Azithromycin use in labour to prevent maternal sepsis among pregnant women undergoing vaginal birth in Nigeria (AZIN-V): a cluster-randomised hybrid type-2 effectiveness implementation trial:

Statistical Analysis Plan

ISRCTN *(if applicable)*	ISRCTN16415327
Funding Body	Bill & Melinda Gates Foundation
Ethics Approval	National Health Research Ethics Committee, Nigeria (30th September 2024)
SAP Version	1.0
Date	23 Jan 2026
Stage	Final
Protocol version	3.0 (24 Oct 2025)

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Abbreviations and Definitions

ADR	Adverse Drug Reaction
AE	Adverse Event
AE(s)	Adverse Event(s)
ANC	Antenatal clinic
CACE	Complier Average Causal Effect
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ES	Effect size
GCP	Good Clinical Practice
GBS	Group B Streptococcus
GA	Gestational Age
ICC	Intra-class correlation
IQR	Interquartile range
ICE	Intercurrent events
IRR	Incidence rate ratio
ITT	Intention to treat
LMICs	Low- and Middle-income countries
MD	Mean difference
MAR	Missing at random
OR	Odds ratio
PPROM	Preterm Pre-labour Rupture of Membranes
PSBI	Possible Serious Bacterial Infection
RCT	Randomised Controlled Trial
RR	Risk ratio
SAE	Serious Adverse Event
SD	Standard deviation
SMF	Statistical Master File
SSA	Sub-Saharan Africa
TSC	Trial Steering Committee
WHO	World Health Organization
SAP	Statistical Analysis Plan

1 Administrative information

1.1 SAP revision history

Any changes to the protocol-specified definitions of aims, outcomes, and statistical analytical approaches will be outlined below immediately. As much as possible, all changes will be made before database lock and unblinding of the study. In extreme cases, changes can be made after the unblinding, but the justification and detailed changes will be outlined.

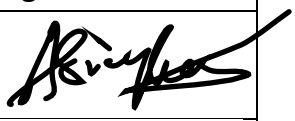
SAP Version	Protocol Version	Date and timing of revision	Details of revision
1.0	3.0	23 Jan 2026	Final SAP prior to database lock

1.2 Administrative details

The Statistical Master File (SMF), which contains the final signed version of this Statistical Analysis Plan, datasets, statistical programs, output tables, and related correspondence, will be maintained at the coordinating centre:

- Location of Statistical Master File: Center for Clinical Trials, Research and Implementation Science (CCTRIS), Lagos University Teaching Hospital, Idi-Araba, Lagos
- Storage Format: The SMF will be stored electronically in a secure, access-controlled trial repository (OneDrive). Hard copies of signed documents will also be archived at the trial sponsor's office
- Archiving: All statistical files will be archived in accordance with Good Clinical Practice (GCP) and institutional guidelines for at least 10 years after trial completion
- Version Control: Version-controlled electronic records will be maintained to ensure traceability of SAP revisions, datasets, and analysis outputs.

1.3 Roles, responsibilities, and approvals

Role	Name and contact details	Date	Signature
Author (Trial statistician)	Ibraheem Abioye	09 Feb 2026	
Statistical Advisor	Anower Hossain	04 Feb 2026	
Chief Investigator	Prof. Bosede Afolabi	09 Feb 2026	
Independent Statistician	Dr. Ebuwa Igho-Osagie	25 Feb 2026	

2 Study Objectives and Endpoints

2.1 Background

Maternal complications during pregnancy and childbirth remain a major global health issue (1), with 287,000 maternal deaths in 2020 (2), 95% in low- and middle-income countries (LMICs), and about 70% in sub-Saharan Africa (SSA) (2). Nigeria alone accounted for almost 30% of these deaths, with extremely high maternal mortality rates. Most deaths arise from direct obstetric causes, including haemorrhage, hypertensive disorders, infections, and unsafe abortion (3). In Nigeria, peripartum infection is the second leading cause of maternal mortality in the hospital population (4).

To reduce maternal deaths, the World Health Organization (WHO) recommends prophylactic antibiotic use in specific birth-related situations (e.g., colonization with group B streptococcus (GBS), preterm pre-labour rupture of membranes (PPROM), caesarean section, repair of third/fourth-degree perineal tear, and manual removal of the placenta (5). However, implementation is inconsistent due to variations in clinical practice, cost, drug availability, misuse, and antimicrobial resistance (6–8). Commonly used antibiotics such as cephalosporins and erythromycin are effective but prone to misuse and resistance issues (6,9,10).

Azithromycin has emerged as a promising alternative because of its broad-spectrum activity, long half-life, placental penetration, good safety profile, ease of administration, and low cost (6). Evidence supports its use in preventing maternal infections during labour and delivery (11,12), PPROM (13), and planned caesarean delivery (14–16). Although widespread prophylactic use may temporarily increase macrolide resistance, this effect appears transient (17–20). These features make azithromycin a suitable prophylactic treatment to implement for vaginal births.

2.2 Primary objectives

a) Determine the incidence of specific maternal infections, including bacterial vaginosis, chorioamnionitis, endometritis, abdominal or pelvic abscess, mastitis or breast abscess, pneumonia, or pyelonephritis or acute cystitis.
b) Determine the proportion of study participants who had additional use of antibiotics. Additional use of antibiotics is defined as the use of subsequent antibiotic therapy after randomisation up to 6 weeks for any reason.

2.3 Trial design

AZIN-V is an open-label cluster-randomised trial in 48 health facilities across six Nigerian states. Facilities are randomised 1:1 to a single 2-g oral azithromycin in labour + usual care (intervention) vs. usual care only (control). Sites are eligible if they are high-volume facilities with antenatal clinics and 24-hour labour wards.

2.4 Randomisation

Randomisation was done by study statisticians and used minimization by state, facility level and empirical postpartum antibiotic use.

2.5 Outcome measures

2.5.1 Primary Outcome

The primary clinical outcome is the incidence of maternal sepsis within six weeks (42 days) post-delivery. Maternal sepsis defined by WHO as a life-threatening condition with organ dysfunction resulting from suspected or confirmed infection during pregnancy, childbirth, post-abortion, or postpartum period. The WHO definition, endorsed by multiple global health organisations, will be used to define sepsis as suspected or confirmed infection based on Table 1 below.

Table 1: Definition of clinical outcomes

Symptoms/Signs	Definitions
Fever	>38 ^{0}C
Hypothermia	<36 ^{0}C
Plus, one or more signs of mild-to-moderate organ dysfunction including	
Tachycardia	≥110 bpm
Low blood pressure	<90/50 mm Hg
Tachypnoea	≥24 breaths/min
Altered mental status	Altered consciousness, which may include coma, disorientation, etc.
Reduced urinary output	<500 ml/24 hours or <20 cc/hr over several hours

2.5.2 Secondary outcomes

a) Incidence of culture confirmed maternal sepsis within 6 weeks of birth, defined as a positive blood culture in the presence of suspected maternal sepsis.
b) Number of new prescriptions of antibiotics for a specific maternal infection after randomisation for any reason (including bacterial vaginosis, chorioamnionitis, endometritis, abdominal or pelvic abscess, mastitis or breast abscess, pneumonia, or pyelonephritis or acute cystitis – as in table 2).
c) Number of new prescriptions of antibiotics for any reason (use of subsequent maternal antibiotic therapy after randomisation to 6 weeks for any reason).
d) Incidence of neonatal sepsis within 28 days of birth, defined as proven or possible serious bacterial infection (PSBI) or pneumonia, or meningitis. PSBI will be determined using WHO criteria of severe chest in-drawing, fever, hypothermia, no movement at all or movement only on stimulation, feeding poorly or not feeding at all and/or convulsions.[52] Clinical and laboratory signs of infection will also be considered for diagnosis. Other neonatal infections (e.g. eye infection, skin infection, omphalitis, urinary tract infection, respiratory rate ≥60 breaths/minute).
e) Incidence of stillbirth, defined as the birth of a baby with no signs of life at or after 24 weeks of gestation.
f) Incidence of neonatal death, defined as death within 28 days of birth.
g) Duration of initial hospital stay for neonate, defined as time of birth until time of hospital discharge.
h) Duration of hospital stay for mother, defined as time from enrolment until discharge (in hours).
i) Incidence of maternal readmission, or admission to a special care unit for any other condition within 6 weeks of delivery.

j) Incidence of neonatal readmission, or admission to a special care unit for any other condition within 28 days of birth.
k) Incidence of adverse drug events (fainting or dizziness, nausea, vomiting, diarrhoea, and dyspepsia) and other reported side effects.
l) Incidence of secondary post-partum haemorrhage, defined as excessive bleeding requiring surgical intervention or blood transfusion from 24hrs after delivery till 6-week post-partum.

2.5.3 Description of key variables

The key variables to be used for analysis are described below.

Table 3. Description of variables

Variable	Description
Maternal sepsis	Binary variable (0, 1). Incidence of maternal sepsis within six weeks (42 days) post-delivery
Culture-confirmed maternal sepsis	Binary variable (0, 1). Incidence of maternal sepsis within six weeks (42 days) post-delivery, based on a positive blood culture in the presence of suspected maternal sepsis
Number of new antibiotic prescription for a specific maternal infection	Count variable (integer). Number of new prescriptions of antibiotics for a specific maternal infection after randomisation for any reason. See Table 2.
Number of new antibiotic prescription	Count variable (integer). Number of new prescriptions of antibiotics for any reason ▪ A secondary endpoint
Neonatal sepsis	Binary variable (0, 1). Incidence of neonatal sepsis within 28 days of birth, defined as proven or possible serious bacterial infection (PSBI) or pneumonia, or meningitis. ▪ A secondary endpoint
Stillbirth	Binary variable (0,1). Assessed at birth ▪ A secondary endpoint
Neonatal death	Binary variable (0, 1). Incidence of offspring death within 28 days of birth. ▪ A secondary endpoint
Duration of hospital stay of neonate	Continuous variable. Time of delivery of neonate until time of hospital discharge. ▪ A secondary endpoint
Duration of hospital stay of mother	Continuous variable. Time of azithromycin administration until time of hospital discharge. ▪ A secondary endpoint
Maternal readmission or admission to a special care unit	Binary variable (0, 1). Maternal readmission or admission to a special care unit for any condition within 6 weeks of delivery. ▪ A secondary endpoint
Neonatal readmission or admission to a special care unit	Binary variable (0, 1). Neonatal readmission or admission to a special care unit for any condition within 28 days of birth. ▪ A secondary endpoint
Secondary postpartum haemorrhage	Binary variable (0, 1). Excessive bleeding requiring surgical intervention or blood transfusion from 24 hours after delivery till 6-week postpartum. ▪ A secondary endpoint

2.6 Sample size

A sample of size 5040 (2520 in each group) is required to detect a 50% reduction in maternal sepsis incidence rate from 6.5% to 3.25% due to azithromycin, at 90% power and 5% level of significance. The sample size yielded an intra-class correlation (ICC) of 0.011 and a 20% loss-to-follow-up rate, which is a rule of thumb for the upper limit of loss-to-follow-up beyond which bias becomes significantly more likely. 6.5% was the incidence of sepsis or severe systemic infection in a study of maternal near-miss at the University of Port Harcourt (UPTH), Rivers State, Nigeria.(21) In an RCT of azithromycin vs placebo in Burkina Faso and The Gambia, the odds ratio of maternal sepsis was 0.62 for any maternal sepsis and ~0.00 for bacterially confirmed sepsis.(22) The incidence of sepsis in this study was much lower than in our setting (0.2% vs. 6.5%). The ICC was derived from an analysis of the WHO Global Survey on Maternal and Perinatal Health(23).

We require 48 health facilities and estimate each will enrol approximately 105 participants on average. Assuming an estimated antenatal clinic attendance of at least 50 pregnant women per month, an average vaginal birth rate of at least 20 women per month, and assuming at least 10 women will be eligible for recruitment, we estimate we will recruit 480 pregnant women per month in the 48 selected sites, once all are open.

2.7 Blinding

AZIN-V is an open-label trial, and no blinding of participants or facilities will be done.

2.8 Timing of final analysis

The final analysis will be conducted when all participants have completed their follow-ups.

2.9 Timing of outcome assessments

Table 2. Schedule of study assessments

Visit	ANC visits	Labour	After delivery	3 days	2 wks	4 wks	6 wks
Assessment window			**+12 hrs**	**±1 day**	**±3 day**	**±5 day**	**±7 day**
Screening for eligibility		X					
Study intervention (AZM or usual care)		X					
Vital Signs		X	X	X	X	X	X
Clinical lab evaluation*		X	X	X	X	X	X
Baseline Information (mother)[1]		X	X				
Baseline newborn information [2]			X				
Maternal outcomes		X	X	X	X	X	X
Neonatal outcomes			X	X	X	X	X
Adverse events		X	X	X	X	X	X

[1] Baseline information of the mother includes Sociodemographic, clinical, medical history, labour and delivery information etc

[2] Baseline information of the newborn includes sex, birthweight, birth outcome, complications etc

3 Monitoring of the Trial

3.1 Operational monitoring of patients

3.1.1 Screening data

Screening data will be collected and summarized in the CONSORT flow diagram (Figure 1).

3.1.2 Eligibility

Pregnant women from 24+0 weeks' gestational age with a planned vaginal birth, following spontaneous or induced labour, at any stage with either a singleton or multiple birth, presenting to the participating health facilities.

Inclusion criteria

- Pregnant women with singleton or multiple pregnancy of at least 24+0 weeks GA in labour, including those in the first stage or second stage of labour
- Pregnant women admitted in labour to the selected health facilities following spontaneous or induced labour with planned vaginal birth
- Women presenting with stillbirth will also be eligible, since they are at risk of postpartum sepsis.

Exclusion criteria

- Gestational age <24 weeks at screening
- Not admitted to the facility with a plan to deliver vaginally
- In preterm contraction and no immediate plan for delivery
- Has fever >38°C with no other explanation
- Known use of a macrolide antibiotic in the previous three days
- Known allergy to azithromycin, its excipients or other macrolide antibiotics
- Known to have an arrhythmia or a known history of cardiomyopathy
- Planned caesarean delivery

3.1.3 Recruitment

Data on participant recruitment will be collected and will be presented in the CONSORT flow diagram.

3.1.4 Withdrawal/follow-up

Participants may withdraw from or be lost to follow-up during the trial at various time points. Data on the timing (e.g., at 3 days, 2 weeks, 4 weeks, and 6 weeks postpartum) will be captured. The CONSORT flow diagram (cluster extension) will display the numbers assessed for eligibility, enrolled, followed up and analysed, with reasons for loss to follow-up at each stage. Kaplan-Meier plots may be used to illustrate time to withdrawal or time to last available contact, if deemed informative, or if withdrawals are many (>5%).

Reasons for withdrawal/loss to follow-up such as participant refusal, relocation, will be presented in tabular format by randomised group, showing the number and percentage of participants withdrawn, with categorization of reasons. Where the reasons are missing or unknown, this will be explicitly reported.

3.1.5 Baseline patient characteristics

Baseline patient characteristics will be summarized for all randomised participants, presented by treatment arm and overall. These summaries will allow assessment of comparability between groups at baseline.

List of baseline characteristics to be summarized:

- Maternal demographics: age (continuous and categorized: <20, 20 – 29, 30 – 39, ≥40 years), parity, educational attainment, marital status
- Clinical characteristics: gestational age at enrolment, mode of delivery (vaginal delivery, cesarean section), parity
- Facility characteristics: facility type (primary/secondary/tertiary), state, routine use of postpartum antibiotics
- Other relevant maternal history: multiple vs. singleton pregnancy

Descriptive summarization methods

- Continuous variables: summarized by number of non-missing observations (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum
- Categorical variables: summarized by frequency counts and percentages for each level
- The number of missing observations will be presented in the footnote of each table.
- No formal statistical testing for between-group differences will be performed; summaries will be descriptive only.

See the Table 3 for reference.

3.1.6 Adherence and protocol deviations

Adherence

In this cluster-randomised trial, adherence refers to the extent to which participating facilities implement the allocated intervention as per protocol. For clusters randomised to the intervention arm, adherence will be assessed as the proportion of eligible women in labour who received the intrapartum oral dose of azithromycin as specified.

Protocol deviations

A protocol deviation is any instance where the trial procedures were not followed exactly as specified in the protocol but where the deviation is unlikely to have a meaningful effect on participant safety, trial integrity or the reliability of the primary endpoint. Examples include delays in scheduled follow-up visits, missing or incomplete non-critical data elements. Protocol deviations will be recorded, summarized descriptively and tabulated.

Protocol violations

Protocol violations are major departures from the trial protocol that may have implications for participant safety, ethical conduct, or the validity of trial results. Examples include enrolment of

ineligible participants, administration of the trial intervention in a control facility and vice versa, or missed primary outcome assessment. Protocol violations will be recorded, summarized descriptively and tabulated (Table 13).

3.1.7 Safety data and harms

Adverse Event (AE)

Refers to any untoward medical occurrence in a participant in the AZIN-V trial, whether or not causally related to the study intervention. All AEs will be recorded on case report forms (CRFs) and coded using the Common Terminology Criteria for Adverse Events (CTCAE) system. Each AE will be characterized by severity (Grade 1 – 5), expectedness (expected vs. unexpected, relative to the study protocol), and timing relative to enrolment. AEs will be summarized by group and analyzed as a secondary study endpoint.

Adverse Drug Reaction (ADR)

Refers to a subset of AEs judged by the site investigator as having at least a reasonable possibility of being caused by azithromycin. ADRs will be graded according to CTCAE severity and summarized by treatment group and timepoint, for the first two weeks postpartum. This distinction will allow differentiation between background events that occur in routine postpartum care and those plausibly attributable to azithromycin.

Serious adverse events (SAE)

Refers to a subset of AEs that results in death, is life-threatening, requires or prolongs hospitalization, results in significant disability or is a congenital anomaly/birth defect. All SAEs will be reported in accordance with GCP, graded using CTCAE, and summarized by treatment arm, with tabulations by type, severity, causality, expectedness and outcome.

3.1.8 Unblinding

This trial is open label at the cluster level, meaning that participating facilities and women are not blinded to allocation. However, to maintain integrity of the analyses, data analysts/statisticians will remain blinded to group allocation until the final database is locked, and analysis datasets have been created.

Unblinding procedures

Requests for unblinding individual participants are not applicable in this trial as treatment allocation is determined at the facility (cluster) level and is not masked. If temporary unblinding of members of the Data Safety Monitoring Board is required, this will be conducted in accordance with the DSMB charter. In that case, interim unblinding will be restricted to the independent statistician and the DSMB.

All instances of interim unblinding will be formally documented, including the date, and the person requesting unblinding, the reason for the request, and the individuals to whom data were disclosed.

3.2 Statistical monitoring during the trial

3.2.1 Assessment of bias

Bias will be monitored throughout the trial to ensure that intervention and control groups are comparable. At interim and final analyses, baseline maternal, neonatal and facility-level characteristics will be compared descriptively across randomised arms to check for imbalances. These will include maternal age, parity, education, facility type and routine postpartum antibiotic practices. If substantial imbalances are identified, sensitivity analyses adjusting for the imbalanced covariates will be conducted.

3.2.2 Non-adherence

The proportion of adherence by the facilities will be summarized by randomised arm (Table 6). If non-adherence exceeds 5%, the impact of non-adherence on effect size may be assessed through using complier average causal effect (CACE) analysis, in addition to the primary intention-to-treat analysis.

3.2.3 Statistical interim analyses and stopping guidance

An interim analysis will be conducted once the primary outcome data are available for 50% of the planned total sample size (n = 2520). An independent statistician will conduct the analysis. The interim analysis will focus on efficacy (maternal sepsis) and safety (serious adverse events), and the results will be reported to the DSMB.

- Multiplicity control: A Haybittle-Peto boundary ($p < 0.001$ at interim) will be used to preserve the overall type 1 error rate (24–26). This conservative threshold is chosen because it spends only a negligible portion of the overall α at the interim analysis, ensuring that the final analysis can still be conducted at the conventional two-sided 5% significance level without adjustment. In other words, unless there is overwhelming evidence of efficacy at interim, the statistical inference at the final analysis remains essentially unchanged, thereby balancing early stopping opportunities with protection against false positives.
- Stopping guidance: The DSMB may recommend early stopping for overwhelming efficacy or unacceptable safety concerns. Non-statistical reasons (e.g. feasibility, regulatory concerns) may also guide the DSMB's early stopping recommendations, in consultation with the Trial Steering Committee (TSC).

4 Analysis Approach

All analyses will be done using the treatment policy strategy, i.e., Intention-to-Treat (ITT). The participants will be analysed according to the treatment arm they were allocated to, irrespective of the treatment they received. All participants will be included in the analysis regardless of whether they adhered to the protocol.

4.1 Observed dataset

This will comprise all the data observed with missing values.

4.2 Imputed dataset

We anticipate that there will be a small amount of missing data for the outcomes. If the proportion of missing outcome data is less than 5% then only complete case analysis will be performed (i.e., excluding cases with missing outcome data). If the proportion of missing outcome data is above 5%, multiple imputation method will be considered under the assumption that data are missing at random (MAR).

4.3 Multiple Testing

All p-values will be presented to the third decimal place. There is a single primary outcome in this trial and no adjustment for multiple testing will be done (27).
Thus, the alpha level for statistical inference in our analysis will be **5%**.

4.4 Handling of multiple gestation

Multiple gestation will be treated as a single unit, for simplicity. If one of the offspring had an adverse outcome of interest such as stillbirth, or neonatal death, the adverse outcome will be recorded for the unit, for the purpose of analysis. For adverse continuous outcomes such as length of stay, the longer duration will be recorded for the unit. In sensitivity analysis, a 3-level mixed effects model with random intercepts for sites and for mothers will be considered for outcomes in the offspring.

5 Estimand Framework and Main Statistical Analysis

5.1 Statistical Principles

5.1.1 General considerations

Continuous variables will be summarized using the number of non-missing observations (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum. Categorical variables will be summarized using counts and percentages. Percentages will be based on the number of participants with non-missing data for that variable.

Missing data will be described explicitly with the number reported for each variable. Where appropriate, multiple imputation methods may be employed.

5.1.2 Confidence intervals and P values

The primary analysis will use a two-sided significance level of 5%. Two-sided confidence intervals will be presented for all primary and secondary outcomes. No formal adjustments for multiplicity will be made for secondary outcomes.

P-values will be reported to three decimal places, with values less than 0.001 reported as "<0.001". CIs will be reported alongside point estimates to emphasize precision rather than sole reliance on hypothesis testing. For subgroup analyses, interaction p-values will be reported without correction for multiple testing, and results will be interpreted cautiously.

5.2 Estimand Framework

Primary estimand

Table 4: Primary estimand and its associated estimator

Estimand attributes	Estimator
Treatment conditions ▪ Comparison of a single 2g oral dose of azithromycin administered intrapartum versus usual care (no azithromycin) across health facilities randomised to each arm	
Target population ▪ All eligible pregnant women presenting to health facilities during the study period	*Analysis set* ▪ All eligible pregnant women presenting to health facilities during the study period, analyzed according to their cluster assignment (intention-to-treat population)
Variable (primary outcome) ▪ Incidence of maternal sepsis, as defined by WHO criteria, occurring within 6 weeks postpartum	Measurement/endpoint obtained to address objective
Summary measure Risk ratio/Odds ratio	*Analysis approach* Logistic regression with random intercepts for clusters
Intercurrent events (ICE) ▪ Use of non-study antibiotics per treatment policy: reflects real world practice and aligns with pragmatic design ▪ Participant death before outcome ascertainment ▪ Missing outcome data	*Strategies for handling intercurrent events, e.g.,* Treatment policy - target the treatment effect regardless of the occurrence of intercurrent event (Intercurrent event considered as part of the treatment) Sensitivity analysis may consider a composite of death or sepsis Multiple imputation may be considered in sensitivity analysis

5.3 Primary Effectiveness Analysis

5.3.1 Analyses approach

All analysis will be intention-to-treat unless specified otherwise. The frequency of occurrence of the primary outcome will be presented as N and percent of the total study population, and by treatment group.

Random effects logistic regression model will be used to obtain the odds ratio (treatment effect) along with 95% confidence intervals. The model will be adjusted for the stratification variables (state, facility level, and whether postpartum antibiotics are used empirically), along with any

imbalance baseline variables that are thought to be clinically important. Specifically, the baseline variables of interest are age, educational attainment, parity and mode of delivery. The unadjusted and adjusted risk difference and risk ratio estimates will also be calculated.

5.3.2 Sensitivity analysis

Sensitivity analysis may consider each of the intercurrent events as follows.

Intercurrent event	Sensitivity analysis
Use of non-study antibiotics	Participants for whom non-study antibiotics were used would be considered as having experienced incident sepsis, and the primary analysis would be repeated and compared
Participant death	For the composite of all-cause death or maternal sepsis, we will use a hierarchical win ratio comparing every treated participant to every control participant. The win ratio is the number of wins for treatment divided by the number of wins for control, with a 95% CI and a two-sided p-value. Pairs classified as ties (both participants have the same outcome status) will not contribute to the numerator or denominator, but the proportion of ties will be reported descriptively.
Missing outcome data	Multiple imputation will be conducted assuming missingness in the outcome is at random.

5.3.3 Subgroup analysis

The following subgroup analysis of the primary outcome (maternal sepsis) will be conducted:

a) Regions (Ebonyi, Edo, Gombe, Kano, Kwara and Lagos)
b) Mode of delivery (vaginal/caesarean)
c) Routine antibiotic use (yes/no)
d) Level of healthcare facility (primary/secondary/tertiary)
e) Gestational age at delivery (<28 weeks/≥28 weeks)
f) Duration of labour (prolonged/not prolonged)
g) Multiple pregnancy (yes/no)

Logistic regression models with an interaction term between the treatment and the subgroup variables will be used. For modifiers with more than two levels, likelihood ratio tests will be used instead. 99% confidence interval will be presented as the study is not powered for these analyses.

Additional exploratory subgroup analysis will focus on neonatal sepsis.

5.4 Secondary Effectiveness Analyses

5.4.1 Analyses of Secondary Endpoints

These analyses will be conducted in the ITT population.

The frequency of occurrence of the categorical endpoints will be presented as N and as a percentage of the total study population, by state, and by treatment group. N, mean, standard deviation (SD), median, interquartile range, minimum, and maximum will be used to summarize continuous variables as appropriate.

For binary outcomes, random effects logistic regression models will be used to obtain the odds ratio and 95% confidence intervals. The unadjusted and adjusted risk difference and risk ratio estimates will also be calculated.

For count outcome variables, mixed-effect Poisson regression models will be used to obtain rate ratios and 95% confidence intervals. The log of the number of days since treatment may be set as the offset term. For continuous outcome variables, linear mixed effect models with random intercepts for cluster will be used to obtain mean differences with confidence intervals.

Same adjustment approach as the primary analysis will be used.

5.5 Safety outcomes analysis

5.5.1 Adverse Events

Analysis approach

The number and the proportion of participants who experience adverse events overall (defined in 3.1.7) will be presented by treatment arm. The count of adverse events experienced overall will also be presented by treatment arm.

5.5.2 Serious Adverse Events (SAE)

Analysis approach

The number and proportion of participants who experience SAEs (defined in 3.1.7) will be analysed and presented. The appropriate grading of the severity of the SAEs will also be presented in counts and proportions. A listing of SAEs experienced will be included per participant.

If any serious adverse events occur in ≥5% of individuals who receive either intervention, the time to occurrence of the adverse event will be summarized using median (IQR) and graphically with Kaplan-Meier curves.

6 Other statistical considerations

6.1 Software

Analyses will be performed using R version 4.5.0 or latest version (R Foundation for Statistical Computing, Vienna, Austria).

6.2 Reporting Conventions

P-values ≥0.001 will be reported to 2 significant decimal places; p-values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

The trial results will be reported in accordance with Consolidated Standards of Reporting Trials (CONSORT extension for cluster randomised trials).

6.3 Quality Assurance of Statistical Programming

A second review statistician will independently check the entire analyses and will explicitly check the code used to produce each table and other results.
To provide high quality code that is understandable, and allows for reproducibility of the analysis, the following details will be provided in annotation preceding code chunks.

- Population of analysis
- date and time included
- Description of desired output from analysis

7 References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.

2. World Health Organization (WHO). Trends in maternal mortality estimates 2000 to 2023: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division [Internet]. Geneva: World Health Organization; 2025 [cited 2026 Jan 23]. Available from: https://iris.who.int/server/api/core/bitstreams/29f43a3d-2228-489c-b1e7-b2f28e9101ce/content

3. World Health Organization. Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division: executive summary. 2023;

4. Olamijulo JA, Olorunfemi G, Okunola H. Trends and causes of maternal death at the Lagos University teaching hospital, Lagos, Nigeria (2007–2019). BMC Pregnancy Childbirth. 2022;22(1):360.

5. Organization WH. WHO recommendations for prevention and treatment of maternal peripartum infections [Internet]. World Health Organization; 2016 [cited 2025 Aug 25]. Available from: https://books.google.com/books?hl=en&lr=&id=bls0DgAAQBAJ&oi=fnd&pg=PP2&dq=WHO+recommendations+for+prevention+and+treatment+of+maternal+peripartum+infections:+highlights+and+key+messages&ots=QX1nd9K72q&sig=rttxJDAwFger23nZf1VkoDOx9YA

6. Jury I, Thompson K, Hirst JE. A scoping review of maternal antibiotic prophylaxis in low- and middle-income countries: Comparison to WHO recommendations for prevention and treatment of maternal peripartum infection. Int J Gynecol Obstet. 2021 Dec;155(3):319–30.

7. Wu S, Tannous E, Haldane V, Ellen ME, Wei X. Barriers and facilitators of implementing interventions to improve appropriate antibiotic use in low- and middle-income countries: a systematic review based on the Consolidated Framework for Implementation Research. Implement Sci. 2022 Dec;17(1):30.

8. Rolfe R, Kwobah C, Muro F, Ruwanpathirana A, Lyamuya F, Bodinayake C, et al. Barriers to implementing antimicrobial stewardship programs in three low- and middle-income country tertiary care settings: findings from a multi-site qualitative study. Antimicrob Resist Infect Control. 2021 Dec;10(1):60.

9. Antonucci R, Cuzzolin L, Locci C, Dessole F, Capobianco G. Use of Azithromycin in Pregnancy: More Doubts than Certainties. Clin Drug Investig. 2022 Nov;42(11):921–35.

10. Larson JM, Tavakkoli A, Drane WE, Toskes PP, Moshiree B. Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. J Neurogastroenterol Motil. 2010;16(4):407.

11. Hume-Nixon M, Quach A, Reyburn R, Nguyen C, Steer A, Russell F. A systematic review and meta-analysis of the effect of administration of azithromycin during pregnancy on perinatal and neonatal outcomes. EClinicalMedicine [Internet]. 2021 [cited 2025 Aug 25];40. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00403-X/fulltext

12. Arnold KC, Flint CJ. Use of Prophylactic Antibiotics in Labor and Delivery. In: Obstetrics Essentials [Internet]. Cham: Springer International Publishing; 2017 [cited 2025 Aug 25]. p. 129–33. Available from: http://link.springer.com/10.1007/978-3-319-57675-6_20

13. Martingano D, Singh S, Mitrofanova A. Azithromycin in the Treatment of Preterm Prelabor Rupture of Membranes Demonstrates a Lower Risk of Chorioamnionitis and Postpartum Endometritis with an Equivalent Latency Period Compared with Erythromycin Antibiotic Regimens. Infect Dis Obstet Gynecol. 2020 July 9;2020:1–8.

14. Tita ATN, Szychowski JM, Boggess K, Saade G, Longo S, Clark E, et al. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. N Engl J Med. 2016 Sept 29;375(13):1231–41.

15. Harper LM, Kilgore M, Szychowski JM, Andrews WW, Tita AT. Economic evaluation of adjunctive azithromycin prophylaxis for cesarean delivery. Obstet Gynecol. 2017;130(2):328–34.

16. Flaherty A. Does Azithromycin Have a Role in Cesarean Sections? Clin Rev. 28:1.

17. Doan T, Worden L, Hinterwirth A, Arzika AM, Maliki R, Abdou A, et al. Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution. N Engl J Med. 2020 Nov 12;383(20):1941–50.

18. Bojang A, Baines SL, Camara B, Guerillot R, Donovan L, Marqués RS, et al. Impact of intrapartum oral azithromycin on the acquired macrolide resistome of infants' nasopharynx: a randomized controlled trial. Clin Infect Dis. 2020;71(12):3222–5.

19. Rambliere L, Guillemot D, Delarocque-Astagneau E, Huynh BT. Impact of mass and systematic antibiotic administration on antibiotic resistance in low-and middle-income countries. A systematic review. Int J Antimicrob Agents. 2021;58(1):106364.

20. Roca A, Bottomley C, Hill PC, Bojang A, Egere U, Antonio M, et al. Effect of age and vaccination with a pneumococcal conjugate vaccine on the density of pneumococcal nasopharyngeal carriage. Clin Infect Dis. 2012 Sept;55(6):816–24.

21. Alegbeleye JO, Alabere ID. Prevalence and Pattern of Maternal Near Miss at a Tertiary Care Hospital in Southern Nigeria. [cited 2025 Nov 13]; Available from: https://www.researchgate.net/profile/Justina-Alegbeleye/publication/382049428_Article_noAJPCB91127_Original_Research_Article_Alegbeleye_and_Alabere/links/6689ab642aa57f3b82747123/Article-noAJPCB91127-Original-Research-Article-Alegbeleye-and-Alabere.pdf

22. Roca A, Camara B, Bognini JD, Nakakana UN, Somé AM, Beloum N, et al. Effect of intrapartum azithromycin vs placebo on neonatal sepsis and death: a randomized clinical trial. Jama. 2023;329(9):716–24.

23. Taljaard M, Donner A, Villar J, Wojdyla D, Velazco A, Bataglia V, et al. Intracluster correlation coefficients from the 2005 WHO Global Survey on Maternal and Perinatal Health: implications for implementation research. Paediatr Perinat Epidemiol. 2008 Mar;22(2):117–25.

24. Dodd LE, Proschan MA. Data and Safety Monitoring Board Monitoring of Clinical Trials for Early Efficacy. Evans SR, Drazen J, editors. NEJM Evid [Internet]. 2022 Feb 22 [cited 2025 Sept 22];1(3). Available from: https://evidence.nejm.org/doi/10.1056/EVIDctw2100025

25. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer. 1976 Dec;34(6):585–612.

26. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793–7.

27. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol. 2017;

8 Template of Tables, Listings and Figures

Figure 1. Flow diagram

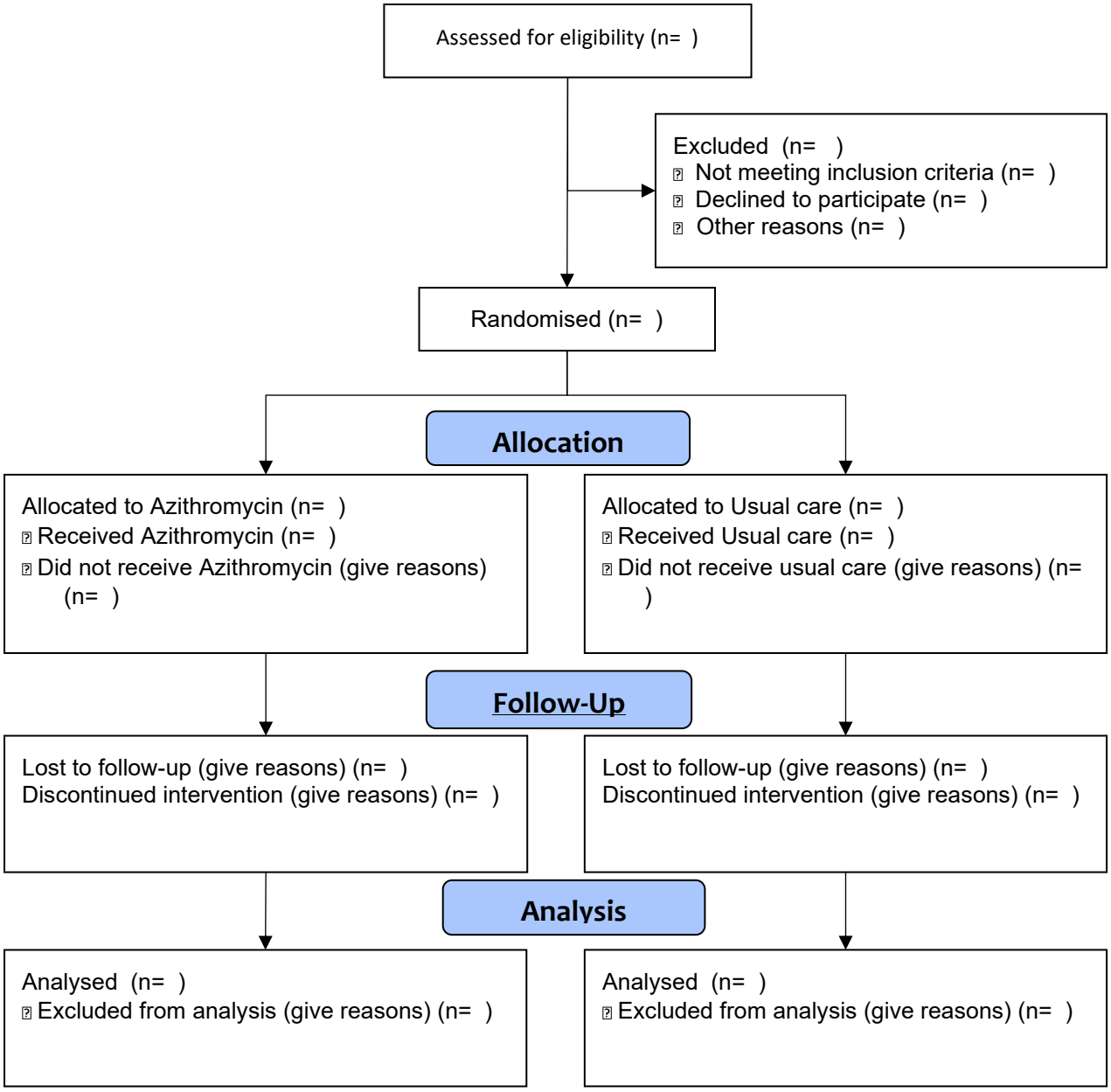


Table 1. Withdrawal and follow-up status by treatment arm

Timepoint	Azithromycin	Usual care	Total
Enrolled			
3 days			
Completed			
Withdrawn before			
2 weeks			
Completed			
Withdrawn before			
4 weeks			
Completed			
Withdrawn before			
6 weeks			
Completed			
Withdrawn before			

Table 2. Reasons for withdrawal by treatment arm

Timepoint	Azithromycin	Usual care	Total
Participant refusal			
Relocation			
Medical reasons			
Death			
Unknown/other			

Table 3. Baseline characteristics

	Cluster 7 (N=XX)	Cluster L (N=XX)	Overall (N=XX)
Age			
Mean (SD)			
Median [Min, Max]			
Age Categories			
<20 y			
20 - <30 y			
30 - <40 y			
40 and above, y			
Education			
Completed Primary			
Completed Secondary			
Completed Tertiary			
No formal education			
State			
Ebonyi			
Edo			
Gombe			
Kano			
Kwara			
Lagos			
Parity			
0			
1 or 2			
3 or 4			
5 or more			
Duration of labour			
Prolonged			
Not prolonged			
Mode of delivery			
Emergency Caesarean Section			
Spontaneous Vaginal Delivery			
Vacuum Delivery			
Forceps Delivery			
Multiple pregnancy			
Yes			
No			
Routine Antibiotics			
No			
Yes			

Table 4: Primary endpoint

Outcome	Level	Azithromycin	Usual care	ES	CI	P-
Incident maternal sepsis	Yes					
	No					

Table 5: Complier average causal effect (CACE) analysis of Primary endpoint

Outcome	Estimand	Azithromycin	Usual care	Effect size	CI	P-value
Incident maternal sepsis	ITT					
	CACE					

Table 6: Compliance summary

Arm	Clusters randomised, N	Clusters compliant, n(%)	Individuals randomised, N	Individuals randomised, n(%)
Azithromycin				
Placebo				

Table 7: Unadjusted and adjusted analysis of primary endpoint

Analysis	Level	Azithromycin	Usual care	ES	CI	P-
Unadjusted	Yes					
	No					
Adjusted	Yes					
	No					

Table 8: Subgroup analysis of primary endpoint

Modifier	Subgroup	Primary outcome level	Azithromycin	Usual care	ES	CI	P-interaction
		Yes					
		No					

Table 9. Maternal outcomes

Outcome	Level	Azithromycin	Usual care	Effect measure	95%CI	P-value
Maternal sepsis, RR	No					
	Yes					
Culture-confirmed maternal	No					
	Yes					
Number of new antibiotic						
Overall	Mean					
For specific infections	Mean (SD)					
Duration of hospital stay, MD	Mean					
Readmission or admission to	Yes					
	No					
Secondary postpartum	Yes					
	No					

Effect measures are risk ratios (RR), incident rate ratios (IRR) or mean difference (MD), with 95% confidence intervals

Table 10. Newborn outcomes

Outcome	Level	Azithromycin	Usual care	RR	CI	P-value
Neonatal sepsis, RR	No					
	Yes					
Stillbirth, RR	No					
	Yes					
Neonatal death, RR	Yes					
	No					
Duration of hospital stay, MD	Mean					
Readmission or admission to special unit	Yes					
	No					

Effect measures are risk ratios (RR), incident rate ratios (IRR) or mean difference (MD), with 95% confidence intervals

Table 11. Adverse events

Adverse Event	Azithromycin	Usual care	Total

Table 12. Protocol deviations

Type of deviation	Azithromycin	Usual care	Total
Out-of-window visit			
Informed consent process			
Lab/Imaging/Other investigation			
Missed visit			
SAE reported out of window			
Total participants with ≥1 deviation			

Note: Each participant may have more than one deviation. Percentages based on number randomised.

Table 13. Protocol violations

Trial arm	Study ID	Date	Category	Description	Action taken