversight of study implementation. They will meet via conference call bi-weekly to monitor study progress and ensure

proper implementation of the trial. The Site Investigators will be responsible for providing guidance on study design, developing site-specific implementation plans, ensuring study staff are properly trained, and providing oversight of the study at the site level. The SC will convene via conference call at least once per quarter and will meet in person twice a year to discuss study design and implementation issues. Members of the Central Study team, NICHD, and RTI will also conduct site visits, as the budget allows, to bolster enthusiasm, provide hands-on training and education to the participating staff, and address site-specific issues, if any.

2. **Data Monitoring Committee (DMC):** The DMC, a standing group that monitors all NICHD-funded Global Network studies, will be responsible for ensuring safe and ethical treatment of study participants through monitoring of the study. The membership will include, at a minimum, a statistician, obstetrician, pediatrician, and an expert in international health. The DMC designated by NICHD will review the data collected at approximate 6-month intervals throughout the course of the study. The DMC reports, which are prepared by the Data coordinating center, will include information on study enrollment rates and participant progress through the study, participant compliance with protocol-specified treatment regimens, protocol violations, adverse events, and efficacy outcomes. The focus of the DMC review will be on monitoring participant safety and study progress/futility. Data on treatment effectiveness will also be presented to frame the DMC discussions on safety and futility. Additionally, one formal interim analyses of efficacy is planned as detailed in **Section 3.5.4**. The DMC will be charged with monitoring adverse events and side effects from azithromycin. All known associated side effects and specific obstetric, fetal, or neonatal concerns will be considered reportable to the DMC. The study will be reviewed by the DMC bi-annually at a minimum but may be reviewed more frequently if concerns are raised about participant safety or about adequate process of the study.

3.5.4 Interim/Adverse Event Monitoring Plan

The DMC designated by NICHD will complete safety reviews of the data bi-annually at minimum during the intervention phase or as often as they decide. Safety reports will be reviewed internally by the DCC quarterly and the DMC chair will be notified if any potential safety signals are identified to allow for more frequent DMC monitoring if needed. Adverse events will be reported and submitted to the DCC (and IRBs) who will report these cumulative masked data to the DMC in the safety reviews. The DMC recommendations about study continuation will be distributed to the IRBs. The DMC will forward their monitoring activities to the project officer representing the NICHD.

Additionally, one formal interim analysis of efficacy and futility will be conducted during the study. Interim analyses will be conducted in both all-comers and high-risk cohort assessing both the primary maternal and neonatal outcomes using the primary analytic approach detailed in **Section 3.1.1 and 3.1.2**. As the maternal and neonatal hypotheses are both of equal importance as well as the treatment effect within the two cohorts, the DMC will not be able to recommend early termination for efficacy unless significance is observed for both outcomes in all comers and the direction and magnitude of effect in the high-risk cohort is consistent with the effect observed in all comers. Cut-off p-values for testing for efficacy at this interim analysis will be determined based on a correction for multiple comparisons to ensure an overall alpha of 0.05. The futility assessment will be based on an analysis of conditional power. The details of the timing of the interim analysis as well as the approaches for correcting for multiplicity and analyzing conditional power will be determined in collaboration with the DMC prior to initiation of study enrollment. Safety and efficacy of the azithromycin will be reviewed and compared

with data from the placebo group according to a data center plan. The primary outcome rate will be calculated, and the data center will develop guidelines for interim analysis decision-making (e.g. the O'Brien-Fleming boundary table).

3.5.5 Risks/Benefits

Based on the preliminary data, there are few risks to this intervention especially given the single oral dose. Severe risks include anaphylaxis and allergic reactions (rash) and liver failure which are rare with azithromycin based on the product insert and our long history of use of prophylactic azithromycin at UAB since 2000. In 2013, the FDA issued an advisory regarding concerns about potential for rare life-threatening arrhythmias with azithromycin use particularly among those with preexisting cardiovascular risk. To minimize the risk of life-threatening side effects, those with arrhythmia, known history of cardiomyopathy, or a known allergy to azithromycin will be excluded. With single 1-2 gram doses, gastrointestinal symptoms (nausea 5-18%, diarrhea/loose stools 7-14%, abdominal pain 5-7%, vomiting 2-7%, and dyspepsia 1%) as well as vaginitis 2% and dizziness (1%) were the most commonly reported side effects. These side effects will be monitored.

3.6 Quality Control

3.6.1 Training

All study personnel must participate in training on the proper implementation of study procedures and the ethics of conducting research with human subjects before beginning any research activity. The SFI and project coordinator will ensure that all study personnel receive the appropriate training and obtain the required certification. RTI will be responsible for developing a certification test. The SFI and project manager will be responsible for overseeing the certification process.

3.6.2 Study Monitoring

Major monitoring responsibilities of the PI/SFI, assisted by the country coordinator, are (1) confirming proper IRB approval; (2) monitoring delivery of the study intervention; (3) assessing and evaluating quality of study implementation; (4) ensuring compliance with the intervention, including proper randomization; (5) evaluating accuracy, precision, and completeness of data collected, entered, and transmitted, along with the DCC; (6) ensuring that all personnel are fulfilling their obligations; (7) maintaining staff morale and enthusiasm; (8) maintaining communication and handling ad hoc problems; (9) ensuring inter-site consistency; and (10) proposing improvements to monitoring activities.

NICHD and the DCC staff will conduct site visits as needed. These visits will include review of individual participant records, including supporting data, to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The SFI/PI will make study documents (e.g., logbooks, data forms, staff training certificates) and pertinent hospital/clinic records readily available for inspection by the local IRB, site monitors, and the NICHD for confirmation of the study data.

3.6.3 Drug Quality Assurance and Monitoring

The study drug manufacturer will have a Good Manufacturing Practices designation vetted by the FDA and a certificate of authenticity will be provided. Each site will adapt best practice guidelines for drug shipment and storage to the needs and infrastructure of their local environment. Study staff will be trained in on the drug shipment and storage plan to ensure that best practices are maintained at all times. Additionally, participants will receive detailed instruction on proper storage of the study drug at

home. Drug stability information will be maintained throughout the study. For quality assurance, a sample of pills from each site will be randomly selected and tested for bioavailability at multiple time points during the study period. A sample from each batch will be tested.

3.6.4 Plan for Sustaining Intervention

We will plan to present abstracts to reputable international obstetric meetings (e.g. SMFM, ACOG or FIGO) and manuscripts within 3-6 months of completion of the primary data collection to high impact journals such as the New England Journal of Medicine, JAMA, or the Lancet. If the results are positive, we will facilitate the change in practice at participating sites and also approach the WHO to instigate guideline updates to reflect the study findings.

4 DATA MANAGEMENT PROCEDURES

Data will be collected both prospectively and from existing medical records, using hard copy forms or Android Tablets. Regardless of data capture methodology, all data will be kept confidential. Each participant will be assigned a unique study ID which will be used to identify the participant. Only the screening log will contain the name (which is not transmitted). If hard copy forms are used, they will be retained in a secure location for possible editing or queries at the central data entry site. Data will be entered into computers using the Data Management System (DMS) developed by RTI and the assigned study number. The DMS will also allow site staff to produce project reports and backup the study database. Electronic data will be transferred from each data management computer to a single Research Unit Data Center in each country, creating a complete data repository. At least once a week, data will be transmitted from the Research Unit Data Center to the DCC at RTI, where the central database will be located. The DCC will conduct training on data collection procedures and the DMS system, as needed.

Precision and accuracy of actual data collected will be checked by chart review (random 5%) and internal procedures using the computer program. Monthly audits and incomplete data reports will be performed by a review team consisting of at least the SFI and country coordinator. Data editing and error resolution will be performed monthly. In addition, a sample of participants will be visited to confirm participation, with procedures determined per site. These activities will be shared between the site and the DCC. The timing of data collection is found in the schedule of study procedures (**Appendix 3**).

4.1 Data Forms

The following forms will be used for this study:

Form Name	Purpose	Key Data Elements	Data Source
Contact and Scheduling Form	To facilitate participant follow-up by documenting contact information and projected study visit schedule	Contact information, date of enrollment, date of follow-up visits	Participant interview, study calendar
Screening and Enrollment Form	To determine eligibility and record consent status	Screening date, review and confirmation of inclusion/exclusion criteria, consent status/date.	Participant interview/report, clinical assessment, provider report, medical records
Randomization Form	To confirm eligibility and track randomization	Eligibility confirmation, randomization date/time, drug administration date/time, any problems with drug administration (e.g., vomiting, dropped med, etc).	Study records, participant interview and observation

Form Name	Purpose	Key Data Elements	Data Source
Maternal Baseline Data Form	To collect additional maternal information	<ul style="list-style-type: none"> Demographic and baseline clinical data: admission date/time, EDD, GA, age, height, weight, pregnancy and medical history, etc. Events during labor and delivery: timing of onset of labor, prolonged labor, premature rupture of membranes, date/time/type of membrane rupture, date/time/type of delivery, indication for induction (if applicable), vital signs during labor (temp, HR, RR, BP), complications, etc. Events after delivery: complications, vital signs, etc. Infection assessment pre- and post-delivery Antibiotic treatment pre- and post-delivery Discharge information 	Participant interview/report, provider report, medical records
Neonatal Baseline Data Form	To collect information about the infant directly after delivery.	<ul style="list-style-type: none"> Sex Birthweight Delivery outcome (live or stillbirth) Complications Infection assessment Discharge information: date/time, status (discharged, transferred, died) 	Participant interview/report, provider report, medical records
Maternal and Neonatal Follow-up Form	To collect maternal and infant health status during follow-up visits at 3 days, 7 days and 42 days after delivery.	<ul style="list-style-type: none"> Timing follow-up Maternal and infant status since discharge: general status, symptoms, indication of infection, clinic visits, hospitalizations, antibiotic use Temperature 	In-person participant interview/report and clinical exam
Supplemental Infection Contact Form	To document signs of maternal or neonatal infection and provide referrals if indicated.	<ul style="list-style-type: none"> Maternal and neonatal infection danger signs. Referral information. 	Participant interview/report by phone
Maternal and Neonatal Unscheduled Medical Visit	To collect information about clinical events reported during follow-up visits	Reason for medical visit, details about medical visit	Participant interview/report, provider report, clinical exam, medical records
Specimen Collection and Result Form	To track specimen collection when there is indication of maternal or infant infection	Date/time of specimen collection; reason for collection; location of wound/infection; tracking information for shipping/storing specimen; results	Study documentation if collected and/or tested by study; medical records if collected and/or tested by health facility.
Serious Adverse Events	To record fatal, life-threatening, or any other serious, unexpected adverse event	Date/time of event, date/time of resolution, nature of adverse event, management of adverse event, attribution to study (yes/no).	Participant interview/report, provider report, medical records
Final Study Status	To document final study status	Final study status (e.g., completion, withdrawal, lost-to-follow-up), Date of final study status. If withdrawal, provide reason.	Participant report, medical records
Protocol Deviation	To record protocol deviations and corrective actions	Date and nature of deviation/violation, corrective action.	Participant report, study records, medical records
Outcome Adjudication	To validate cases of infection using standard study definitions	Primary and secondary outcomes	Study documentation, provider reports/interviews, medical records

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APPENDIX 1. DESCRIPTION OF PARTICIPATING GLOBAL NETWORK SITES

The Global Network for Women's and Children's Health Research (GN) was created as a private-public partnership between the U.S. National Institutes of Health (NIH) and the Bill and Melinda Gates Foundation in response to the alarming rates of morbidity and mortality in women and children and the lack of research expertise and infrastructure in the developing world. Its mission is to expand scientific knowledge, develop research infrastructures, and improve health outcomes by building research partnerships to conduct research on feasible, cost-effective, sustainable interventions to address the major causes of perinatal morbidity and mortality of women and children in the developing world. It is currently funded only by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

The current configuration of the GN is comprised of eight multidisciplinary research sites in seven developing countries (Bangladesh, Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, and Zambia), each with an established collaboration between an institution in the U.S. and one or more in the developing country. Each site has a U.S.-based senior principal investigator (PI) and a senior foreign investigator (SFI) based in the developing world, who lead a team of in-country research staff.

In 2005, the GN implemented its first multicounty protocol, the First Breath (FB) study, a community-based cluster trial to determine whether education and training in the American Academy of Pediatrics Neonatal Resuscitation Program (NRP) and the Essential Newborn Care Program (ENC) of the World Health Organization (WHO) reduced neonatal mortality (7 days) more than education and training in ENC alone. More than 3,700 birth attendants from 100 GN communities with > 150,000 deliveries were taught the appropriate procedures and provided with the necessary equipment to resuscitate infants at birth. Communities were randomized to ENC plus NRP or continued ENC.

The GN has continued to build on the capacity developed in the FB trial through the implementation of more than 10 additional multicounty protocols to address priority research needs to improve maternal and child health in low-resource settings. Current projects include:

- **The Maternal Newborn Health Registry** is a prospective, population-based study of pregnancies and their outcomes in low-middle income countries (DRC, Guatemala, India, Pakistan, Bangladesh, Zambia and Kenya). All pregnant women in participating clusters are registered and their outcomes tracked for 6 weeks post-delivery. The primary purpose of this prospective, population-based observational study of approximately 60,000 women per year is to quantify and understand the trends in pregnancy services and outcomes over time in defined, low-resource geographic clusters. The goal is to provide population-based statistics on stillbirths, neonatal and maternal mortality as the basis of health care policy. The data from the registry also provide the mortality and morbidity outcomes for Global Network trials and help investigators plan future studies for the Global Network.
- Preterm birth remains the leading cause of neonatal mortality and long-term disability throughout the developed and developing world. A growing body of evidence suggests that 1st

trimester administration of low dose aspirin can reduce the rate of PTB substantially. The **ASPIRIN Study** is a prospective, randomized, placebo-controlled, double-masked, multi-center clinical trial to examine whether low dose aspirin initiated between 6 0/7 weeks- 12 6/7 weeks gestation reduces the risk of preterm birth. The study has enrolled 11,920 women across seven sites in Africa, Asia, and Latin America.

- Attention is increasingly directed to the role of maternal nutrition during the 1st trimester for normal growth and development during the first thousand days, from conception to the child's second birthday. The primary hypothesis of the **Women First: Preconception Maternal Nutrition study** is that for women in poor communities, a comprehensive maternal nutrition intervention commencing at least 3 months prior to conception and continuing throughout pregnancy, will be associated with a significantly greater newborn length than for offspring whose mothers start to receive the same intervention at 12 weeks gestation or who do not receive the intervention at all. The results of this trial will make a major contribution to refining evidence-based strategies for maternal nutrition supplementation and evaluating the cost-benefits of extending such strategies beyond pregnancy to virtually all women of child-bearing age, including adolescent girls.

APPENDIX 2. SAMPLE INFORMED CONSENT

Global Network for Women's & Children's Health Research

Single oral dose of azithromycin 2 gm in laboring women to prevent neonatal infection/death and maternal peripartum infection/death

INVESTIGATORS:

[LIST SITE INVESTIGATORS]

SPONSOR:

The Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD)

You are being asked to participate in a research study for pregnant mothers. This study is funded by the U.S. National Institutes of Health and the Bill and Melinda Gates Foundation. This form provides you with information about the study so that you can decide whether you would like to participate. A member of the research team will describe the study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part. You may also request that the research staff read the form to you.

What is the purpose of the study?

The purpose of this study is to learn whether an antibiotic, called azithromycin, given orally (by mouth) to pregnant women during labor can reduce the risk of infection for the woman and her baby.

Who will be in the study?

A total of 34,000 women will be enrolled in this study from eight sites in sub-Saharan Africa, South Asia, and Latin America. If needed, up to 2000 additional women across all sites who meet high-risk criteria will be enrolled (defined as 8 hours or more of membrane rupture before delivery or 18 hours or more of labor). In [insert site name], no more than [insert max sample size] will be enrolled.

You qualify for this study if you are a pregnant woman of the legal age of consent who is in labor with one or more live fetuses and a pregnancy ≥ 28 weeks, plan to deliver vaginally in a health facility, have no known infections that require antibiotics, have no known problems taking azithromycin or similar antibiotics (such as amoxicillin), and have not used azithromycin, erythromycin, or similar antibiotic in the past 3 days. We will ask you some questions about your pregnancy and health status to make sure you qualify to participate.

What will happen if I join this study?

Before participating, you will be provided with information about the study procedures and given an opportunity to ask questions. If you qualify and agree to participate, you will be asked to sign this form to indicate your consent.

If you agree to participate, you will be assigned to either the treatment group or the control group. The assignment is made randomly, like flipping a coin or choosing a grain of rice from a bag. The women in the treatment group will take four 500 mg azithromycin pills. For comparison, the women in the control group will take four pills that look identical to azithromycin but do not contain any medication. This will

allow the researchers to compare how well azithromycin works to prevent infection in mothers and their babies. Neither you nor the study staff will know whether you are assigned to the treatment or control group.

After you have been assigned to a treatment group, you will be given 4 small 500 mg pills to take by mouth. A member of the study team will watch you take the pills. After you take the pills, you will receive care during your labor, delivery, and recovery from the health facility staff, according to the local standard of care. It will take approximately 30 minutes to complete the consent form and take the pills.

While you are at the health facility to deliver your baby, the study team will also collect:

- Information about your health status during labor, at the time of delivery, and after delivery. This includes collecting your temperature and vital signs, such as heart rate and blood pressure;
- Information about your baby's health status during and after delivery. This includes collecting your baby's temperature and vital signs, such as heart rate and blood pressure;
- If you or your baby develop an infection before you are discharged from the health facility, a specimen will be collected to help identify the bacteria that is causing the infection. This may be blood sample, a urine sample, or a sample taken from the site of the infection (for example, pus from a wound or breast milk in the case of a breast infection).

It will take no more than 30 minutes to collect health information about you and your baby. In the case of suspected infection, it may take an additional 30 minutes to collect samples from you or your baby.

After delivery, a member of the study team will visit you a total of three times to assess the health status of you and your baby. These visits will be scheduled to take place at your home or a health facility at 3 days, 1 week (7 days) and 6 weeks (42 days) after delivery. If you or your baby are hospitalized at the scheduled time, the study team will visit you in the hospital. During the visit, the study team will assess you and your baby for current or past signs of infection. This will include collecting health information and measuring temperature for you and your baby. Each visit will take approximately 30 minutes.

A member of the study team will also contact you by phone at 14 days and 28 days after delivery to review the signs and symptoms of infection. If you do not have a phone, the study team will arrange to visit you at home or at the study facility. Each phone contact will take approximately 15 minutes.

If a sign of infection is identified in you or your baby during the in-person visits or phone contact, you will be referred to a health facility for further assessment. You will also be asked to provide a sample, such as blood, pus, or urine, to help identify the bacteria causing the infection. The samples will be labelled with a study identification number in place of your name or your baby's name. Only dedicated members of our study team will have access to the samples.

To ensure that we have accurate and complete information about the health of you and your baby, we will access and collect information from the medical records at the health facilities where you and your baby have received care. By agreeing to participate in this study, you are also agreeing to give permission for the study staff to access your medical records. We will take precautions to protect the information that is collected from your medical records. Only study staff will have access to this information. To further protect you and your baby, all of your information will be coded with a number in place of your name.

The local research staff have been selected because of their skills, knowledge, and familiarity with your community. The research staff are here to support you during the study and should be contacted between visits if you have any questions or concerns.

What are the risks and discomforts

Azithromycin is a sometimes used to treat infections in pregnant women and children. Research shows that the risks of taking azithromycin are minimal. A commonly reported side effect is gastric discomfort (nausea, stomach pain, diarrhea, vomiting); however, you will be given pills with a special coating which will help prevent stomach discomfort. There is also a small but rare risk that azithromycin could cause arrhythmia (irregular or abnormal heartbeat) or an allergic reaction; therefore, you will not be able to participate if you have a known history of heart problems or have had a bad reaction to azithromycin or a similar drug in the past.

If it is necessary to take a sample because of infection, you or your baby may feel temporary discomfort, but this will only last a few seconds. To minimize this, we will ensure research staff are well trained in the procedure.

Another possible risk of participating in this study is that your name and personal information may be seen by persons who are not part of the project. To prevent this, you will be given an identification number that will be used in place of your name on all study documents.

Information from this research study will be retained by [local institution] and RTI International in the United States (U.S.) and in the future may be included in a de-identified public use database managed by NICHD Data and Specimen Hub (DASH) in compliance with the U.S. National Institutes of Health (NIH) Public Access Policy. De-identified means that you and your baby will not be individually identified by name or other personal identifiers in the database. Your full name or any address details will not be included. Information released will not identify you or your baby's participation in this research study.

What are the benefits of participating?

You will not receive any money from participating in this study, but your participation may provide important information that can be used in the future to prevent infection in mothers and babies. Also, there is preliminary information suggesting that the use of azithromycin in pregnancy can reduce the risk of maternal and infant infection.

If new information about the benefits or risks of azithromycin use in pregnancy becomes available during the study, this information will be given to you by [Insert name of Senior Investigator] or his/her staff.

Will I have to pay for anything?

It will not cost you anything to be in the study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to refuse to participate or to withdraw your participation at any time. If you refuse or decide to withdraw, you will not lose any benefits or rights to which you are entitled. These actions will not have any negative effect on the health care you receive from your local health providers. You will still receive your normal medical care.

Can I be removed from this study?

You will be withdrawn from the study if the research staff thinks that your participation may cause harm to you or your baby. The research staff may also remove you from the study for other reasons at their discretion. Also, the sponsor may stop the study at any time.

What will happen if you are injured by this research?

Although the risk of injury is expected to be very low, all research involves a chance that something bad might happen to you. Despite all safety measures, your participation could result in a reaction or injury. If you or your infant is injured as a result of your participation, you will be provided with emergency care by the study and referred to a doctor for ongoing care, if needed. Ongoing care will not be paid for by the study. [Insert name of Research Institution] and NICHD have not set aside funds to pay you for any such reactions, injuries or related medical care. However, by signing this form, you do not give up any of your legal rights.

What should you do if you have additional questions?

If you have questions about this study or a project-related injury, you should contact [investigator contact]. If you have questions about your or your baby's rights as a project participant, please contact [insert ethics committee contact].

Agreement to be in this study

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I know that being in this study is voluntary and I choose to be in this study. I understand I will get a copy of this consent form.

Signature (or thumbprint): _____ Date: _____
(Mother)

Print Name: _____
(Mother)

Signature (or thumbprint): _____ Date: _____
(Parent/Guardian/Husband)

Print Name: _____
(Parent/Guardian/Husband)

Future Contact

We may wish to contact you in the future about participating in other related research studies. Please indicate below if you are willing to be contacted.

☐ Yes, I agree to be contacted

☐ No, I do not agree to be contacted

APPENDIX 3. SCHEDULE OF STUDY PROCEDURES

	ANC Visits	During Labor/ Before Delivery	After Delivery/ Before Discharge	3-day postpartum (pp)	7-day pp	14-day pp	28-day pp	42-day pp	As Needed
Community Sensitization	X								
Screening									
• <i>Eligibility confirmation</i>		X							
• <i>Clinical assessment</i>		X							
Consent		X							
Randomization		X							
Drug Administration		X							
Baseline Data Collection									
• <i>Sociodemographic information</i>		X	X						
• <i>Medical history</i>		X	X						
• <i>Labor and delivery information</i>			X						
Monitoring									
• <i>Drug side effects</i>		X	X	X	X			X	X
• <i>Maternal events during labor/delivery</i>		X	X						
• <i>Neonatal events during labor/delivery</i>			X						
• <i>Maternal infection/sepsis assessment</i>			X	X	X			X	X
• <i>Neonatal infection/sepsis assessment</i>			X	X	X			X	X
• <i>Maternal death</i>			X	X	X			X	X
• <i>Stillbirth or neonatal death within 28 days of birth</i>			X	X	X	X	X	X	X
• <i>Infant mortality after 28 days of birth</i>								X	X
• <i>Pyloric stenosis</i>			X	X	X			X	X
• <i>Other maternal outcomes</i>			X	X	X			X	X
• <i>Other neonatal outcomes</i>			X	X	X			X	X
• <i>Unintended medical visits</i>			X	X	X			X	X
Serious Adverse Events			X	X	X			X	X

STATISTICAL ANALYSIS PLAN

Prevention of maternal and neonatal death/infections with a single oral dose of azithromycin in women in labor (in low- and middle-income countries): a randomized controlled trial (A-PLUS)

The A-PLUS Study

SAP VERSION: Version 2.0

SAP DATE: October 13, 2022

SPONSOR: NICHD

PREPARED BY: RTI International
3040 Cornwallis Rd
Research Triangle Park, NC 27709-2104

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Contents

1. BACKGROUND AND PROTOCOL HISTORY	6
2. PURPOSE OF THE ANALYSES	6
3. STUDY OBJECTIVES AND OUTCOMES	7
3.1 PRIMARY HYPOTHESIS AND ASSOCIATED OUTCOMES	7
3.2 SECONDARY AIMS AND ASSOCIATED OUTCOMES	8
4. STUDY METHODS	10
4.1 OVERALL STUDY DESIGN	10
4.2 STUDY POPULATION	11
4.3 STUDY ARM ASSIGNMENT AND RANDOMIZATION	12
4.4 MASKING AND DATA LOCK	12
5. ANALYSIS POPULATIONS	13
6. SAMPLE SIZE DETERMINATION	14
6.1 OVERALL (ALL-COMER) SAMPLE SIZE FOR PRIMARY OUTCOMES	14
6.2 HIGH RISK COHORT SAMPLE SIZE FOR PRIMARY OUTCOMES	16
7. STATISTICAL / ANALYTICAL ISSUES	17
7.1 GENERAL RULES	17
7.2 ADJUSTMENTS FOR COVARIATES	17
7.3 MISSING DATA APPROACHES:	17
7.4 MULTICENTER STUDIES	18
7.5 MULTIPLE COMPARISONS AND MULTIPLICITY	18
7.6 MASKED DATA REVIEW	18
8. STUDY PARTICIPANTS, TREATMENT EXPOSURE AND COMPLIANCE	19
8.1 PARTICIPANT DISPOSITION	19
8.2 STUDY TREATMENT EXPOSURE AND COMPLIANCE	19

8.3	PROTOCOL DEVIATIONS	19
8.4	DEMOGRAPHIC AND BASELINE CHARACTERISTICS	19
9.	EFFICACY ANALYSES	19
9.1	OVERVIEW OF EFFICACY ANALYSIS METHODS	19
9.2	DEFINITION OF ANALYSIS VARIABLES	20
9.3	PRIMARY ANALYSIS	33
9.4	SECONDARY ANALYSES FOR HIGH RISK COHORT	33
9.5	SECONDARY OUTCOME ANALYSES	34
10.	SAFETY ANALYSIS:	35
11.	INTERIM ANALYSES AND DATA MONITORING	35
12.	CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL	36
13.	REFERENCES	36

LIST OF ABBREVIATIONS

Acronym	Definition
AC	All-Comers
ACOG	American Congress of Obstetricians and Gynecologists
ANC	Antenatal Care
BP	Blood Pressure
DCC	Data Coordinating Center
DMC	Data Monitoring Committee
DMS	Data Management System
DRC	Democratic Republic of the Congo
EmONC	Emergency Obstetric and Neonatal Care
ERC	Ethical Review Committee
FDA	Food And Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GA	Gestational Age
GEE	Generalized Estimating Equation
GI	Gastrointestinal
GN	Global Network
HR	High Risk
IRB	Institutional Review Board
ITT	Intention to Treat
JAMA	Journal of the American Medical Association
LIC	Low income country
LMIC	Low middle income country
LMP	Last menstrual period
MDG	Millennium Development Goals
mITT	Modified intention to treat
MNH	Maternal and Neonatal Health
NEJM	New England Journal of Medicine
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNT	Number needed to treat
OHRP	U.S. Office of Research Protections
PI	Principal Investigator
PP	Per protocol
pSBI	possible serious bacterial infection

RCT	Randomized Clinical Trial
RTI	Research Triangle International
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SFI	Senior Foreign Investigator
SMFM	Society for Maternal-Fetal Medicine
UAB	University of Alabama at Birmingham
UN	United Nations
WHO	World Health Organization

1. BACKGROUND AND PROTOCOL HISTORY

Background and Rationale

Maternal infection and sepsis are a priority to reduce maternal and neonatal deaths. Compared to postpartum hemorrhage and preeclampsia/eclampsia, maternal infection has received less attention as a major cause of maternal death; proportionally it accounts for increasing deaths. In addition, maternal infection significantly increases the risk of neonatal sepsis which is one of the leading causes of neonatal death in LICs. Drawing from our findings on azithromycin prophylaxis for cesarean delivery in the US and data from another preliminary trial in The Gambia, Africa, we proposed to evaluate the role of a single oral dose of azithromycin (plus usual care) to prevent maternal death or peripartum sepsis and intrapartum/neonatal death or sepsis in laboring women as well as the targeted sub-population of those at the highest risk for infection because they have prolonged labor (≥ 18 hours) and/or prolonged membrane rupture (≥ 8 hours).

Azithromycin is available as a generic agent with easy storage requirements. It has a bimodal half-life of up to 70 hours in the non-pregnant population. Although its pharmacokinetic characteristics are not as well studied in the pregnant population, it is commonly used during pregnancy for treatment of chlamydia and other infections. Azithromycin covers a broad spectrum of bacteria (including gram-positive cocci, genital ureaplasmas and mycoplasmas, and certain gram-negative bacilli and anaerobes) that are associated with maternal infections which are often polymicrobial (chorioamnionitis, endometritis, and perineal/cesarean wound infection) and sepsis. In addition to the aforementioned organisms which may play a role in neonatal infection, azithromycin also has activity against Group B streptococcus which is a major cause of neonatal sepsis in developed countries and may be implicated in LICs and low-resources settings as well. Therefore, a successful prophylaxis intervention is likely to reduce infections and death and may also reduce health care costs and need for prolonged antibiotic therapy to treat infections which may be associated with resistance.

Protocol History

The protocol in place at time of study implementation was finalized in July 2022 under Protocol version 1.6.

2. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) contains detailed information about statistical analyses to be performed to assess the primary and secondary hypotheses outlined in the protocol including one formal interim analysis. The results of these analyses will be included in the study manuscript(s). Result of the formal interim analysis will be provided only to the Data and Safety Monitoring Board until study completion or early termination. Additional exploratory analyses may be performed to support further manuscript development. These analyses will not require an update to the SAP, but abbreviated analysis plans will be prepared prior to conducting those analyses.

3. STUDY OBJECTIVES AND OUTCOMES

3.1 Primary Hypothesis and Associated Outcomes

This study had two primary hypotheses, one with a maternal focus and one with a neonatal focus.

1. First, a single, prophylactic intrapartum oral dose of 2 g azithromycin given to women in labor in low and middle-income settings will reduce maternal death or sepsis.
2. Second, a single, prophylactic intrapartum oral dose of 2 g azithromycin given to women in labor in low and middle-income settings will reduce intrapartum/neonatal death or sepsis.

The primary outcomes are:

1. Maternal: Incidence of maternal death or sepsis within 6 weeks (42 days) post-delivery in intervention vs. placebo group.
2. Neonatal: Incidence of intrapartum/neonatal death or sepsis within 4 weeks (28 days) post-delivery in intervention vs. placebo group.

Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from suspected or confirmed infection that occurs post-randomization during labor or the postpartum period. This WHO definition, endorsed by multiple global health organizations, will be operationalized as suspected or confirmed infection based on the presence of fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) or hypothermia ($<96.8^{\circ}\text{F}/36^{\circ}\text{C}$) plus one or more signs of mild to moderate organ dysfunction including tachycardia (≥ 120 bpm), low BP (systolic <90 mm Hg), tachypnea (>24 breaths/min), altered mental status/confusion, reduced urinary output (<500 cc over 24 hours), jaundice, or renal failure (>1.2 mg/dl). Components of peripartum infection which will be considered in making the diagnosis of suspected or confirmed infection include clinical chorioamnionitis, endometritis, wound infections (perineal or Cesarean), abdominal or pelvic abscess, mastitis/breast abscess or infection, pyelonephritis, pneumonia, and other bacterial infection.

Neonatal sepsis is defined as a newborn with proven or possible serious bacterial infection (pSBI) or pneumonia, meningitis, urinary tract infection, or omphalitis. Possible serious bacterial infection will be determined using WHO criteria of pSBI defined as severe chest in-drawing, fever (temperature $\geq 100.4^{\circ}\text{F}/38^{\circ}\text{C}$), hypothermia (temperature $<95.9^{\circ}\text{F}/35.5^{\circ}\text{C}$), no movement at all or movement only on stimulation, feeding poorly or not feeding at all, and/or convulsions. Clinical and laboratory signs of infection will also be considered in making the diagnosis of suspected or confirmed infection.

Only infections that occur post-randomization will count as study outcomes.

Masked adjudication of key infection outcomes will be implemented by the DCC and investigators during the trial to standardize and enhance the reproducibility of trial results. In addition to the above specified criteria, reported antibiotic treatment and culture status will also be considered as part of the adjudication process in making the diagnoses for both maternal and neonatal sepsis. Local site investigators will review and validate the diagnosis for all participants identified to have the primary outcomes applying pre-specified criteria. These reviews will be conducted masked to treatment group. If a case requires additional input and cannot be adjudicated locally, then it will

move to central adjudication where the study PIs will review the participant's information and make a final outcome determination. A random portion of the locally adjudicated cases will be selected for central review to ensure there are no systemic site difference in adjudication. This process will be coordinated by the DCC.

3.2 Secondary Aims and Associated Outcomes

The single dose of intrapartum azithromycin prophylaxis (2 g) will be compared to placebo to accomplish the following secondary aims:

Main Secondary Aim for Women at High Risk for Infection Cohort:

- a. To evaluate whether the risk of maternal death or sepsis differs among laboring women with and without high-risk for infection (high risk is defined as women with prolonged labor [≥ 18 hours] and/or prolonged membrane rupture [≥ 8 hours]).

Other Secondary Specific Aims:

- b. To evaluate the effectiveness in reducing the risk of individual components of the primary composite endpoints (i.e., maternal death, maternal sepsis, intrapartum/neonatal death, neonatal sepsis including specifically all-cause neonatal deaths and neonatal deaths due to sepsis).
- c. To evaluate the effectiveness on the risk of intrapartum/neonatal death or sepsis in infants of laboring women at high-risk for infection because of prolonged labor (≥ 18 hours) and/or prolonged membrane rupture (≥ 8 hours).
- d. To evaluate the effectiveness on the risk of maternal infections including clinical chorioamnionitis, endometritis, wound infections (perineal or subsequent cesarean), abdominal or pelvic abscess, mastitis/breast abscess, pyelonephritis and pneumonia in all laboring women as well as in those at high-risk for infection.
- e. To evaluate the effectiveness in reducing the use of subsequent maternal antibiotic therapy from randomization to 42 days postpartum for any reason in all laboring women as well as in those at high-risk for infection.
- f. To compare the use of health care resources. Use of health care resources will be measured in terms of maternal and neonatal duration of hospital stay, unscheduled visits, readmissions, and admission to special care units/intensive care units in all laboring women and newborns as well as in those at high-risk for infection.
- g. To assess maternal GI symptoms (e.g., nausea, vomiting, and diarrhea) and other reported side effects, as well as infant pyloric stenosis and type of culture positive infections (antimicrobial resistance and maternal and infant microbiome diversity are compared in an ancillary study).
- h. To determine whether the effect on each of the primary outcomes differs by region (Africa, Latin America or Asia), any other antibiotic use during labor, and mode of delivery (cesarean or vaginal). Note that antibiotic use will not include use to treat any infections diagnosed after randomization as those will be outcomes.

These secondary aims will be assessed using the following outcomes.

- The individual components of the primary outcomes (i.e., maternal death, maternal sepsis, maternal death due to sepsis, intrapartum/neonatal death, neonatal sepsis including specifically all-cause neonatal deaths and neonatal deaths due to sepsis)

- Other Maternal Outcomes
 - Chorioamnionitis: Fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) in addition to one or more of the following: fetal tachycardia ≥ 160 bpm, maternal tachycardia > 100 bpm, tender uterus between contractions, or purulent/foul discharge from uterus prior to delivery.
 - Endometritis: Fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) in addition to one or more of maternal tachycardia > 100 bpm, tender uterine fundus, or purulent/foul discharge from uterus after delivery.
 - Wound infection refers to purulent infection (superficial or deep infection including necrotizing fasciitis) of a perineal wound or wound of a cesarean with or without fever; In the absence of purulence, a wound infection requires presence of fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and at least one of the following signs of local infection: pain or tenderness, swelling, heat, or redness around the incision/laceration.
 - Other infections:
 - Abdominopelvic abscess is evidence of pus in the abdomen or pelvis noted during open surgery, interventional aspiration or imaging;
 - Mastitis/breast abscess or infection refers to fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and one or more of the following: breast pain, swelling, warmth, redness, or purulent drainage (for breast abscess).
 - Pyelonephritis refers to fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and one or more of the following: urinalysis/dip suggestive of infection or costovertebral angle tenderness or confirmatory urine culture.
 - Pneumonia refers to fever ($>100.4^{\circ}\text{F}/38^{\circ}\text{C}$) and clinical symptoms suggestive of lung infection including cough and/or tachypnea or radiological confirmation.
 - Use of subsequent maternal antibiotic therapy after randomization to 42 days postpartum for any reason.
 - Time from drug administration until initial discharge after delivery (time may vary by site).
 - Maternal readmission within 42 days of delivery.
 - Maternal admission to special care units.
 - Maternal unscheduled visit for care.
 - Maternal GI symptoms including nausea, vomiting, and diarrhea and other reported side effects.
 - Maternal death due to sepsis using the Global Network algorithm of causes of death.
- Other Neonatal Outcomes
 - Other neonatal infections (e.g. eye infection, skin infection, omphalitis, urinary tract infection, respiratory rate ≥ 60 breaths/minute)

- Neonatal initial hospital length of stay, defined as time of delivery until initial discharge (time may vary by site).
- Neonatal readmission within 42 days of delivery.
- Neonatal admission to special care units.
- Neonatal unscheduled visit for care.
- Neonatal death due to sepsis using the Global Network algorithm for causes of death.
- Pyloric stenosis within 42 days of delivery, defined as clinical suspicion based on severe vomiting leading to death, surgical intervention (pyloromyotomy) as verified from medical records, or radiological confirmation.

Detailed definitions for deriving the associated variables are included in Section 9.

Type of culture positive infections, antimicrobial resistance and maternal and infant microbiome diversity were compared in an ancillary study and the associated analyses described in a separate analysis plan.

4. STUDY METHODS

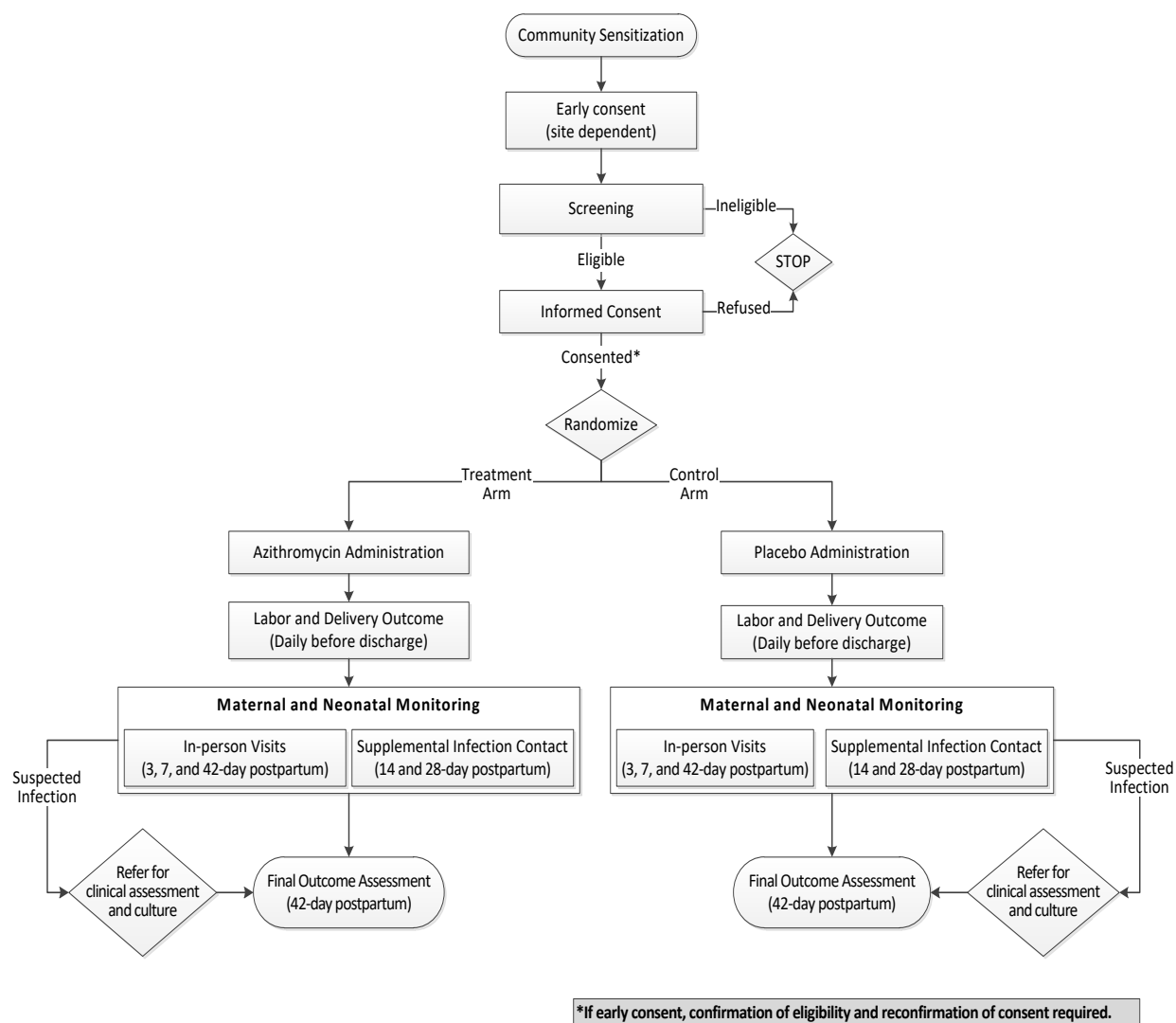
4.1 Overall Study Design

This study was a masked, placebo-controlled RCT of pregnant women laboring in health facilities of the eight Global Network sites/other health facilities. The investigational regimen is 2 g of azithromycin and the comparison arm is an identical placebo which is given orally. Both groups received the standard of care during labor, delivery and postpartum per local standards.

Women were followed up until discharge and surveillance maintained (in-person), with visits at 3-day, 7-day and 42-day postpartum to identify maternal or infant infection, unexpected medical visits, side effects, and other study outcomes. Supplemental phone contacts will be conducted at 14-day and 28-day postpartum to review maternal and neonatal signs of infection using WHO criteria. If signs of infection are identified during the review, participants will be asked to visit a study facility for further assessment. These supplemental contacts will reinforce the participants' ability to self-assess for signs of maternal and neonatal infection and improve identification of infection between the 7-day and 42-day postpartum visits. If phone contact is not feasible, in-person visits may be conducted.

A study schematic is shown below

Study Schematic



4.2 Study Population

Pregnant women laboring in health facilities of the eight Global Network sites/other health facilities were eligible. Health facilities may include any hospitals and health centers where women routinely deliver within the study sites.

Inclusion Criteria

- Pregnant women in labor ≥ 28 weeks GA (by best estimate) with a pregnancy with one or more live fetuses who plan to deliver vaginally in a facility.
- Admitted to health facility with clear plan for spontaneous or induced delivery.
- Live fetus must be confirmed via presence of a fetal heart rate prior to randomization.
- ≥ 18 years of age or minors 14-17 years of age in countries where married or pregnant minors (or their authorized representatives) are legally permitted to give consent.

- Have provided written informed consent [Note: written informed consent may be obtained during antenatal care, but verbal re-confirmation may be needed (per local regulations) at the time of randomization].

Exclusion Criteria

- Non-emancipated minors (as per local regulations)
- Evidence of chorioamnionitis or other infection requiring antibiotic therapy at time of eligibility (however, women given single prophylactic antibiotics with no plans to continue after delivery should not be excluded).
- Arrhythmia or known history of cardiomyopathy.
- Allergy to azithromycin or other macrolides that is self-reported or documented in the medical record.
- Any use of azithromycin, erythromycin, or other macrolide in the 3 days or less prior to randomization.
- Plan for cesarean delivery prior to randomization.
- Preterm labor undergoing management with no immediate plan to proceed to delivery.
- Advanced stage of labor (>6 cm or 10 cm cervical dilation per local standards) and pushing **or** too distressed to understand, confirm, or give informed consent regardless of cervical dilation.
- Are not capable of giving consent due to other health problems such as obstetric emergencies (for example, antepartum haemorrhage) or mental disorder.
- Any other medical conditions that may be considered a contraindication per the judgment of the site investigator.
- Previous randomization in the trial.

4.3 Study Arm Assignment and Randomization

Randomization of participants was carried out to obtain a 1:1 allocation ratio between the treatment and placebo arms. Randomization was stratified by site. A computer algorithm generated by the data coordinating center (DCC) created the random assignment to one of the treatment arms based on randomly permuted block design with randomly varied block sizes. The block sizes were known only by the DCC personnel. Each site received a lot of the study drug to be distributed sequentially at the participating health facilities which are randomizing women for the study site.

4.4 Masking and Data Lock

Both the azithromycin and placebo were procured from the same manufacturer. The packaging was standardized across sites and will be labeled as: “Azithromycin 2 g or Placebo”, with the expiration data and a unique identifier. A certificate of authenticity was provided.

Clinical and research staff involved with participant follow-up and/or clinical care as well as the women were masked to treatment status unless there was a serious adverse event potentially related to the treatment modality that required unmasking for safety reasons. There was one individual identified at each site for the role of pharmacist who monitored randomization, drug supply, and safety. Under the instruction of the DCC, the study pharmacist was trained and

authorized to apply un-masking procedures, if concerns about randomization or participant safety were identified.

Data Lock: Most data were to be entered real time into a tablet-based electronic data capture system with paper forms provided as back up if needed. Some delay in entry was anticipated for data obtained from records of readmissions/hospitalizations and unexpected visits for clinical care.

At the end of the study, data were locked at the site level with final analysis data sets generated and locked once data from all sites have been received and all queries processed. For each site, data collection for the protocol was stopped approximately 42 days after the last pregnant woman was randomized into the study at that site. Site will transmit all final data to the central database at the DCC within one month of this date, and data will be locked within two to four months post last follow-up visit.

The outcomes of occurrence of infectious diseases and of pyloric stenosis will be determined programmatically where possible. Any remaining cases will go through an adjudication process for final outcome determination. The details of the adjudication process and the programmatic algorithm for determining endpoints or routing the cases for review are detailed in a separate adjudication plan.

A single interim analysis is planned for this study. A data snapshot will be taken for that interim analysis. Resolution of queries on and adjudication of data required for the interim analysis will be a focus prior to the snapshot but timely completion of the interim analysis will be prioritized over resolving all outstanding data issues. The details and timeline of the interim analyses are described in section 11. For the interim analysis, only a senior statistician and the study statistician at the DCC and the Data Monitoring Committee (DMC) will be unmasked to analysis results.

Otherwise, the study will not be unmasked until after study completion or early termination and subsequent data lock.

5. ANALYSIS POPULATIONS

As Treated (i.e. Safety [SAF]) Population

The as-treated population will comprise all randomized participants and their infants who received any study treatment grouped by actual treatment received, irrespective of amount or duration of treatment received. Unless specified otherwise, data for this population will be analyzed as available (i.e. irrespective of protocol deviation occurrence, subsequent study participation termination, or study drug withdrawal).

Intention to Treat (ITT) Population

The primary analysis population will be the ITT population, which will include all randomized participants and their infants. All participants will be assigned to the arm to which they were randomized irrespective of treatment received. Unless specified otherwise, all participants will be included in analyses using this population (with data as available or imputed when specified per

section 7.3 and irrespective of protocol deviation occurrence, subsequent study participation termination, or study drug withdrawal).

High Risk for Infection (HR) Population

The HR sub-group will include all women in the ITT and their infants meeting criteria for being high risk (i.e., prolonged labor [≥ 18 hours] and/or rupture of membranes [≥ 8 hours]) at the time of randomization. All participants will be assigned to the arm to which they were randomized irrespective of treatment received. Unless specified otherwise, all participants will be included in analyses using this population (with data as available or imputed when specified per section 7.3 and irrespective of protocol deviation occurrence, subsequent study participation termination, or study drug withdrawal).

Per Protocol (PP) Population

This population will be used to conduct sensitivity analyses for the primary outcome. This population will include randomized participants that received all planned study drug and did not throw up within 15 minutes of taking study drug. Any individuals subsequently identified as ineligible for the study or who were documented as receiving azithromycin during study follow-up excluding study drug will be excluded. Participants will be grouped by actual treatment received. Additional exclusion reasons may be identified after completion of participant enrollment.

The final determination of HR and PP analysis population membership will be via a masked data review prior to final study analyses in order to address any potential anomalous cases that may arise in this large of a study population (e.g. randomization/treatment of a woman who is discharged prior to delivery due to false labor or unresponsiveness to induction). Final decisions with respect to populations used for the interim analyses as well as the final study analyses will be documented in an addendum to this SAP.

6. SAMPLE SIZE DETERMINATION

6.1 Overall (All-comer) Sample Size for Primary Outcomes

Sample size estimates were generated to evaluate the potential benefits of peripartum prophylactic azithromycin to reduce the risk of adverse maternal and neonatal outcomes in two population cohorts of women in low and low-middle income settings. The first population of interest comprises all women delivering in facilities (overall).

Power calculations for the study in the overall study population were generated for two primary outcome measures, one being the risk of maternal death or sepsis among women in the target population and the other being intrapartum /neonatal death or sepsis in infants delivered by women in the target population. For each of these outcome measures estimates of the required sample size needed to detect a risk reduction of 20%, 25%, and 30% were generated for power of 0.8, 0.85, and 0.9. The risk of sepsis or maternal death was assumed to be 3%. That number is slightly higher than the current risk in the GN population, which is slightly less than 2%. However, we anticipate that with active surveillance rather than passive reporting based on the new WHO

definition of maternal sepsis (designed to catch more cases of sepsis), the risk will be at least 3%. For the neonatal outcome, the underlying risk of the combined outcome of intrapartum stillbirth, neonatal death, or sepsis was assumed to be between approximately 8% and 14%. This estimate was based on recent data from the GN indicating that the risk of intrapartum stillbirth is approximately 1.8% and the risk of neonatal death during the first 28 days after delivery is 2.3%; we assumed that the risk of sepsis not resulting in death is approximately 4% to 10%. The resulting required evaluable sample sizes are shown in Table 1 below.

Table 1. Sample Sizes for the Overall Population, Alpha=0.05

Baseline Risk	Risk Reduction	Evaluable Sample Size per Arm		
		Power=0.80	Power=0.85	Power=0.90
3%	20%	11455	13103	15334
3%	25%	7133	8159	9548
3%	30%	4815	5508	6446
8%	20%	4096	4686	5483
8%	25%	2554	2921	3419
8%	30%	1727	1975	2311
14%	20%	2204	2521	2950
14%	25%	1377	1575	1842
14%	30%	932	1066	1247

The sample sizes shown above assume that the hypothesis test of interest is for the overall population and that the Type 1 error is controlled at the neonatal and maternal hypothesis level via testing each at an alpha = 0.05 level. Interest has been expressed for the overall study for being able to test the neonatal risk separately in south Asia and sub-Saharan Africa. Controlling the Type I error rate at the 0.025 level for each of those two areas within this sub-analysis of neonatal risk will be conducted to avoid multiple comparison concerns. The resulting sample sizes for that comparison are shown in Table 2 below. Note that this sample size would be the size required separately for the African and Asian sites. It is planned that each site will enroll approximately equal number of participants. As such, approximately 37.5% of randomized mothers will be from sub-Saharan Africa and 50% will be from Asia. This planned enrollment distribution is approximately equivalent to the rates of in-facility deliveries observed in the GN registry database. Specifically, approximately a third of the facility deliveries are conducted in sub-Saharan Africa and between 45% and 50% of the facility deliveries are conducted in Asia. These estimates are also consistent with the enrollment rates for the ASPIRIN study that is currently being conducted at these sites. Therefore, to get the total study sample size required, the numbers in the table would need to be multiplied by 3 to achieve reasonable power for the African sites.

Table 2. Sample Sizes Within Region, Alpha=0.025

Baseline risk	Risk Reduction	Evaluable Sample Size per Arm		
		Power=0.80	Power=0.85	Power=0.90
8%	20%	4961	5607	6477
8%	25%	3093	3496	4038
8%	30%	2091	2363	2729

14%	20%	2669	3017	3485
14%	25%	1677	1884	2176
14%	30%	1129	1276	1474

Given the above information, we propose a sample size of 34,000 participants for the overall study. For the primary neonatal outcome of interest of intrapartum/neonatal sepsis or death, assuming that the loss to follow-up will be in the 2% to 3% range (consistent with the current ASPIRIN trial and the Global Network Maternal and Newborn Health registry), this sample size will be sufficient to provide 90% power to detect a 25% reduction in neonatal mortality and sepsis in the sub-Saharan African region and will provide 90% power to detect a 20% reduction in Asia assuming the baseline risk is at least 8%. For the primary maternal outcome of maternal death or sepsis, the sample size will provide 90% power to detect a 20% reduction from 3% in the population aggregated across all study sites.

6.2 High Risk Cohort Sample Size for Primary Outcomes

The second population of interest comprises the cohort of high-risk population of women delivering in facilities with high risk being defined as term and preterm pregnant women who experience prolonged labor or prolonged membrane rupture. As a major secondary aim, sample size estimates for the high-risk cohort were also obtained to ensure adequate power for this analysis.

The primary objective of the high-risk component of the study is to test the effectiveness of a single oral dose of intrapartum azithromycin prophylaxis compared to placebo (all receive usual care) in reducing the risk of maternal sepsis or death in high risk laboring women. To estimate the sample size required for this component of the study, we assumed conservatively that the underlying risk of the combined outcome in the target population is 6%. Comparable to the other study estimates of the required sample size needed to detect a risk reduction of 20%, 25%, and 30% were generated for power of 0.8, 0.85, and 0.9. Because the interest for this study is in testing the hypothesis overall rather than by region, the estimates were generated using an alpha of 0.05. The results of these calculations are shown in Table 3 below.

Table 3. Sample Sizes for the High-Risk Cohort, Alpha=0.05

Baseline risk	Risk Reduction	Evaluable Sample Size per Arm		
		Power=0.80	Power=0.85	Power=0.90
6%	20%	5568	6369	7453
6%	25%	3470	3969	4644
6%	30%	2344	2681	3138

Because a risk reduction of at least 30% is expected in this population, we propose a sample size for this HR cohort of 5,500 women. That sample size will be sufficient to detect a 30% risk reduction with a power of 0.85 with an assumed 2% to 3% loss to follow-up. Assuming that 20% of the women are at high risk, the overall study sample size of 34,000 should allow for sufficient enrollment into the HR cohort.

7. STATISTICAL / ANALYTICAL ISSUES

7.1 General Rules

All statistical computations will be performed and data summaries will be created using SAS 9.3 or higher. If additional statistical packages are required, these will be discussed in the study report. For summaries of study data, categorical measures will be summarized in tables listing the frequency and the percentage of participants in each study arm; continuous data will be summarized by presenting mean, standard deviation, median, minimum, and maximum; and ordinal data will be summarized by presenting median and the limits of the interquartile range.

7.2 Adjustments for Covariates

As this is a randomized trial and the randomization process was not compromised during execution, the treatment effect estimate from trial is unbiased, even without adjusting for any baseline covariates. Therefore, no adjustments for covariates other than site as a randomization stratification factor are planned for the primary analysis. However, baseline clinical and demographic variables that are known predictors of neonatal and maternal outcomes will be included in secondary analyses of intervention efficacy.

7.3 Missing Data Approaches:

The two primary reasons for missing data are expected to be 1) participant loss to follow-up and 2) lack of record availability of unscheduled clinic visit, hospitalizations and readmissions required to diagnose infections.

Based on the historical data available from the MNH registry, we anticipate that the rate of missing responses due to loss to follow-up for maternal and neonatal morbidity and mortality measures are likely to be 2% or less. This rate has been confirmed based on the pilot data where the current rate is 1.1% for participants loss to follow-up or who were withdrawn or withdrew themselves from study participation.

All suspected infections that cannot be programmatically confirmed will go through a local site and central adjudication process to determine final outcome status using all available information as described in the adjudication plan. We anticipate the rate of cases that cannot be adjudicated to be low; estimates of that proportion will be obtained using pilot data prior to any unmasking or analyses of the main trial data.

For the primary analyses of sepsis and/or death in the ITT population, missing responses due to loss to follow-up and cases of suspected infection that cannot be adjudicated will be included via multiple imputation procedures. Multiple imputation assumes that the mechanism that caused the missing is independent of the value of the unobserved data (i.e. data are missing at random – MAR). Although there is potential that missing data due to record availability may not be MAR, we anticipate this proportion of missing data will be small and multiple imputation processes have been shown to be robust even if the missing mechanism is dependent on the values of the unobserved data, i.e. even if the missing data are non-ignorable non-response. As secondary/sensitivity

analyses, the primary analyses will also be repeated on the ITT populations using data as available and assuming all missing outcomes are sepsis or death as well as assuming all missing outcomes are not sepsis nor death.

If more than 4% of data in within either or across both arms are missing for any reason, we will conduct additional sensitivity analysis on the effect of missing data on the inference including analyzing data as available and other approaches that will assess the robustness of the findings to different assumptions about the missing data. The exact approaches for these sensitivity analyses will be determined based on the pattern of missingness and detailed in the final study report.

7.4 Multicenter Studies

For this multicenter study, randomization of study participants was stratified within site. Consequently, for all test-based analyses of treatment effect and model-based primary and secondary analyses, site will be included as a fixed effect in the models. As an ancillary analysis associated with the primary outcome as well as secondary outcomes, we will examine descriptively whether the treatment effects vary across sites; however, these analyses of site differences in treatment effect are considered to be descriptive because sample sizes are likely inadequate to provide adequate power to detect site by treatment interaction effects.

7.5 Multiple Comparisons and Multiplicity

There is one formal hypothesis test for each of the maternal and neonatal population of the study. Each population will be analyzed and interpreted separately and thus analyses are not adjusted for multiplicity between these populations. The statistical test of the primary outcome in each population will be conducted at an overall 5% type I error rate (two-sided) with p-value allocation between the interim and final analyses as detailed in Section 11.

The study sample size was determined to provide sufficient power to test for treatment effects within the high-risk cohort as the main secondary aim and also within region. As these are secondary aims, no adjustment multiplicity was applied to the planned primary study analyses. However, to avoid over-interpretation of regional findings the sub-analysis of the primary neonatal outcome within the Asian and African regions will be conducted controlling the Type I error rate at the 0.025 level.

However, all other analyses of secondary outcomes are exploratory in nature; therefore, p-values and confidence intervals are provided for descriptive purposes only. Additionally all p-values provided for any baseline and demographic characteristics and safety parameters will be for descriptive purposes only. As such, unless otherwise specified, p-values presented will be on a per analysis basis, with no further control for multiple tests.

7.6 Masked Data Review

Masked data review processes will be performed throughout the conduct of the study to define study analysis populations and to adjudicate key outcome variables. With respect to the outcome adjudication process, details will be defined in the adjudication plan. Prior to the interim and final

analyses, masked reviews of protocol deviations and other study operational aspects and data will be reviewed to address any questions about data handling for analyses (e.g. analysis population membership) Detailed documentation of the masked data review and resulting decisions will be described in a SAP addendum. The study team individuals (i.e. statisticians) privy to interim analysis results may generate reports for subsequent masked data reviews but will not be responsible for any decisions making in these subsequent reviews.

8. STUDY PARTICIPANTS, TREATMENT EXPOSURE AND COMPLIANCE

8.1 Participant Disposition

Participant eligibility status will be summarized by study arm and overall disposition of study participants will be described using a standard CONSORT diagram. The number of participants randomized; receiving study therapy; and completing the study follow-up will be summarized by study arm. Reasons for study withdrawal will also be summarized by treatment arm to assess whether they are balanced across treatment arm and to assure that any imbalances are unlikely to affect inference.

8.2 Study Treatment Exposure and Compliance

Each participant will receive a single dose of azithromycin or placebo in the form of 4 capsules at time of randomization during labor. Treatment exposure with respect to the number of randomized participants treated, if they received their assigned treatment or not, and if they vomited shortly after delivery will be summarized. While treatment compliance in dosing is anticipated, the number of pills taken will also be summarized.

8.3 Protocol Deviations

Protocol deviations will be summarized by treatment arm and by site with information such as type of deviation and time of occurrence. Incidence rate of protocol deviations will also be summarized overall and for each protocol deviation category by treatment arm. Incidence rate of protocol deviations will be calculated as: number of deviations divided by the number of participant weeks at the site.

8.4 Demographic and Baseline Characteristics

Demographic and baseline clinical characteristics for the study participants will be summarized by treatment group using the general analysis rules describe above for the ITT population. Variables of interest include maternal age, maternal education, marital status, parity, occurrence of any infection during pregnancy, and if last pregnancy resulted in live birth.

9. EFFICACY ANALYSES

9.1 Overview of Efficacy Analysis Methods

The data will be summarized by treatment arm, overall and by region. All model-based analyses and test-statistics examining the treatment effect will adjust for GN site as a randomization variable. Additional details are presented in the sections below.

9.2 Definition of Analysis Variables

As clinical assessments/diagnoses and associated care may lag behind actual occurrence, any infection events, antibiotic use, or other medical care (e.g. admissions, unscheduled visits) documented prior to the end of the relevant visit window will be counted. Mortality outcomes will be defined in accordance with traditional Global Network algorithms only including events occurring specifically within the window detailed in the outcome definition below.

Additionally, most infections are expected to occur within the first week following delivery. Therefore, mothers or infants that are lost to follow-up after completion of a Day 7 visit with no signs or symptoms of infection prior to becoming lost to follow-up will be considered to meet criteria to have the primary outcome ascertained as no infection or death. Mothers or infants lost to follow-up prior to completion of a Day 7 visit with no signs or symptoms of infection will be considered to have missing outcomes.

Variable	Type	Definition
Primary Outcomes		
Maternal death and/or sepsis through 42 days Primary Composite Outcome	Binary	<p>The event will be defined as “Yes” if either component of this composite outcome is “Yes” and “No” if both components of the composite are “No.” Any subsequent missing values will be included in the primary analyses using multiple imputation procedures.</p> <p>Analysis population(s): ITT (all-comer and high risk; with and without imputation), Per-Protocol</p>
Intrapartum/neonatal death and/or sepsis through 28 days Primary Composite Outcome	Binary	<p>The event will be defined as “Yes” if either component of this composite outcome is “Yes” and “No” if both components of the composite are “No.” Any subsequent missing values will be included in the primary analyses using multiple imputation procedures.</p> <p>Analysis population(s): ITT (all-comer and high risk; with and without imputation), Per-Protocol</p>
Secondary Outcomes		
Maternal death through 42 days Component	Binary	<p>The event will be defined as “Yes” if the woman dies prior to 42 days after delivery and “No” otherwise. This outcome measure will be obtained from form MN06 (i.e. presence of a form indicating a death has occurred). If the 42-day outcome is missing and the woman was alive at the last known follow-up, this outcome will be treated as missing when analyzed alone.</p> <p>Analysis population(s): ITT (all-comer and high risk), As Treated</p>

Variable	Type	Definition
Maternal death due to sepsis through 42 days	Binary	<p>The event will be defined as “Yes” if the woman dies prior to 42 days after delivery with the cause of death determined to be sepsis and “No” otherwise (i.e. if the women is alive or died due to other causes). This outcome measure will be obtained from form MN06 (i.e.as defined by the MNH algorithm). If the 42-day outcome is missing and the woman was alive at the last known follow-up, this outcome will be treated as missing when analyzed alone.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Maternal sepsis through 42 days Component	Binary	<p>The event will be defined as “Yes” if the woman is diagnosed with sepsis prior to 42 days after delivery and “No” otherwise.</p> <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). If the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing. For sepsis confirmed by algorithm, the date of sepsis will be the visit date when the first confirmation criterion is met. For sepsis confirmed by adjudication the diagnosis date will be the diagnosis date recorded on the maternal adjudication form (AZ13A). If the adjudication diagnosis date is before delivery, then it is set to delivery date. If the adjudication diagnosis date is more than 3 days after the last unplanned care date with adjudication triggers, then it is set to the maximum of delivery date and unplanned care visit with adjudication triggers presentation and discharge dates. If the algorithm date is 1, 2 or 3 days before delivery and is equal to the first unplanned care date then the diagnosis date is set to delivery date. Analysis population(s): ITT (all-comer and high risk)</p>
Intrapartum/neonatal death through 28 days Component	Binary	<p>The event will be defined as “Yes” if there is any intrapartum pregnancy loss including stillbirth after randomization or if there is neonatal death prior to 28 days after delivery and “No” otherwise. This outcome measure will be obtained from form MN05 (i.e. presence of a form indicating a death has occurred). If the 28-day and 42-day outcomes are both missing this outcome will be treated as missing when analyzed alone.</p> <p>Analysis population(s): ITT (all-comer and high risk), As Treated</p>

Variable	Type	Definition
Neonatal sepsis through 28 days Component	Binary	<p>The event will be defined as “Yes” if the infant is diagnosed with sepsis prior to 28 days after delivery and “No” otherwise.</p> <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). If the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing. For sepsis confirmed by algorithm, the date of sepsis will be the visit date when the first confirmation criterion is met. For sepsis confirmed by adjudication the diagnosis date will be the diagnosis date recorded on the neonatal adjudication form (AZ13B). If the adjudication date is before the delivery date, then the sepsis diagnosis date will be the delivery date. If the adjudication sepsis diagnosis date is 4 or more days after the maximum visit date for delivery or unplanned care forms with adjudication triggers or the diagnosis date is missing, then the sepsis diagnosis date will be the maximum visit date from forms with adjudication triggers.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
All cause neonatal death through 28 days	Binary	<p>The event will be defined only for live births. It will be defined as “Yes” if there is any subsequent neonatal death prior to 28 days after delivery and “No” otherwise. This outcome measure will be obtained from forms MN05 (i.e. presence of a form indicating a death has occurred and defined only for individuals with response to question A.2 “Was the death a stillbirth” of No). If the 28-day and 42-day outcomes are both missing, this outcome will be treated as missing.</p> <p>Analysis population(s): ITT (all-comer and high risk), As Treated</p>
Neonatal deaths due to sepsis through 28 days	Binary	<p>The event will be defined only for live births. It will be defined as “Yes” if there is any subsequent neonatal death determined to be due to sepsis prior to 28 days after delivery and “No” otherwise (i.e. if the infant is alive or died due to other causes). This outcome measure will be obtained from forms MN05 (i.e. as defined by the MNH algorithm and defined only for individuals with response to question A.2 “Was the death a stillbirth” of No). If the 28-day and 42-day outcomes are both, this outcome will be treated as missing.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Maternal Chorioamnionitis	Binary	<p>The event will be defined as “Yes” if the mother is diagnosed with chorioamnionitis prior to delivery and “No” otherwise.</p> <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). If the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>
Maternal Endometritis	Binary	<p>The event will be defined as “Yes” if the mother is diagnosed with endometritis prior to day 42 and “No” otherwise.</p> <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). If the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Wound infection (cesarean or perineal)	Binary	<p>The event will be defined as “Yes” if the mother is diagnosed with wound infection (cesarean or perineal) prior to day 42 and “No” otherwise.</p> <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). If the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Maternal Other Infections	Binary	<p>The event will be defined as “Yes” if the criteria for any of the following infections are met prior to day 42 and “No” otherwise. Indicators will be also defined separately for each infection type.</p> <ul style="list-style-type: none"> • Abdominopelvic abscess • Mastitis/breast abscess or infection • Pyelonephritis • Pneumonia • Other bacterial infection <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). For each type, if the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing. For the overall, if no criteria were met for any of the infections and at least one is “Insufficient data to make a determination,” then composite outcome will be treated as missing.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>
Maternal antibiotic therapy after randomization to 42 days for any reason	Binary	<p>The outcome will be defined as “Yes” if any antibiotic therapy is reported on AZ03 during initial hospitalization, or on AZ05a, AZ06 or AZ07 during follow-up and prior to day 42 and “No” otherwise. The outcome will only be missing for mothers that are lost to follow-up prior to completion of a Day 7 visit and had no antibiotic use reported prior to becoming LTF.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Time from drug administration until initial discharge after delivery (days)	Continuous	Defined as the date/time of initial discharge reported on AZ03 or AZ07 – date/time of study drug administration reported on AZ02 Analysis population(s): ITT (all-comer and high risk)
Maternal readmission within 42 days of delivery	Binary	Only defined for women who were initially discharged from the hospital following delivery as documented on AZ03 or AZ07 (i.e. women that die during the initial hospitalization for delivery will be excluded from the numerator and denominator). The outcome will be defined as “Yes” if the location of any subsequent study visit on AZ05a is In-patient (hospitalized), or if there is an AZ07 form where the woman is noted as admitted or has a non-missing admission date; and “No” otherwise. The outcome will only be missing for mothers that are lost to follow-up prior to completion of a Day 7 visit and had no readmission reported prior to becoming LTF. Analysis population(s): ITT (all-comer and high risk)
Maternal admission to special care units	Binary	The outcome will be defined as “Yes” if there is an AZ03 or AZ07 form where the woman is noted as having received care or treatment at an intensive care or specialized care unit while at the facility; and “No” otherwise. The outcome will only be missing for mothers that are lost to follow-up prior to completion of a Day 7 visit and had no specialized care reported prior to becoming LTF. Analysis population(s): ITT (all-comer and high risk)

Variable	Type	Definition
Maternal unscheduled visit for care	Binary	<p>The outcome will be defined as “Yes” if occurrence of unscheduled care after initial delivery discharge is reported on either AZ05a (with a non-missing date of care) or on AZ07 form (with a non-missing exact or estimated date of care); and “No” otherwise. The outcome will only be missing for mothers that are lost to follow-up prior to completion of a Day 7 visit and had no unscheduled visit for care reported prior to becoming LTF.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>
Maternal GI symptoms including nausea, vomiting, and diarrhea and other reported side effects.	Binary	<p>The outcome will be defined as “Yes” if vomiting or diarrhea are reported after delivery on AZ03 or AZ05a; an unscheduled care visit for nausea, vomiting, or diarrhea is reported on AZ05a; or an unscheduled care visit for nausea, vomiting and/or diarrhea is reported on AZ07; or a mechanistically-related AE is reported (e.g. abdominal pain); and “No” otherwise. The outcome will only be missing for mothers that are lost to follow-up prior to completion of a Day 7 visit and had no symptoms or side effects reported prior to becoming LTF.</p> <p>Analysis population(s): As Treated</p>
Neonatal Other Infections	Binary	<p>The event will be defined as “Yes” if any infection is reported that does not qualify for sepsis prior to day 28 and “No” otherwise. Other neonatal infections include eye infection with swelling and drainage, skin infection with 10 or more pustules or bullae, omphalitis, urinary tract infection, pyelonephritis or kidney infection, pneumonia or lung infection, meningitis, other infection documented in clinical record or respiratory rate ≥ 60. The outcome will only be missing for infants that are lost to follow-up prior to completion of a Day 7 visit and neonatal deaths prior to 7 days that do not qualify for sepsis or other infections.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Neonatal initial hospital length of stay	Ordinal	<p>Defined as the date/time of initial discharge reported on AZ04 or AZ08 – date/time of delivery reported on AZ03</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>
Neonatal readmissions within 42 days of delivery	Binary	<p>Only defined for live births who were initially discharged from the hospital following delivery as documented on AZ04 or AZ08 (i.e. stillbirths or infants that die during the initial hospitalization for delivery will be excluded from the numerator and denominator). The outcome will be defined as “Yes” if the location of any subsequent study visit on AZ05b is In-patient (hospitalized), or if there is an AZ08 form where the infant is noted as admitted or has a non-missing admission date; and “No” otherwise. The outcome will only be missing for infants that are lost to follow-up prior to completion of a Day 7 visit and had no readmission reported prior to becoming LTF.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>
Neonatal admission to special care units	Binary	<p>The outcome will be defined as “Yes” if there is an AZ04 or AZ08 form where the infant is noted as having received care or treatment at an intensive care or specialized care unit while at the facility; and “No” otherwise. The outcome will only be missing for infants that are lost to follow-up prior to completion of a Day 7 visit and had no specialized care reported prior to becoming LTF.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>

Variable	Type	Definition
Neonatal Unscheduled Clinical or ER Visit	Binary	<p>The outcome will be defined as “Yes” if occurrence of unscheduled care after initial delivery discharge is reported on either AZ05b (with a non-missing date of care) or there is an AZ08 form (with a non-missing exact or estimated date of care); and “No” otherwise. The outcome will only be missing for infants that are lost to follow-up prior to completion of a Day 7 visit and had no unscheduled care visit reported prior to becoming LTF.</p> <p>Analysis population(s): ITT (all-comer and high risk)</p>
Pyloric stenosis within 42 days of delivery	Binary	<p>The event will be defined only for live births. The event will be defined as “Yes” if the infant is diagnosed with pyloric stenosis prior to day 42 and “No” otherwise.</p> <p>The details of defining this outcome are in the adjudication plan. In brief, where possible the outcome will be defined programmatically per the algorithm defined in the adjudication plan with cases that are unable to be programmatically determined route to adjudication. For the adjudicated outcomes, the value will be determined based on the reported final outcome reported by the site via form AZ13 (and confirmed via central adjudication). If the final outcome is “Insufficient data to make a determination,” the outcome will be treated as missing.</p> <p>Analysis population(s): As Treated</p>

9.3 Primary Analysis

The primary outcomes of incidence of maternal death or sepsis and incidence of intrapartum/neonatal death or sepsis will be compared between the two treatment arms using generalized linear models. These generalized linear models will be fit with each binary outcome separately as the outcome measure. Estimates of relative risk and associated 95% confidence intervals will be reported. The model will include terms for treatment and site. As randomization occurs at the pregnancy level and approximately 1-2% of pregnancies are anticipated to be multiple gestations, models for neonatal outcomes will account for correlation among multiples assuming an exchangeable covariance structure. If a model for neonatal outcomes has convergence issues, then the generalized linear model will be fit without the adjustment for correlation among multiples. For the two primary outcomes, these analyses will be conducted using the ITT population and the p-values associated with the treatment term will be used to formally test each of the two primary hypotheses at the $\alpha = 0.05$ level.

The primary analyses using the ITT population will use multiple imputation for missing outcomes implemented separately for mothers vs. infants via logistic regression imputation using site and high-risk status prior to randomization as covariates. As sensitivity analyses, the primary outcomes will also be analyzed without imputation for individuals in the ITT population, without imputation for individuals in the per-protocol population; and in the ITT population assuming all missing outcomes are sepsis or death as well as assuming all missing outcomes are not sepsis nor death.

As secondary analyses of the primary outcomes, the models will be run including region (Africa, Latin America, or Asia) and a treatment by region interaction term. If the interaction term has a $p < 0.1$, then effect estimates and associated confidence intervals will be reported by region with treatment effect within region for Africa and Asia tested at the 0.025 level.

For secondary publications, additional exploratory models will also be run including individually: 1) a treatment by site interaction term, 2) any other antibiotic use during labor (yes or no) and its interaction with treatment, and 3) mode of delivery (cesarean or vaginal) and its interaction with treatment. If the interaction term for any of these models has a $p < 0.1$, then effects will also be reported by the relevant subgroups. These exploratory secondary models will also include any demographic or clinical variables found to differ significantly between the treatment arms in the preliminary analyses described above. From each final model, adjusted relative risk estimates for treatment will be obtained. Kaplan-Meier survival curves will be fit to the data in order to get cumulative incidence curves by treatment group of the timing of the first occurrence of maternal death or sepsis and intrapartum/neonatal death or sepsis.

9.4 Secondary Analyses for High Risk Cohort

The major secondary aim is assessing the two primary outcomes (i.e. incidence of maternal death or sepsis and incidence of intrapartum/neonatal death or sepsis) in the women at high risk for infection cohort. Analyses for this aim will be the same as that specified in 10.4 but subset only on women that meet the high risk definition prior to randomization.

Analyses will also assess if the treatment effect differs between the HR cohort vs. non-high risk women where non-high risk women comprise all women and their infants in the ITT population that delivered prior to meeting criteria for high risk (i.e. they delivered after < 18 hours of labor and < 8 hours post-rupture of membranes). Specifically, the model for the primary analysis of both the maternal and neonatal primary outcomes will be run including a treatment by risk status interaction term and excluding any data from individuals that meet high risk criteria after randomization.

The exclusion of data from individuals meeting high risk criteria between randomization and delivery is intended to provide the most distinct groups regarding the HR risk cohort to non-high risk women comparison. As this exclusion is based on a post-randomization event, sensitivity analyses will be conducted to examine any treatment group differences in meeting high risk criteria post randomization and if there is a difference, to determine the potential magnitude of impact this difference has on treatment effect.

An exploratory analysis will also be completed that assesses if there is a difference in treatment effect between women randomized prior to high risk classification vs. those randomized after high risk classification. Finally, an exploratory analysis will be conducted that assesses the definition of high risk to determine if there is a broader group of individuals that remain at higher risk of infection and/or are observed to have a greater treatment effect (e.g. prolonged labor [≥ 18 hours] and/or rupture of membranes [≥ 8 hours]).

9.5 Secondary Outcome Analyses

Binary secondary outcomes (e.g. individual components of the primary outcome, all other infection indicators, use of antibiotics, maternal and neonatal readmission as well as admission special care unit, maternal GI symptoms, and pyloric stenosis) will be analyzed in a similar manner to the primary analysis of the primary outcomes. Models will be focused on providing estimates of relative risk and associated confidence intervals as opposed to being used for formal tests of hypothesis. If regional differences are observed for the primary outcome, then region-specific models for all secondary outcomes will be run in order to get region-specific estimates of relative risk.

For secondary publications, secondary outcomes may also be explored using additional exploratory models including individually: 1) a treatment by site interaction term, 2) any other antibiotic use during labor (yes or no) and its interaction with treatment, and 3) mode of delivery (cesarean or vaginal) and its interaction with treatment. If the interaction term for any of these models has a $p < 0.1$, then effects will also be reported by the relevant subgroups. These exploratory secondary models will also include any demographic or clinical variables found to differ significantly between the treatment arms in the preliminary analyses described above. From each final model, adjusted relative risk estimates for treatment will be obtained.

For the outcome of time from drug administration until initial discharge after delivery and the outcome of neonatal initial hospital length of stay, the same analysis steps will be employed but using models appropriate for the distribution of these variables (Brock 2011). Specifically, Kaplan-Meier survival curves will be fit to the data in order to get cumulative incidence curves by treatment group of hospital discharge, obtained by treating in-hospital mortality as a competing risk.

10. SAFETY ANALYSIS:

No formal safety analyses are planned as a part of this study, although SAEs and side effects will be summarized. No formal hypothesis tests will be conducted, but descriptive p-values generated using Cochran-Mantel-Haenszel statistics with stratification by GN site will be generated.

11. INTERIM ANALYSES AND DATA MONITORING

Additionally, one formal interim analysis of efficacy and futility will be conducted during the study. Interim analyses will be conducted assessing both the primary maternal and neonatal outcomes using the primary analytic approach detailed in Section 3.1.1 and 3.1.2. As the maternal and neonatal hypotheses are both of equal importance as well as the treatment effect within the high-risk cohort, the DMC should not recommend early termination for efficacy unless significance is observed for both outcomes in all comers and the direction and magnitude of effect in the high-risk cohort is consistent with the effect observed in all comers.

Given the study is extremely well powered for the composite neonatal outcome of death or sepsis, it is possible that an effect will be detected much earlier in the study for this outcome (given the high frequency of sepsis) than for the maternal outcome. In such a situation, it is important to continue the study to be able to reach a conclusion on whether this prophylactic regimen also benefits maternal outcomes, as effective therapeutics for reducing risk of maternal mortality and sepsis are sorely needed and this is a maternally administered intervention. Additionally, with respect to the neonatal outcome, it is important to assess if the effect is present in sepsis alone vs. the more important death outcome. As such, caution should be taken in terminating this study early.

However, if efficacy is observed in only a subset of outcomes or subgroups and the study has no conditional power to draw conclusions in the remaining outcomes or subgroups, then the DMC may still recommend early termination for efficacy. Cut-off p-values for testing for efficacy at this interim analysis will be determined based on a correction for multiple comparisons to ensure an overall alpha of 0.05. The futility assessment will be based on an analysis of conditional power.

The details of the timing of the interim analysis as well as the approaches for correcting for multiplicity and analyzing conditional power were determined in collaboration with the DMC. The single, formal interim analysis of efficacy and futility will be conducted after approximately 70% of women have been enrolled and reached primary endpoint. Interim analyses will be conducted using the overall study population and the primary analytic approach detailed in Section 9.3. Cut-off p-values for testing for efficacy at this interim analysis will be determined based on a Bonferroni-type correction for multiple comparisons with a nominal α of 0.0001 at the interim analysis and a nominal α of 0.0499 for the final analysis (Casella and Berger 2002). Specifically, if the p-values are < 0.0001 for the treatment versus placebo comparison, then the DSMC may recommend stopping enrollment. The DMC can recommend stopping enrollment for futility if the conditional power is less than 0.5 at this time.

Additionally, the DMC will review the study at periodic intervals, to evaluate whether any safety or study progress issues warrant possible study stopping. These periodic reviews are based on DMC reports prepared by the Data coordinating center, which included information on study enrollment rates and participant progress through the study, protocol violations, adverse events, and efficacy outcomes. The focus of the DMC review is on monitoring participant safety and study progress/futility but data on treatment effectiveness will also be presented to frame the DMC discussions on safety and futility.

The DMC will also review the study for study progress and futility, with futility for these analyses defined in terms of inability to achieve study enrollment goals. To effectively complete the study within the parameters defined by NICHD and the Global Network Steering Committee, the goal of study is to complete enrollment in a 24-month period, and enrollment be completed within 30 months. Should the DMC have concern about study progress, the DMC will request from the protocol committee an action plan for increasing enrollment that should be delivered to the DMC for review within a 1-month period. Should the DMC consider the plan inadequate or should the plan not result in increased enrollment by the next review, the DMC may consider recommending to the NICHD closing the study for futility.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

13. REFERENCES

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Summary of SAP Changes (V.1.0 to V.2.0)

Section	Changes
3.1	Change: Clarify the adjudication process If a case requires additional input and cannot be adjudicated locally, then it will move to central adjudication where the study PIs will review the participant's information and make a final outcome determination..
3.2	Change: Moved wound infection definition to between Endometritis and Other infections since it is not a component of the other infections definition in the protocol.
5.0	Change: Added word for clarity The final determination of HR and PP analysis population membership will be via a masked data review prior to final study analyses in order to address any potential anomalous cases that may arise in this large of a study population (e.g. randomization/treatment of a woman who is discharged prior to delivery due to false labor or unresponsiveness to induction).
9.2	Definition of Analysis Variables: Changes made to clarify Secondary Outcome definitions as the variables were being defined in the analysis datasets.
Maternal sepsis through 42 days - Component	Change: Clarify the definition of the sepsis diagnosis date for adjudicated cases. If the adjudication diagnosis date is before delivery, then it is set to delivery date. If the adjudication diagnosis date is more than 3 days after the last unplanned care date with adjudication triggers, then it is set to the maximum of delivery date and unplanned care visit with adjudication triggers presentation and discharge dates. If the algorithm date is 1, 2 or 3 days before delivery and is equal to the first unplanned care date then the diagnosis date is set to delivery date. Analysis population(s): ITT (all-comer and high risk)
Maternal antibiotic therapy after randomization to 42 days for any reason	Change: Added forms missing from the definition. The outcome will be defined as "Yes" if any antibiotic therapy is reported on AZ03 during initial hospitalization, or on AZ05a, AZ06 or AZ07 during follow-up and prior to day 42 and "No" otherwise.
Time from drug administration until initial discharge after delivery	Change: Corrected unit to be days instead of hours Time from drug administration until initial discharge after delivery (days)
Maternal admission to special care units	Change: Added form missing from the definition. The outcome will be defined as "Yes" if there is an AZ03 or AZ07 form where the woman is noted as having received care or treatment at an intensive care or specialized care unit while at the facility; and "No" otherwise.
Maternal unscheduled	Change: Clarify definition The outcome will be defined as "Yes" if occurrence of unscheduled care after initial

visit for care	delivery discharge is reported on either AZ05a (with a non-missing date of care) or on AZ07 form (with a non-missing exact or estimated date of care); and “No” otherwise.
Neonatal Other Infections	Change: Revised definition to be more precise and removed adjudication text. The event will be defined as “Yes” if any infection is reported that does not qualify for sepsis prior to day 28 and “No” otherwise. Other neonatal infections include eye infection with swelling and drainage, skin infection with 10 or more pustules or bullae, omphalitis, urinary tract infection, pyelonephritis or kidney infection, pneumonia or lung infection, meningitis, other infection documented in clinical record or respiratory rate ≥ 60 . The outcome will only be missing for infants that are lost to follow-up prior to completion of a Day 7 visit and neonatal deaths prior to 7 days that do not qualify for sepsis or other infections.
Neonatal admission to special care units	Change: Added form missing from the definition. The outcome will be defined as “Yes” if there is an AZ04 or AZ08 form where the infant is noted as having received care or treatment at an intensive care or specialized care unit while at the facility; and “No” otherwise.
Neonatal Unscheduled Clinical or ER Visit	Change: Clarify definition. The outcome will be defined as “Yes” if occurrence of unscheduled care after initial delivery discharge is reported on either AZ05b (with a non-missing date of care) or there is an AZ08 form (with a non-missing exact or estimated date of care); and “No” otherwise.
9.3	Change: Added specific exploratory analysis. Kaplan-Meier survival curves will be fit to the data in order to get cumulative incidence curves by treatment group of the timing of the first occurrence of maternal death or sepsis and intrapartum/neonatal death or sepsis.