APT-Sepsis

The Active Prevention and Treatment of Maternal Sepsis – a cluster randomised trial.

Statistical Analysis Plan

Trial registration No: ISRCTN42347014

Version 2.0 04/08/2025

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1 Approval and Agreement

SAP Version Number being approved: 2.0

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2 Table of Contents

3 Glossary

AE	Adverse Event
APT-SEPSIS	Active Prevention and Treatment of Maternal Sepsis
CI	Chief Investigator
CRF	Case Report Form
FAST-M	Fluids, Antibiotics, Source identification and Transfer and Monitoring
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trials Number
LCTC	Liverpool Clinical Trials Centre
LMIC	Low/Middle Income Countries
QC	Quality Control
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WHO	World Health Organisation

4 Roles and Responsibilities

D. Lissauer, Chief Investigator; G. Burnside, Lead Statistician; Aiswarya Anilkumar, Trial Statistician; Anna Rosala-Hallas, Trial Statistician; K. Hemming, Statistical co-investigator and Trial Management Group (TMG) member; J. Martin, Statistical co-investigator and TMG member.

Contributions

ARH and GB drafted the Statistical Analysis Plan (SAP). DL, KH and JM reviewed and made amendments. DL and GB signed off the SAP.

5 Statement of Compliance

This Statistical Analysis Plan provides a detailed and comprehensive description of the pre-planned analyses for the study APT-Sepsis. The planned statistical analyses described within this document are compliant with those specified in brief within the APT-Sepsis protocols: Malawi version 6.0, 07/11/2024 and Uganda version 3.0, 07/11/2024.

The purpose of the plan is to:

a. Ensure that all analyses are appropriate for the aims of the trial, reflect good statistical practice, and minimise bias by preventing inappropriate post hoc analyses.
b. Ensure that the analyses performed are consistent with the conditions of the protocol.
c. Explain in detail how the data will be handled, covariates derived and analysed to enable the analysis to be replicated, if necessary.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Liverpool Clinical Trials Centre (LCTC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004. This SAP is written in accordance with ICH E3 [1], ICH E9 [2] and Guidance on Statistical Analysis Plans [3].

6 Introduction

The interim reporting will be described in a confidential Independent oversight committee report. The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan. Where analyses are presented which are not included in the SAP, justification as to their inclusion must be provided.

All analyses are performed with standard statistical software (SAS version 9.4 or later, Stata version 16 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP GE012 Archiving Procedures in LCTC.

7 Background and Rationale

A full background can be found within the protocols (Malawi version 6.0 07/11/2024; Uganda version 3.0 07/11/2024). In brief, maternal infection has been found to contribute largely to intra-hospital maternal deaths, and Low- and Middle-Income Countries (LMICs) are by far the most affected. In order to reduce maternal mortality, it is important to target maternal infection.

The Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) programme is designed to be used in countries and settings where resources are limited. The aim is to improve health care worker behaviours to prevent and manage infections.

8 Objectives

The primary objective of the study is:

- To examine if the APT-Sepsis programme is effective at reducing individual-level infection related maternal mortality and severe morbidity, and superior compared to usual care with passive guideline dissemination

The secondary objectives are:

- To evaluate if the APT-Sepsis programme is effective at reducing individual level secondary clinical outcomes of: Stillbirth, early neonatal death (infection related and total), maternal mortality (any cause), maternal near miss (any cause)
- To explore differential or subgroup individual-level effects of the APT-Sepsis programme.
- Implementation: To understand the cluster-level implementation of the APT-Sepsis programme in Malawi and Uganda, to facilitate interpretation of trial outcomes and development of a longer-term implementation strategy. A separate analysis plan will be developed for this objective.
- Health economic analysis: To determine if the APT-Sepsis programme is cost effective. A separate analysis plan will be developed for this objective.

9 Study Design

9.1 Overall study design

A schematic of the trial design can be found in Section 8.1 of the protocol.

This study is a multi-country, two-arm parallel cluster randomised trial with a baseline control phase of at least 6 months, a transition phase of 3 months and a post intervention roll out period of 9 months. The clusters are the health facilities of which we aim to open 64 in total (32 in Malawi and 32 in Uganda). The trial has a cross-sectional design, with different participants in each phase. Data from the transition phase will not be included in the analysis.

9.2 Blinding

This is an open-label trial.

10 Consent process

Full details on the consent process can be found in Section 24 of the protocol. Informed consent will be sought from healthcare providers who participate in interviews, surveys and complete diaries.

As patients are not research participants in the trial their informed consent in the APT-Sepsis study is not required.

11 Study population

11.1 Inclusion criteria

See protocol section 9.1 for inclusion criteria for facilities and research participants.

11.2 Exclusion criteria

See protocol for inclusion criteria for facilities and research participants.

11.3 Removal of participants from intervention or follow-up

At present there are no planned instances where a participant or facility would be removed from the intervention or post intervention roll out period. Facilities that drop out during the baseline period will not be included in the final analysis.

12 Method of assignment to intervention

A minimisation system was configured by an independent statistician at LCTC. Health facilities were allocated to treatment arms using a minimisation algorithm, to ensure balance of important factors between facilities allocated to the intervention and control groups. The minimisation factors within each country were

1. number of births per cluster per week: three categories: cut points 70.8 and 118.5 (Malawi), 60.5 and 83.9 (Uganda).
2. proportion of births with the composite primary outcome (infection related maternal mortality, infection related maternal near-miss and severe infection related morbidity - see Section 15.1): two categories: cut points 1.96 (Malawi), 3.19 (Uganda).

These were be measured at each facility within the baseline period. The cut points for the minimisation factors were determined separately for each country. Weekly average births were assigned into 3 categories using the 33rd and 67th percentile of the observed values within up to the first four months of the baseline periods. Start dates were staggered, therefore, we had between two and four months of baseline data for each facility to determine cut-points. Proportion of births with the composite primary outcome were assigned into 2 categories using the median as a cut-off point. Facilities were allocated during the fifth month of their baseline period, using their baseline data up to this point (at least four months for each facility).

The minimisation algorithm will calculate the allocation which will minimise imbalance over all minimisation factors. A random element of 90% will be incorporated to reduce predictability of allocation, with facilities allocated to the group which minimises imbalance with probability 0.9, or to the other group with probability 0.1. If both allocations would result in equal imbalance, the allocation will be determined completely at random [1].

13 Schedule of assessments

There will not be scheduled visit assessments in APT-Sepsis, rather daily observations of the routine health facility records from the pre-implementation phase to the end of the study. Outcomes will be collected from all women who are admitted to the healthcare facility during pregnancy or within 42 days of delivery. No follow-up events occurring after discharge from the healthcare facility will be carried out.

14 Interventions

See section 10 of the protocol for a full outline of the study intervention. In brief, the APT-Sepsis programme focusses on improving 3 main clinical behaviours:

1. Hand hygiene

2. Infection prevention and treatment
3. Sepsis management.

Healthcare facilities randomised to the intervention will identify the local Champions who will receive their allocated training (train the trainers training). The Champions will be supported to then roll out the training at the facility. Following the interactive, scenario-based training delivered by the Champions (approximately 2 days provided to each individual), the Champions will then provide ongoing coaching (supported by training and coaching materials and videos) to the facility staff. The changes at a facility are supported by reminder posters and aide memoires and practitioner actions guided by paper-based tools and checklists.

15 Listing of Outcomes

15.1 Primary outcome(s)

The primary outcome is maternal infection related mortality and severe morbidity. This is a composite of infection related maternal mortality, infection related maternal near-miss and severe infection related morbidity (deep surgical site infection or body cavity infection).

15.2 Secondary outcomes

- Clinical outcomes:
  - Stillbirth
  - Early neonatal death (infection related and total)
  - Maternal mortality (any cause)
  - Maternal near miss (any cause)
  - Maternal severe acute respiratory infections
- Quantitative implementation outcomes:
  - Compliance with hand hygiene (as per WHO 5 movements of hand hygiene standard assessment)
  - Correct use of antibiotic prophylaxis for prevention of peripartum infection (as per WHO guidelines)
  - Complete vital sign recording at admission
  - Sepsis management compliance
- Implementation outcomes (a separate analysis plan will be generated for the implementation analysis):
  - Fidelity
  - Sustainability
  - Acceptability
  - Understand the mediators of implementation including the impact of context
- Health economic analysis (a separate analysis plan will be generated by the health economist).

16 Sample size calculation

Power calculations have allowed for the clustered nature of the design. In addition, to allow for variation in clustering over time, we have allowed for a cluster by period random effect. This has been

incorporated in the sample size calculations using the cluster autocorrelation (CAC) in addition to the ICC. To estimate these correlations (and their confidence intervals) we have used existing maternal health data for a similar composite outcome used in the Carbetocin Haemorrhage Prevention (CHAMPION) trial, with 23 clusters and 26,000 observations [5]. The estimated within-period ICC was 0.03 (95% CI 0.02 to 0.05) and the estimated CAC was 0.995 (95% CI 0.978 to 1.000). However, we have used bounds in our calculations slightly wider than our observed confidence being guided by general patterns and determinants of ICCs and CACs as per current guidance [6, 7].

16.1 Revision of sample size calculation

There was a planned re-estimation of the sample size at the end of the baseline period. This re-estimation was conducted and reported to the IDMC and TSC. This re-estimation was planned because at this point additional information was available to inform the power calculation. This included an up-to-date estimate of the number of women delivering per facility, alongside a more accurate estimate of the overall primary outcome rate and a calculation of the ICC from the baseline period. With a larger than anticipated number of women delivering per cluster we revisited the sample size calculation and explored shortening the length of the follow-up period, over a range of durations. We simulated a range of scenarios as with the previous calculation, now using an estimate of the ICC from the baseline period of 0.021. Based on this shortening of the follow-up period has a very small effect on power, and with a revised follow-up period of 9 months (following a 3-month transition period) we will still have at least 80% power to detect a relative reduction of 25% in most likely scenarios. This change was recommended by the IDMC and endorsed by the TMG and TSC. We did not consider any further shortening the implementation period as it was deemed important for the sites to have a long enough experience of implementing the intervention for the implementation/process evaluation to be able to explore issues of intervention sustainability over time.

16.2 Original sample size calculation

To this end, we have assumed an ICC of 0.03 but considered sensitivity across the range 0.001 to 0.05. We have assumed a CAC of 0.97 but considered sensitivity across the range 0.9 to 1.0. Each health facility will have a minimum of 1,500 births each year, so each health facility will contribute 2,875 (=1,500*23/12) births to the analysis (750 during the baseline phase and 2,125 post randomisation). Assuming 60 health facilities, the total sample size will be 172,500. Using methods to calculate the sample size in a parallel CRT with a baseline period previously described [6, 8] this will give over 95% power (at 5% significance) to detect a 25% relative reduction in the composite primary outcome from 3% to 2.25% after adjusting for clustering through the ICC and CAC for our base case scenario. The ICC and CAC ranges were considered through sensitivity analysis, and the study has at least 80% power in most likely scenarios. Our calculations have not allowed for varying cluster size, but our allocation process will balance on cluster size to ensure total cluster sizes are similar across the two arms of the study (see Section 12).

To allow for the possibility of health facilities dropping out, we will recruit an extra two facilities per country. It is anticipated that drop out is most likely to happen during the baseline period, in which case, these facilities will not be randomised or included in the final analysis.

17 Study Framework

The overall objectives of the primary and secondary outcomes is to test superiority of the APT-Sepsis programme compared to usual care with passive guideline dissemination

18 Timing and Objectives of Analyses

18.1 Interim Reporting

18.1.1 Reports to Independent Oversight Committees

Reports to the Independent Oversight Committees (IOCs) will be at least annually. Frequency of reporting will be agreed by the IOCs.

18.1.2 Assessments of progression criteria

There is no pilot phase and no progression criteria.

18.1.3 Formal Interim Analyses

There are no planned interim analyses of outcomes or harms planned for this study. During the baseline phase data will be collected on the number of births per week and the proportion of births with the composite primary outcome, to inform the minimisation factors for the randomisation. The report to the IDMC at the end of the baseline period will include a re-estimation of the planned sample size.

18.2 Final Analysis

The end of the trial is defined to be the date on which all data for all participants is frozen and data entry privileges are withdrawn from the trial database. The final analysis will take place after this.

19 Disposition of Participants

A CONSORT flow diagram [4] will be used to summarise the number of facilities:

- assessed for eligibility in the baseline phase
- eligible at baseline
- ineligible at baseline*
- eligible and randomised into the post intervention roll out period
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up (facility withdraws from post intervention roll out period)*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

The CONSORT will also show the number of participants that have observations in the baseline and post intervention roll out period and the number that were analysed for the primary outcome and implementation outcomes.

19.1 Screening, eligibility and recruitment

A recruitment summary table will be presented showing the following for each facility: country, facility name, dates site opened/closed to recruitment, total number of live births, total number of early pregnancy losses and total number of still births. A summary of the randomisation process by facility name, date of facility opening, date of randomisation, start date of the transition phase, and date of implementation of the intervention will be presented.

19.2 Post randomisation discontinuations

It is anticipated that facility drop out is most likely to happen during the baseline period, in which case, these facilities will not be randomised or included in the final analysis. If a facility drops out during the post intervention roll out period they will be included in the analysis up until the point of drop out.

20 Protocol Deviations

Possible protocol deviations are specified as minor or major in the Trial Monitoring Plan, stored in the Trial Master File.

The number (and percentage) of facilities with at least one major/minor protocol deviation will be summarised by treatment allocation.

21 Unblinding

The study is not blinded. Due to the nature of the study, it is not possible to blind the study statistician. However, the SAP has been prepared by statisticians blinded to study allocations.

22 Analysis Datasets

22.1 Efficacy Analyses

The primary aim of the study is to assess the effectiveness of the intervention.

The analysis set for the primary outcome and all the secondary outcomes will include data from all randomised facilities, in the group to which they were allocated. All recorded deaths, near-misses and severe infections in each facility will be included in the analysis set.

22.2 Safety Analyses

Facilities randomised to APT-Sepsis who do not begin the APT-Sepsis programme will be included in the control safety group. Facilities randomised to control who begin the APT-Sepsis programme will be included in the APT-Sepsis safety group.

23 Facility and patient Characteristics

Characteristics of both the facilities and the included participants will be presented, split by treatment allocation and by time-period (baseline or post intervention roll out). Categorical data will be presented using counts and percentages, continuous data will be presented using mean, standard deviation, median, interquartile range, minimum and maximum. There will be no statistical testing of baseline characteristics.

For characteristics collected weekly, the weekly average at site will be computed and then the average of all sites will be presented. For characteristics collected as available, limited or none, the average proportion of time that they had full availability, limited availability or no availability will be presented.

The following characteristics collected weekly will be presented summarised by facility

- Labour ward theatres in operation
- Functioning autoclaves within the facility
- Equipment available
    - X-ray
    - Ultrasound facilities
    - FBC testing

  - Renal function testing
  - Blood culture testing
  - Wound swab testing
  - Urine microscopy
  - Pregnancy tests
- Beds available
- Beds occupied
- Nurses/midwives working
- Equipment for IV-line insertion
- Working thermometers
- Working BP devices
- Working pulse oximetry machines
- Availability of:
  - Fetoscopes/pinards/fetal stethoscopes
  - Clocks/watches
  - Spare batteries
  - Urine dipsticks
  - Malaria rapid tests
  - Working O2 concentrators
  - Bottled or piped O2
  - Gloves
  - Soap
  - Running/flowing water for handwashing
  - Hand drying facilities
  - Alcohol rub for hand cleaning
- Availability of Oral Antibiotics
  - Azithromycin
  - Amoxicillin
  - Augmentin
  - Cephalosporin
  - Ciprofloxacin
  - Clindamycin
  - Co-amoxiclav
  - Doxycycline
  - Erythromycin
  - Flucloxacillin
  - Metronidazole
- Availability of IV antibiotics:
  - Ampicillin
  - Benzylpenicillin
  - Cefazolin

  - Cephalosporin
  - Chloramphenicol
  - Ciprofloxacin
  - Clindamycin
  - Co-amoxiclav
  - Gentamycin
  - Metronidazole
  - Penicillin G
  - Vancomycin
  - Meropenem
  - Tazobactam (Tazocin) or Piperacillin/Tazobactam
- Availability of other supplies
  - IV fluids (0.9% Saline or Hartmann's or Ringers lactate)
- Availability of labour ward equipment (additional)
  - Antiseptics for skin preparation
  - Surgical gloves
  - Sterile (clean) linen packs
  - Disposable delivery kit ("Mamta kit")
  - Sufficient sterilized delivery sets
  - Sterilized gowns
  - Sterilized forceps set
  - Working vacuum extractor
  - Suction apparatus with suction tube
  - Laceration repair pack
  - Emergency drugs (with expiration limits)
  - Mucus extractor for neonates
  - Bag valve mask (ambu bag) for newborn

The following 'participant' characteristics will be presented based on numbers reported at each site:

- Total number of births (total, caesarean and vaginal)
- Total number of early pregnancy losses
- Proportion of cases of PPH blood loss more than 1 litre
- Proportion of those with pre-eclampsia/eclampsia
- Proportion of instrumental deliveries (forceps, vacuum, ventouse)
- Proportion of neonatal deaths (inpatients)

The following participant characteristics will be presented for all women who are included in the trial data set due to severe infection, near miss or death, and also for those who were judged to have had severe infection, infection related near miss or infection related death.

- Age

- Pregnancy/post-delivery status on admission
- Surgical procedure during current pregnancy/post-delivery period

24 Compliance with Intervention

Key quantitative implementation outcomes will be collected in order to assess APT-Sepsis programme compliance. These are calculated from observations taken at quarterly visits to facilities by the study team. Summaries of these will be presented by facility for those randomised to the intervention.

- compliance with hand hygiene (as per WHO 5 movements of hand hygiene standard assessment)
    - proportion of observed hand hygiene opportunities which were taken
- correct use of antibiotic prophylaxis for prevention of peripartum infection (as per WHO guidelines),
    - proportion of caesarean sections given antibiotic prophylaxis
- complete vital sign recording at admission
    - proportion of in-patients with complete vital signs recorded at admission
- sepsis management compliance:
    - proportion of infection cases with complete vital signs recorded at diagnosis
    - proportion of infection cases given fluids within 1 hour
    - proportion of infection cases given antibiotics within 1 hour

25 Analysis of Outcomes

25.1 Interim Reporting

25.1.1 Reports to independent oversight committees

There are no planned formal interim analyses of outcomes or harms for this trial. There is unlikely to be sufficient power to show benefit, and the interventions are well formulated and tested, and developed to prevent harms. The report to the IDMC at the end of the baseline period will include a re-estimation of the planned sample size. If the study is found to be underpowered, consideration will be given to increasing the number of facilities included.

25.1.2 Assessment of progression criteria

Not applicable.

25.1.3 Formal Interim Analysis

Not applicable.

25.2 Final Analysis

25.2.1 Levels of significance and multiplicity

All applicable statistical tests will be two-sided and will be performed using a 5% significance level; confidence intervals presented will be 95%.

There will be no adjustment for multiplicity. However, results from secondary outcomes will be considered as exploratory and results will be interpreted with caution.

Analyses will be conducted with all clusters assigned to the group they were assigned at randomisation. All observations from randomised facilities (excluding observations from the transition phase) will be included in the analysis.

25.2.2 Primary Outcome

The primary outcome is maternal infection related mortality and severe morbidity. This is a composite of infection related maternal mortality, infection related maternal near-miss and severe infection related morbidity (deep surgical site infection or body cavity infection).

Assessments on whether maternal mortality, maternal near-miss or morbidity is infection-related will be made both at site, and by the local hub-team. Should the assessments disagree, an independent review panel will make the final decision.

25.2.2.1 Derivation

A participant will be recorded as having the composite primary outcome if any of the following apply:

- Their reason for inclusion was recorded as severe infection
- Their reason for inclusion was recorded as death or near-miss, and:
    - both site and hub agree that the cause of the event was infection related OR
- site and hub disagree on whether the cause of the event was infection related, and the independent panel review concluded that it was infection-related
- Their reason for inclusion was near miss, deemed not infection-related by the process above, but experienced a subsequent near miss which was deemed to be infection-related

25.2.2.2 Analysis

Summary statistics of the number and percentage who experienced the outcome will be presented by trial arm, country and time-period. The denominator for the percentage calculation will be the number of live births recorded in the facility in the time period.

Outcome rates over time will be presented in a line graph, split by intervention vs control, with pre-randomisation, transition and post-randomisation phases marked. Time will be anchored around date of allocation to the transition phase for each facility.

The primary analysis will use a mixed effects logistic regression models with robust standard errors. A small sample correction will not be used as there are over 40 clusters [8] The model will incorporate a constrained baseline analysis [9], where both pre-randomisation and post-randomisation time points are included as outcomes, but with the treatment effect assumed to be zero in the pre-randomisation phase. This will be implemented using two binary covariates, one indicating period (0= pre-randomisation, 1=post-randomisation), and one indicating exposure to the intervention (taking the value 0 for all clusters in the pre-randomisation period, and control clusters in the post-randomisation period, and the value 1 for the intervention clusters in the post-randomisation period). Facility and facility by period will be included as random effects, with country, and the categorical minimisation factor facility size included as covariates. The second minimisation factor (proportion of births with the composite primary outcome) is not included as proportion of births is already in the model as the outcome variable. Relative risk and risk differences will be derived using marginal standardisation, as in Kirkwood et al [10]. Under this approach, the mean risk under the control condition and intervention condition is obtained. The risk ratio is then derived using the mean risk in intervention condition and by the mean risk in the control condition, with the calculation being performed on the log scale. The risk difference is derived as the mean risk in intervention condition minus the mean risk in the control condition. We will use the unconditional standard errors to obtain the confidence interval, as this allows for correlation amongst the observations. Point estimates, 95% confidence intervals and exact p-Values will be reported. Estimation of the relative risks and risk differences, and their standard errors and confidence intervals

will be carried out using the 'margins' command in Stata, as this method has not been implemented in SAS.

If the full mixed effects model fails to converge, we will follow the sequence of analyses:

1. Remove the random facility by period effect and fit a mixed effects model with random effect for facility only.
2. If this model also fails to converge, we will perform a cluster level analysis weighted by cluster size, calculating a cluster-level summary statistic for the pre-randomisation period and post randomisation period separately.

Queries will be raised where daily reporting of aggregate data appear to be inconsistent within care areas (e.g. a care area has reported births on one day but not the next) or where days with reporting are missing within the week.

Covariate data (country and facility size) will be complete. Country is known for each cluster and facility size is based on the number of births per cluster per week in the pre-randomisation phase.

Additional analysis

Subgroup analyses will be carried out by including a treatment group by subgroup interaction parameter in the regression model and reporting adjusted treatment effects with 95% confidence intervals. Treatment effects will be compared between subgroups using ratios of ratios using post-estimation commands. Results of subgroup analyses will be interpreted cautiously. Subgroups will include country, facility size and month of post intervention roll-out period.

Intracluster correlation coefficients and cluster autocorrelation

Estimates of ICC and CAC will be calculated on the proportion scale by fitting multilevel linear models to the binary data. Within-period ICCs for the pre-randomisation and post-randomisation periods, and between period CAC will be reported.

25.2.3 Secondary Outcomes

All secondary outcomes are binary and will be analysed using the same methods as the primary outcome. Treatment effects and confidence intervals will be presented, but these outcomes will not be subject to statistical testing.

25.2.3.1 Components of the composite primary outcome

The three components of the composite primary outcome (infection related maternal mortality, infection related maternal near-miss and severe infection related morbidity (deep surgical site infection or body cavity infection), will each be analysed individually using the methods described in section 25.2.2.

25.2.3.2 Stillbirth

25.2.3.2.1 Derivation

Stillbirth is collected on the 'Facilities' database within the instrument named 'Daily Form Area' under the following variables: 'Fresh stillbirths' and 'Macerated stillbirths. These variables are collected daily.

25.2.3.2.2 Analysis

This outcome will be analysed using the methods described in section 25.2.2. The denominator for this outcome will be the sum of all live births and still births.

25.2.3.3 Early neonatal death (infection related and total)

25.2.3.3.1 Derivation

Early neonatal death is collected on the 'Facilities' database within the instrument named 'Daily Form Area' under the following variables: 'Neonatal deaths (inpatients) <28 days after delivery (infection related)' and 'Neonatal deaths (inpatients) <28 days after delivery (not infection-related)'. These variables are collected daily. Total neonatal deaths will be calculated by the summation of the two variables.

25.2.3.3.2 Analysis

This outcome will be analysed using the methods described in section 25.2.2.

25.2.3.4 Maternal mortality (any cause)

25.2.3.4.1 Derivation

This outcome is present where the event details form indicates that the participant has died and gives a date of death.

25.2.3.4.2 Analysis

This outcome will be analysed using the methods described in section 25.2.2.

25.2.3.5 Maternal severe acute respiratory infections

25.2.3.5.1 Derivation

This outcome is present where the event details form indicates that any cause of death or near miss is infection related, and the suspected type of infection is selected as either "Respiratory infection" or "COVID-19"

25.2.3.5.2 Analysis

This outcome will be analysed using the methods described in section 25.2.2.

25.2.3.6 Quantitative implementation outcomes

25.2.3.6.1 Derivation

Quantitative implementation outcomes are measured in all APT-Sepsis and control facilities.

- compliance with hand hygiene (as per WHO 5 movements of hand hygiene standard assessment)
    - proportion of observed hand hygiene opportunities which were taken
- correct use of antibiotic prophylaxis for prevention of peripartum infection (as per WHO guidelines),
    - proportion of caesarean sections given antibiotic prophylaxis
- complete vital sign recording at admission
    - proportion of in-patients with complete vital signs recorded at admission
- Sepsis management compliance:
    - proportion of infection cases with complete vital signs recorded
    - proportion of infection cases given fluids within 1 hour
    - proportion of infection cases given antibiotics within 1 hour

25.2.3.6.2 Analysis

All implementation outcomes are only measured in the post-intervention period, with each site receiving three visits to assess these outcomes. Analysis will focus on the cluster level, with cluster-level outcomes being calculated as proportions at each of the three visits. Analysis will use mixed-effect

repeated-measures linear regression models to compare APT-Sepsis and Control sites. Country, and the minimisation factor facility size will be included as covariates.

26 Safety Evaluations

The primary and secondary outcomes are all related to safety, and other outcomes. Other safety outcomes, that may potentially be influenced by the intervention, such as caesarean section rates, are presented descriptively as described above in the Facility and Patient characteristics section.

27 Additional Analyses

There are no planned additional analyses. We are not collecting information on individual women who did not experience a severe infection, near-miss or maternal mortality therefore a fully covariate adjusted analysis will not be possible.

28 Document History

Statistical Analysis Plan Version	Protocol Version	Section number(s) changed	Description of changes	Justification for changes	Date Implemented
2.0	Malawi: version 6.0 07/11/2024 Uganda: version 3.0 07/11/2024	25.2.3.4.1	Changed the derivation of the outcome to use the patient database rather than the facility database	The derivation was incorrect, the maternal mortality outcome should be based on deaths recorded in the patient database, rather than summary numbers in the facility database.	04/08/2025

29 References

29.1 Non-standard statistical methods

29.2 Data Management Plan

APT-Sepsis Data Management Plan V2.0 (22/10/2022)

29.3 Trial Master File and Trial Statistical File

APT-Sepsis Trial Master File

APT-Sepsis Trial Statistical File

29.4 Other Standard Operating Procedures to be adhered to

LCTC_ST005: Statistical Programmed Data Checks

29.5 Other references

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