STUDY TITLE: The Active Prevention and Treatment of Maternal Sepsis: A cluster randomised, hybrid implementation effectiveness trial, to improve prevention and management of maternal sepsis in health care facilities in Malawi.

STUDY ACRONYM: APT-Sepsis study

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EXECUTIVE SUMMARY

Type of the study

Hybrid implementation/effectiveness trial. Multi-country, parallel cluster randomised trial with baseline phase.

Setting

Healthcare facilities in Malawi will participate, as part of a multi-country study.

The problem

Maternal infections and sepsis are reported to cause 11% of direct maternal deaths (1), and recently the WHO GLOSS (Global maternal Sepsis) study, although based on small numbers, suggests maternal infection may contribute to over half of all intra-hospital maternal deaths (2), with by far the greatest burden borne by women in Low- and Middle-Income Countries (LMICs). There is an urgent need to identify ways to combat this problem which are implementable at scale, and are clinically effective, cost effective and sustainable. This study aims at assessing the effectiveness of implementing APT-Sepsis bundle which is the quality of care for mothers, and adherence to WHO evidence-based practices in infection prevention and management. APT-Sepsis is a carefully developed programme designed specifically to be used in countries and facilities where there are limited resources available. APT-Sepsis aims to change health care workers' behaviours to ensure mothers get the best care possible to better prevent and manage infections.

Broad Objective

The broad objective of this study is to examine if the APT-Sepsis programme is effective at reducing infection related maternal mortality and severe maternal morbidity, at any time prior to discharge from health care facilities in Malawi and Uganda.

Specific Objectives

The specific objectives are, to evaluate if the APT-Sepsis programme is effective at reducing secondary clinical outcomes of stillbirth, early neonatal death, maternal mortality, maternal near miss; to explore differential or subgroup effects of the APT-Sepsis programme; to understand the implementation of the APT-Sepsis programme in Malawi, to facilitate interpretation of trial outcomes and development of a longer-term implementation strategy; and finally to determine if the APT-Sepsis programme is cost effective.

Methods

The study is a multi-country, parallel cluster randomised trial with a baseline control phase. There is an integrated implementation evaluation and health economic evaluation. The overall trial will include clusters in Malawi and Uganda, each of which is a health facility. This protocol specifies the activities to be conducted in Malawi. During the first six months each cluster will continue with their current practices and data will be collected to establish weekly rates of maternal infection and mortality. After the baseline period, the clusters will be

randomly allocated in a 1:1 ratio to the APT-Sepsis programme or current practice with passive guideline dissemination, using a minimisation algorithm. The intervention seeks to change the behaviours of health care providers to improve adherence to WHO guidelines and best practice in infection prevention and management, and detection and management of maternal sepsis.

Expected Findings

In this study, we anticipate implementing the APT-Sepsis programme across 15 randomised sites in Malawi. We hope that staff will engage fully with the programme and improve their adherence to WHO recommendations for evidence-based practice in maternal infection prevention and management. If successful we will offer the intervention to all sites, including control sites.

Dissemination

The study report will be submitted to College of Medicine Research and Ethics committee (COMREC), and College of Medicine Library. Research findings will be disseminated via download on relevant websites and will also be shared with both and global stakeholders. This will be done through research dissemination conferences, peer reviewed publications and via participant and public information groups, national and international forums.

GLOSSARY

AE	Adverse Event
CI	Chief Investigator
COM-B	Capability, Opportunity, Motivation-Behaviour Model
CRF	Case Report Form
EDD	Expected Date of Delivery
FAST	Fluids, Antibiotics, Source identification and Transfer
FAST-M	Fluids, Antibiotics, Source identification and Transfer and Monitoring
GCP	Good Clinical Practice
HCP	Health Care Professional
HIC	High Income Countries
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
LCTC	Liverpool Clinical Trials Centre
LIC	Low Income Countries
MRC	Medical Research Council
NICE	National Institute for HealthCare Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
PII	Personal Identifying Information
PICF	Participant Information and Consent form
PIS	Participant information Sheet
PPI	Patient and Public Engagement Group
QA	Quality Assurance
QALY	Quality-adjusted life year
QC	Quality Control
REC	Research Ethics Committee
RM	Research Midwife (Registered)
RN	Research Nurse (Registered)
SDG	Sustainable Development Goal
SDV	Source Data Verification
SOFA	Sequential Organ Failure Assessment score
SOP	Standard Operating Procedure
TDF	Theoretical Domains Framework
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

UN	United Nations
WHO	World Health Organisation

1 INTRODUCTION

Infections and sepsis are reported to cause 11% of direct maternal deaths (1, and recently the World Health Organisation (WHO) GLOSS (Global maternal Sepsis) study, although based on small numbers, suggests maternal infection may contribute to over half of all intra-hospital maternal deaths (2), with by far the greatest burden borne by women in Low- and Middle-Income Countries (LMICs). International organizations such as the WHO are committed to reducing the numbers of women who die during pregnancy, childbirth and postpartum. Tackling maternal sepsis is an important part of this effort. However, there is an urgent need to identify effective ways to combat this problem. Reducing maternal mortality to reach the Sustainable Development Goal (SDG) target of less than 70 deaths per 100,000 births requires a comprehensive response (3).

The Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) is a carefully developed programme designed specifically to be used in countries and facilities where there are limited resources available. It aims to change health care workers behaviors to ensure mothers get the best care possible to better prevent and manage infections. The programme will improve care by ensuring that health care workers:

1. Always wash their hands to prevent the transmission of infections,
2. Prevent and manage infections by following WHO guidelines on infection prevention and management during pregnancy and birth.
3. Detect sepsis early by carrying out regular vital sign monitoring and act rapidly to ensure women with suspected sepsis are given all the correct initial treatments using a specially developed maternal sepsis treatment "bundle".

This approach helps provide local healthcare facility staff with the information, motivation and tools needed to reduced sepsis. We will provide training delivered by expert teams at the local facilities. We will provide paper-based checklists and reminders and create a network of local Champions. Champions will help encourage change and provide ongoing feedback and coaching, involvement of the cluster management, re-organising sharing of tasks between healthcare facility staff and helping motivate clusters and individuals.

Extensive formative work has been conducted to co-develop the intervention and tools. This includes pilot studies across 15 health facilities in Malawi (which will not be eligible for inclusion in APT-Sepsis). The sites demonstrated large improvements in the detection and management of maternal sepsis: the percentage of women with a complete set of vital sign observations on admission rose from 0% at baseline to 77.4% after 6 months, and the percentage of those with suspected sepsis who received antibiotics within 1 hour rose from 13.3% to 64.0%. The qualitative evaluation (35 semi-structured interviews and 9 focus groups) provided insights into the process of implementation, that have been integrated into the APT-Sepsis programme (4) A further pilot

study was conducted across three sites in Malawi evaluating the introduction of the adapted WHO multi-modal hand hygiene improvement strategy alongside the other components of APT-Sepsis. The programme increased hand hygiene compliance from less than 10% at baseline to greater than 80% post intervention. The mixed-methods evaluation provided insights into locally appropriate adaptations that could be used to improve individual and institutional behavioural change. Innovative features include the use of role play, dance and low-cost ultraviolet light visualisation of hand hygiene performance (5) but these studies were not powered to evaluate differences in clinical outcomes.

To understand if the APT-Sepsis programme reduces women dying or having the most severe infections we will conduct an appropriately powered, randomised clinical trial. Working with 64 health care facilities in Malawi and Uganda, we will collect data prior to the implementation of APT-Sepsis and then 15 health care facilities in each country will be randomised to test the APT-Sepsis intervention the remaining facilities will continue their usual practices.

Facilities randomised to APT-Sepsis will then receive the intervention, including the site initiation, health care staff training and materials. Subsequently there will be a 3-month transition period whilst these practices are well established and then a further 9 months during which time we will monitor and compare the outcomes in the facilities (clusters) taking part in APT-Sepsis and those where usual practice is continuing. We will examine in detail the way the programme is implemented. This will involve measuring the way in which the APT-Sepsis intervention is implemented in practice, understanding the influence of modifying and contextual factors on this. This part of the evaluation will involve monitoring what is happening at the facilities, conducting surveys, reviewing the processes of care and detailed interviews to understand the opinions of the HealthCare facility staff and HUB team members.

2 RATIONALE

Maternal sepsis is one of the major causes of maternal mortality and morbidity. Although maternal death due to sepsis is the final devastating event, the origins of the problem lie in multiple areas of poor quality of care including inconsistent infection prevention, poor infection management, delayed diagnosis of sepsis, and inadequate sepsis management. The APT-Sepsis intervention brings together evidence-based practice to address these issues via an integrated programme with three interventional domains and an implementation strategy.

3 OBJECTIVES

3.1 Broad objective

To examine the implementation of the APT-Sepsis programme and understand if it is effective at reducing infection related maternal mortality and severe morbidity in resource limited settings.

3.2 Specific objectives

1. To examine if the APT-Sepsis programme reduces maternal infection related mortality and severe morbidity. This primary outcome will be a composite of infection related maternal mortality, infection related maternal near-miss or severe infection related morbidity.
2. To evaluate the effectiveness of the APT-Sepsis programme in reducing secondary clinical outcomes of stillbirths, early neonatal death, maternal mortality, and maternal near miss.
3. To explore differential or subgroup effects of the APT-Sepsis programme by country, facility size and fidelity of implementation.
4. To understand the implementation of the APT-Sepsis programme through a process evaluation, facilitating interpretation of trial outcomes and longer-term implementation strategies
5. To determine the cost-effectiveness of the APT-Sepsis programme

4 METHODS

4.1 Type of the study

The study is a multi-country, parallel cluster randomised trial with a baseline control phase. There is an integrated implementation evaluation and health economic evaluation. The trial will include 33 clusters from Malawi, each of which is a health facility.

During the first six months each cluster will continue with their current practices and data will be collected to establish weekly rates of maternal infection and mortality experienced which will act as baseline period.

After the baseline period, the clusters will be randomly allocated in a 1:1 ratio to the APT-Sepsis programme or current practice with passive guideline dissemination, using a minimisation algorithm. There will be a three-month transition period during which the APT-Sepsis programme will be introduced to the clusters randomised to the intervention. Data collected during the three-month transition will not contribute to the analysis.

The intervention is delivered at a health facility level and targets the health care providers and systems within the facility. The intervention seeks to change the behaviours of health care providers to improve adherence to WHO guidelines and best practice in infection prevention and management, and detection and management of maternal sepsis.

The post-randomisation phase (including the transition period) will be for a period of twelve months. A detailed understanding of how the intervention is operationalised in practice, will be assessed from a behaviour change perspective.

In the final months of the study, we will complete the data analysis and work with the PPI team and Maternal Sepsis Support groups to disseminate the information about findings.

5 STUDY PLACE

The study will be conducted in at least 33 health care facilities across Malawi**.** These health care facilities are anticipated to include: Balaka district hospital, St Gabriel mission hospital, Chikwawa district hospital, Chiradzulu district hospital, Holy Family mission hospital, Phalombe district hospital, Dedza district hospital, Mulanje mission hospital, Malamulo mission hospital, Thyolo district hospital, Karonga district hospital, Kasungu district hospital, Monkeybay community hospital, Machinga district hospital, Mangochi district hospital, Mchinji district hospital, Mulanje district hospital, Mwanza district hospital, Mzimba South district hospital, Ekwendeni mission hospital, Nkhata Bay district hospital, Nkhotakota district hospital, Ntcheu district hospital, Ntchisi district hospital, Rumphi district hospital, Salima district hospital, St Lukes mission hospital, Pirimiti mission hospital, Lisungwi community hospital, Nkhoma mission hospital, Nsanje district hospital, Mua mission hospital, and Mlambe mission hospital. Participating health care facilities have been identified and selected following a suitability assessment process (para 4.4) performed by the Malawi study teams in collaboration with the Ministry of Health.

We will invite a minimum of 33 facilities to commence the baseline data collection phase, this enables a contingency of 2 facilities. In case any facilities chose to withdraw, or they are identified as unable to fulfil the inclusion/ exclusion criteria i.e. less than 1500 annual deliveries are anticipated during the initiation or baseline phase. We will attempt to add additional facilities to compensate, provided there is sufficient time remaining to collect the data required prior to randomisation.

The trial will include 64 clusters, at least 33 of which are health facilities in Malawi.

5.1 Selection of Participating Facilities

Facilities with at least 1500 births and provide that providing comprehensive obstetric care and are willing to participate will be included in the study.

Prior to study commencement, in collaboration with the ministries of health, the district health management team, or other appropriate facility governing bodies discussions will be undertaken to identify healthcare facilities suitable for participation in their areas.
After which identified facilities will be visited and a “site readiness assessment” will be completed with the country hub team, facility leadership and clinicians. Human and physical

resource available at the facilities will be assessed as part of the site readiness assessment process with the aim to ensure that other resources required to enable the intervention to function are routinely available. This will ensure that the minimum prerequisites are met, including minimum basic human and physical resources to enable participation in the programme. Healthcare facilities that meet the selection criteria will then receive training in preparation for the baseline data collection. This will be described in a separate document and Site Suitability Assessment' maintained in the Trial Master File (TMF).

Healthcare facilities fulfilling the trial-specific criteria will be selected to be a cluster for the APT-Sepsis study and will be opened upon successful completion of all global approvals and study-specific conditions (e.g., Ethics and facility personnel training requirements) and once all necessary documents have been returned to the LCTC.

5.2 Project officers

Each participating healthcare facility will identify and assign a project officer(s)/research assistant who will provide local leadership and be responsible for the collection of the study daily and weekly facility data. Project officers will ideally be local staff members working in the facility, but who are currently working in maternal health and therefore are expected to undertake the APT-Sepsis training package, if the facility is randomised to the intervention. Project officers will collect data during the baseline. This is to ensure that they are familiar with the eCRF, identification of cases, locality structures and to minimise influence during implementation phase by any training received for sepsis identification.

Each Project Officer will receive training prior to the start of the baseline period. Training will include background study information and guidance for data completion and capture. The Project officers will report to the APT-Sepsis country specific HUB team and trial co-ordinator. The Trial co-ordinator will communicate with the project officers regularly offering guidance, support, and a central point of contact for any study related issues encountered. In some facilities a Data Collection officer may also be required to support the project officer with data collection.

5.3 Champions

In healthcare facilities randomised to the intervention approximately 5 to 12 Champions will be identified by the local management team. The Champions will be from a range of staff including for example medical officers, Midwives, Pharmacists, Laboratory staff, Healthcare support workers and others who work within maternal health. The Champions will be enthusiastic about maternal health improvements and willing to undertake the APT-Sepsis training and train others.

6 STUDY INTERVENTIONS

APT-Sepsis is a complex intervention, developed to target care provider's behaviours across the care continuum, culminating in adherence to best practice in prevention and management of maternal sepsis. The behaviours targeted are:

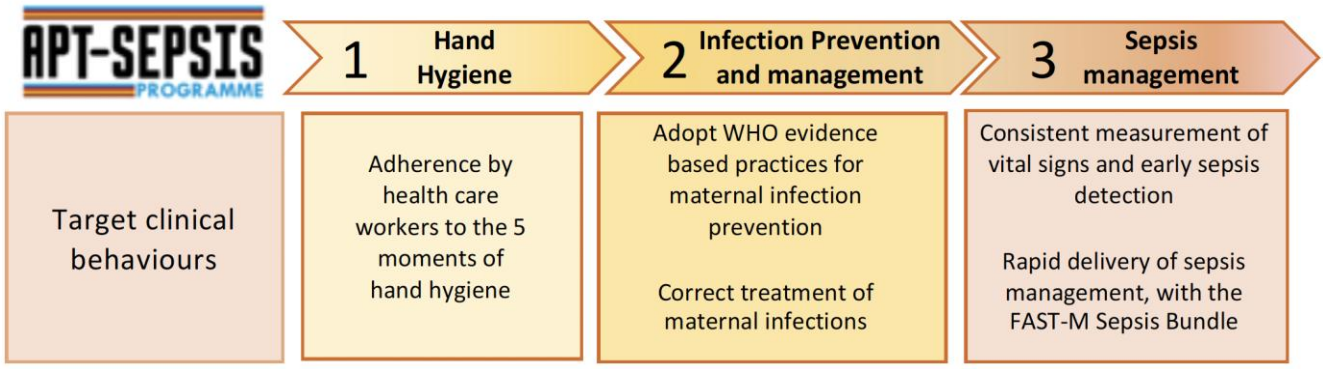

Figure 1. APT-Sepsis programme intervention overview

1) "hand hygiene", which consists of implementing a modified version of the WHO multimodal hand-hygiene strategy adapted for low resource, maternity settings.
2) "Infection prevention and treatment" which entails compliance with evidence based best practice around antibiotic prophylaxis, infection treatment and surgical practices.
3) "Sepsis management" which consists of ensuring comprehensive vital sign monitoring of all inpatients, early detection of suspected sepsis and triggering of the FAST-M maternal sepsis bundle.

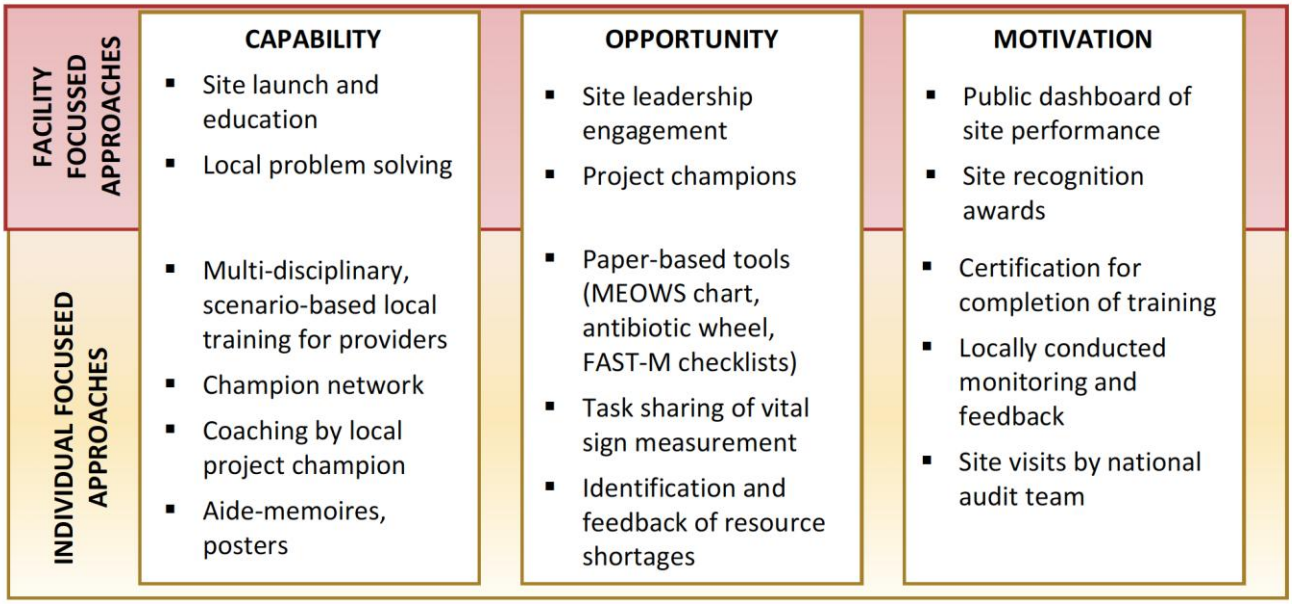

Figure 2. Summary of co-interventions that seek to support health care provider behavioural change

7 CLUSTER SUPPLIES AND STANDARD OF CARE

The intervention seeks to change health care behaviours to promote adherence with best practice. This will require incorporation of the implementation components into care pathways in the intervention clusters. However, we will not be enforcing compliance with these components but will seek to support positive behaviour change through the intervention and then assess compliance during the process evaluation.

The intervention has been developed to be feasible to implement in a low resource setting. However, the intervention requires some specific resources such as paper-based tools, posters, training materials etc. and these will be provided as part of delivering the intervention.

The study will continue to monitor such resource availability on a weekly basis in all clusters throughout the study. We will provide information around resource limitations to the ministry of health and support their efforts to provide appropriate resources irrespective of the cluster allocation to the intervention or control group. We will record and report all variations in resource availability during the study.

8 STUDY PERIOD

The study will take an estimated patient months to complete.

Task	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan - Jun23	July - Sep23	Oct23 - Feb24	Feb24 - April25	May25-Oct25
UoL Sponsorship																	
COMREC Ethics (Malawi)																	
UoL Ethics Submission																	
Baseline phase																	
Randomisation																	
Training of champions, site staff																	
Transition phase																	
Intervention phase																	

Task	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan - Jun23	July - Sep23	Oct23 - Feb24	Feb24 - April25	May25-Oct25
Process evaluation																	
Data Analysis																	
Write up and publication																	

8.1 Study Implementation phases

8.1.1 Baseline Period

The Baseline period will last at least 6 months during which time comprehensive data collection will be undertaken. Facilities in each country will start their baseline periods over a period of three months, with start times staggered. Initial analysis of baseline data to determine cut points for the minimisation factors will take place after 4 months, with at least 4 months of data available for the first facilities allocated, and at least 2 months of data for all facilities (average weekly rates of the primary outcome and number of births will be collected). Allocation to test or control using minimisation will be staggered with each facility (cluster) being allocated during month 5 of their baseline period at the earliest. The baseline period will continue for a further month once allocation is known to allow facilities to prepare for implementation.

8.1.2 Randomisation Process

Facilities will be allocated to the APT-Sepsis intervention, or continuation of usual care, using a secure web-based minimisation program managed centrally by the LCTC.

A personal username and password provided by the LCTC will be required to access the system, which will be issued following training in the use of the system and signature on the delegation log. When a facility is ready to be allocated, the study co-ordinator (or other authorised person) will contact the study statistical team to confirm values of the minimisation factors (number of births per week and proportion of births with the composite primary outcome), based on data collected in the baseline phase. These can then be entered into the minimisation system. The allocation will be displayed on screen, and sent by email to the study co-ordinator, and principal investigator.

8.1.3 Transition Period

Once the research team are made aware of the randomisation allocation, the facilities (clusters) will be informed. Following the randomisation of clusters, the Project Officers will continue to collect data throughout the (lasting up to 3 months) transition phase regardless of the treatment allocation.

8.2 Intervention Implementation

8.2.1 Intervention Facilities

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 cluster by the HUB team. The APT-Sepsis training package,

materials and ongoing support will be provided to each randomised cluster. The healthcare facility will be allowed a transition (set up) period of three months, to complete the delivery of training to all relevant staff, and embed behaviour change and improved practices into routine clinical care.

8.3 Training

Following the interactive, scenario-based training delivered by the Champions with the HUB teams support (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 Champions will also provide performance monitoring and feedback, and will be encouraged to share best practice and learning across their network. The changes at a cluster are supported by reminder posters and aide memoires and practitioner actions guided by paper-based tools and checklists. Task shifting of vital signs observations to patient attendants (with appropriate training and support) was highly acceptable and effective in improving vital sign monitoring compliance. Clusters are launched with full engagement of the leadership and performance will be displayed on a public noticeboard by the local Champion and supported by the HUB team. Provider motivation is encouraged through recognition of achievements and feedback from the project champions and national team. The full implementation approach is manualised to ensure consistency across clusters and countries.

8.4 Language Considerations

English is the designated language of healthcare teaching, provision and medical records in both Malawi and Uganda.

Most healthcare workers speak English, but at all training sessions there will be trainers who are bi-lingual in both English and local languages as required, to ensure comprehensive understanding and ensure no staff are excluded from participating. For staff groups in which English is less likely to be their chosen language, such as clerical or auxiliary workers, then special attention will be given to ensuring that they have access to training in an appropriate format and language to maximise accessibility.

Participant information sheets and consent forms are available in both English and appropriate local languages where required. Attached in appendixes A English, B Chichewa, C Tumbuka to be used in this study.

Any other training materials where it is deemed by the country HUB that understanding would be improved by also offering additional language versions then these may be translated from English into the most appropriate local language.

8.5 Control Facilities

Facilities not randomised to the APT-Sepsis package will continue with local practice. but will be provided with printed WHO guidelines that inform the APT-Sepsis programme (passive guideline dissemination).

Monitoring of study outcomes will be conducted in an identical manner at the control facilities. This will include understanding any contextual changes in facility practices or policies that could impact on the trial outcomes, and monitoring for contamination of the control clusters with elements of the intervention. The local team Project Officers and HUB will monitor the introduction of any changes introduced and record their onset date.

9 IMPLEMENTATION EVALUATION

Key quantitative implementation outcomes will also be reported alongside the comparative analysis. These are compliance with hand hygiene (as per WHO 5 moments 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 (4), and FAST-M bundle compliance (10).

In addition, a mixed-methods process evaluation will be undertaken to explore further implementation outcomes and provide a rich and detailed understanding of the process of implementing the APT-Sepsis programme. These findings will also inform more accurate interpretation of trial outcomes, and development of a longer-term implementation and scalability strategy.

The process evaluation will be based on the four components of the MRC Process Evaluation guidance (11) (Figure 1 and 4) and the Proctor et al. implementation outcomes framework (12).

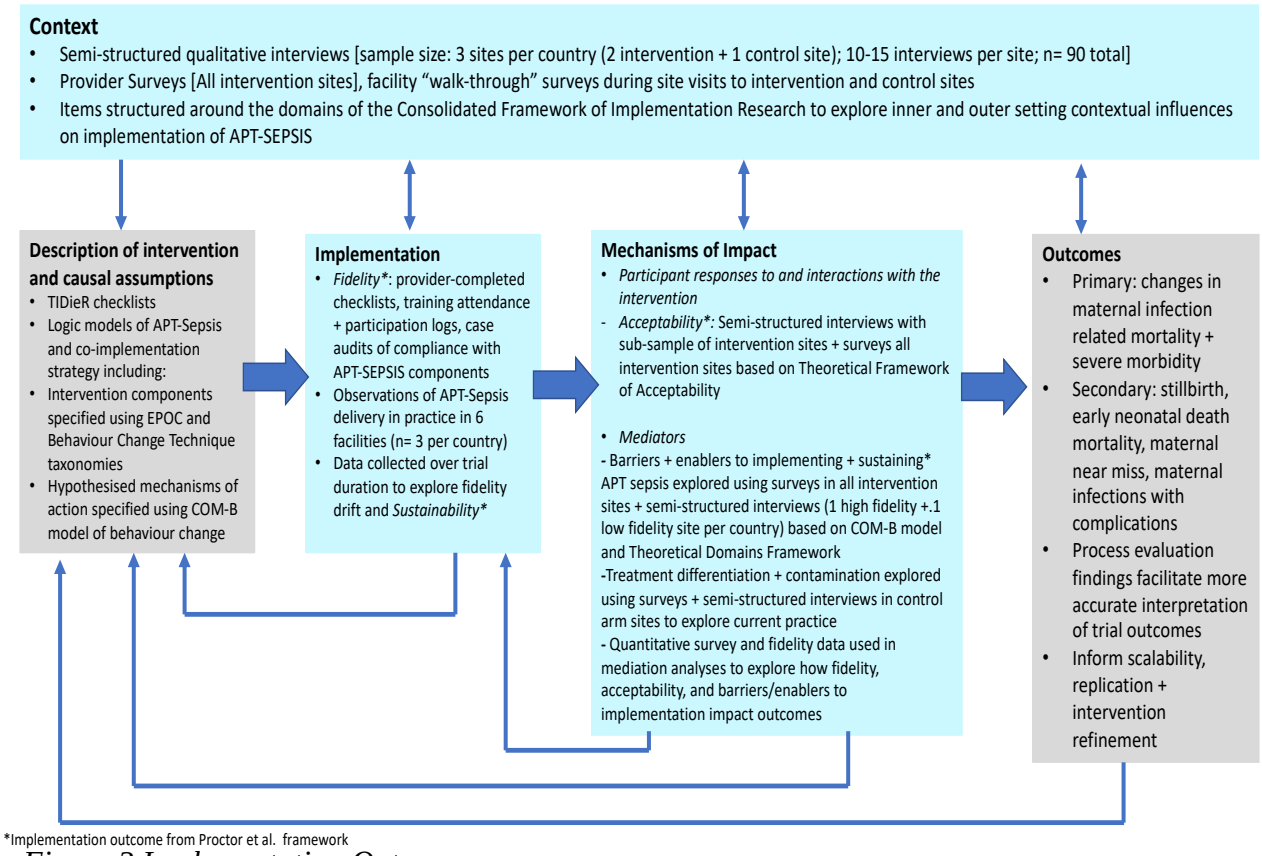

Figure 3 Implementation Outcome

1) Description of the intervention and causal assumptions: APT-Sepsis and the implementation co-intervention strategy will be described in logic models and using TIDieR checklists. Intervention components will be specified using the Behaviour Change Wheel and Behaviour Change Technique Taxonomy. Hypothesised mechanisms of change will be specified according to the COM-B model and Theoretical Domains Frameworks (TDF) (13,14).

(2) Implementation: Fidelity and Sustainability will be assessed in all participating facilities quantitatively using: APT-Sepsis delivery checklists, training attendance and participation logs, and case audits of compliance with hand hygiene, antibiotic prophylaxis and sepsis management guidelines. Data will be collected over the trial duration to explore possible loss of fidelity over time and extent to which implementation is sustained. Mediation analyses will explore relationships between extent of fidelity and trial outcomes. In a sub-sample of six clusters (n=3 per country), we will conduct observations and take field notes of training delivery and APT-SEPSIS in current practice.

(3) Mechanisms of Impact: Acceptability of APT-Sepsis and the implementation co-intervention will be assessed quantitatively in all intervention clusters using surveys based on a framework of intervention acceptability (15).

(4) Context: To assess inner and external contextual factors that may help or hinder implementation of APT-Sepsis, the aforementioned surveys and interviews will include items based on the Consolidated Framework of Implementation Research (16), which includes domains related to inner- and outer-setting.

Surveys will be summarised using descriptive statistics as appropriate, and responses compared across facilities and HCP roles. Interviews will be analysed using combined deductive framework and inductive thematic analysis (13).

10 HEALTH ECONOMICS

The objective of the economic evaluation is to compare the cost-effectiveness of APT-Sepsis against usual care. This will be done from the healthcare provider perspective.

We will perform a cost-consequence analysis in the first instance, based on costs and outcome for both trial arms and presented in a disaggregated summary format on the cost-effectiveness plane. We will use bootstrapping to derive cost-effectiveness acceptability frontiers. The distribution of costs and outcomes and missing data, censoring and correlations between costs and outcomes will be explored. Multiple imputation will be used for missing data.

We will explore the extent to which is feasible or appropriate to conduct an incremental cost effectiveness analysis presented in terms of cost per quality-adjusted life year (QALYs using WHO weightings. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions and analytical methods used, and to consider the broader issue of generalisability of the study's results.

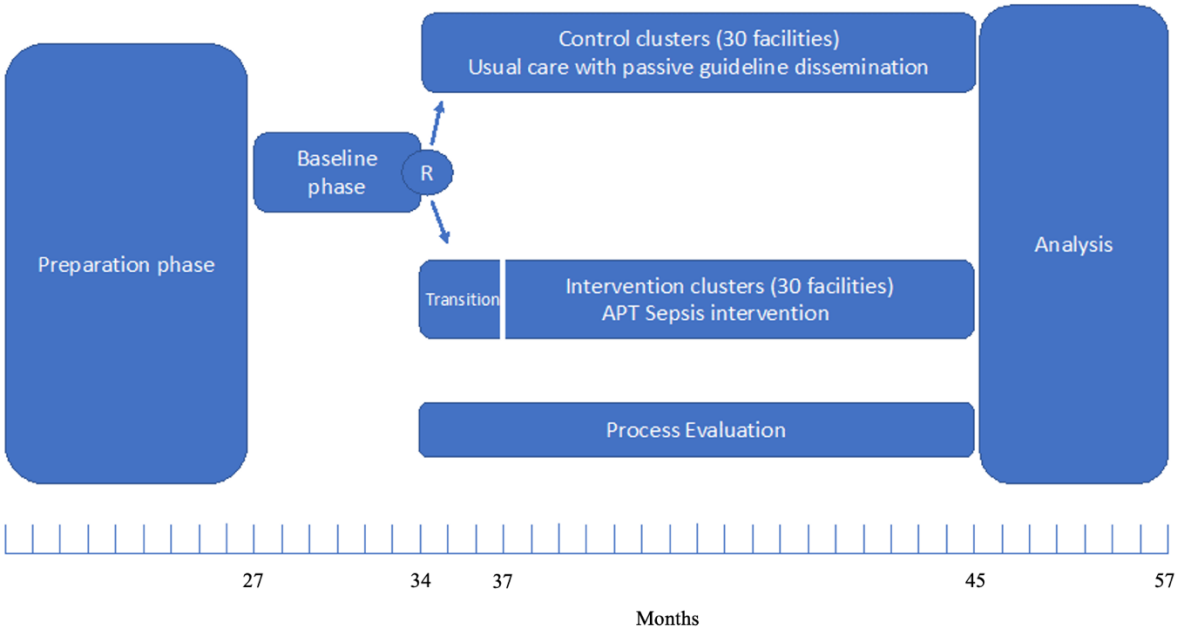

Figure 4 schematic of study design

11 SAMPLE SIZE

Power calculations have allowed for the clustered nature of the design (6). 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 (6). 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 [7]. 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, 8)

11.1 Original Sample Size Calculation

To this end, we 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, 9) 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.

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.

11.2 Revision of sample size calculation

As planned the sample size calculation was revisited once the ICC, baseline event rate and number of participants per cluster was known from the baseline data. We simulated a range of scenarios as with the previous calculation using an ICC determined from the baseline period of 0.021, and number of patients per cluster based on figures from the baseline period. Based on this a shortening of the intervention period has a minimal effect on power, and with a revised intervention period of 12 months (3-month transition period, followed by a 9 month follow-up intervention period) we will still have at least 80% power to detect a relative reduction of 25% in most likely scenarios.

12 METHOD OF RANDOMISATION

12.1 Allocation Sequence Generation

Health facilities will be allocated to groups using a minimisation algorithm, to ensure balance of important factors between facilities allocated to the intervention and control groups. The minimisation factors will be:

Allocation will be stratified by country. The minimisation factors within each country will be:

1. number of births per cluster per week
2. proportion of births with the composite primary outcome

These will be measured at each facility within the baseline period. The cut points for the factors will be determined separately for each country using quantiles of the observed values within up to the first four months of the baseline periods: start dates will be staggered, we will have between two and four months of baseline data for each facility to determine cut-points. Facilities will be allocated no earlier than the fifth month of their baseline period, using their baseline data up to this point (at least four months for each facility).

The algorithm will be implemented using the minimisation option in the LCTC generic randomisation system, which has been fully tested and validated. The 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.

12.2 Eligibility Criteria

APT-Sepsis is a complex intervention, developed to target care provider's behaviours to improve adherence to best practice in prevention and management of maternal sepsis.

APT-Sepsis will recruit 64 clusters (sites) and based on sample size calculations described previously.

12.3 Inclusion Criteria for Clusters

Cluster: Health care facilities offering maternity care, will be included as a cluster following completion of a successful feasibility report requiring the minimum prerequisites of:

- A minimum of 1,500 births per year.
- Providers of a comprehensive emergency obstetric care (e.g., able to perform caesarean sections and blood transfusions).
- Completed the site readiness assessment process.

Research participant: Healthcare workers and managers responsible for the care of women during or after pregnancy in the study facility

12.4 Exclusion Criteria for Clusters

Cluster exclusion criteria: Facilities not willing to participate in the study

Research participant exclusion criteria: Healthcare workers not willing to consent to participation

12.5 Co-enrolment Guidelines

Clusters enrolled in the study may also seek to engage in other research activities. Details of local studies conducted will be collected by the Malawi or Uganda HUB teams and recorded so that any impact on APT-Sepsis can be assessed. After randomisation, the commencement of a new study in the cluster should be discussed with the HUB team, and Chief investigator to consider study impact.

13 QUALITATIVE DATA COLLECTION

We propose to conduct in-depth qualitative interviews in a sub-set of sites to explore how APT-Sepsis has been implemented and factors influencing this. We will purposively sample four clusters (facilities) to take part in the interviews: 2 per country (1 high fidelity, 1 low fidelity), and also a range of facility sizes and baseline outcome rates. In each cluster, we aim to conduct 10-15 interviews, totally approximately ~60 interviews across the four sampled clusters.

Interview participants at each cluster will be purposively selected to include a representative sample of roles across the leadership team, project champions, medical staff (doctors or clinical officers), midwives, patient attendants and other auxiliary or clerical staff. The number of interviews required per cluster has been estimated based on our prior formative work in which similar approaches were used to understand the implementation of the intervention during multi-site feasibility studies. However, the final samples size will be based on thematic data saturation, with further interviews conducted as necessary until no new themes emerge. Staff will be invited to participate in interviews which will be conducted at least three months following implementation to ensure that practice has been embedded.

The interview topic guide questions will be structured to explore barriers and enablers to delivering and sustaining APT-Sepsis and the implementation co-intervention. The interviews will also focus on broader areas of acceptability including key ethical principles of justice, beneficence and autonomy as well as identifying any unintended positive or negative effects of the intervention. Questions to explore barriers and enablers to delivering APT-Sepsis will be guided by COM-B and the Theoretical Domains Framework (TDF) (17, 18). This approach allows for a more detailed, investigation of the potential individual, socio-cultural and contextual issues influences on implementation.

We will also conduct 10-15 interviews with a purposive sample of healthcare providers (nurses, midwives, doctors) in the two control arm clusters (1 per country; n=30 interviews) to explore current maternal infection management and practice. This will enable us to explore extent of differentiation between intervention and control arms in terms of current practice and also identify any risk of possible contamination between intervention and control arms.

Lastly, we will also conduct either individual interviews or focus group with research staff in each country, who are part of the hubs responsible for helping to train and introduce APT-Sepsis in participating facilities, and to subsequently conduct the quarterly visits to observe implementation. This will provide an opportunity to hear about their experience of training and introducing facilities in APT-Sepsis- what went well, what was challenging, what changes were needed etc. As well as their impressions of how APT-Sepsis is being implemented across sites, both in terms of extent of implementation and their observations on any barriers and enablers to implementation. We will be flexible in conducting either interviews or focus groups, depending on what is most feasible and preferable to hub staff. There are a maximum of N=

14 hub staff (n=7 Malawi and N=7 Uganda), representing the maximum sample for the qualitative data collection with hub staff.

For all qualitative data collection across participant groups, any personal identifying information (PII) will be stored on a password-protected server and no PII will be shared beyond the research team. Following transcription and checking of transcripts for accuracy, all recordings will be deleted. Transcripts will be fully anonymised so that no individual or organisation can be identified from the data. Transcript data will then be coded and analysed in Excel and NVivo using a combination of inductive thematic analysis and deductive framework qualitative analysis methods.

If the outcomes require further sampling, then the inclusion of additional clusters for diversity will be considered. Analysis of the interviews will be undertaken by the local qualitative researchers, with support from the wider implementation process evaluation team. Results of this qualitative evaluation will be provided to local facility staff (Champions and Project officers) to inform and refine the implementation of APT-Sepsis programme.

13.1 Surveys

13.1.1 Facilities

A facility "walk-through" survey will be conducted by the study team during their quarterly visits with a focus on site infrastructure and human and physical resource availability. *Please See* Appendix GA and GB, a Quarterly site visit form to be used in the study.

A daily and weekly "facility form" will also be completed by the project officer to report facility level indicators and outcomes and other contextual changes such as human and physical resource availability over time, and any other critical policy or practice changes taking place at the sites during the study period. See attached on appendix H, a daily facility and appendix IA and IB, a weekly facility form to be used in the study.

13.1.2 Staff Surveys

Cross-sectional, electronic surveys will take place in all intervention clusters in each country (30 facilities total). We will engage the same range of health professionals as for the interview data collection (i.e. leadership team, doctors, nurses, midwives, project champions) . Surveys will be conducted at each quarterly visit over the 9-month intervention period (3-4 quarterly visits are estimated). We will aim to purposively recruit approximately 5 staff members at each intervention site per quarter. A total of 225 survey responses (5 responses x 3 quarterly visits x 15 intervention facilities = 225 responses total per country over the 9-month intervention period).

Staff surveys will include items which self-report their ability to adhere to the APT-Sepsis recommendations and goals, use of the resources and engagement with training, and barriers and enablers to practice change based on COM-B/TDF (13,14) models of behavioural change. We will also explore perceived acceptability of APT-Sepsis and broader contextual factors that can help or hinder implementation (e.g. leadership and organisational culture).

Survey responses will be entered directly on to a tablet or laptop using data compliant survey software. Responses may be collected offline and uploaded by project team. Responses will be pseudonymised – project staff will maintain a local record of respondent's name, job title and place of work to monitor the number of times a person completes the survey during the study. Respondents will be assigned a unique identification number. Only the identification number and corresponding survey responses will be sent to the Liverpool Clinical Trials Centre (LCTC). Although staff will be encouraged to complete these by the Champions, the Champions will not be able to access the information entered. The analysis plan will be described in a statistical analysis plan, but in summary participant responses will be summarised using descriptive statistics and compared across countries, facilities, participant roles, and over time (i.e. overly quarterly visits). Where data permits, we will explore association between implementation outcomes (i.e. perceived acceptability, different types of barriers and enablers) and extent of adherence to APT-Sepsis and variations in primary and secondary outcomes.

14 DATA MANAGEMENT AND ANALYSIS

For the APT-Sepsis trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical, and legal obligations.

15 SOURCE DOCUMENTS

An APT-Sepsis source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes APT-Sepsis-specific source data.

For the APT-Sepsis trial source documents will include site and theatre registers, birth registers, medical records, handover books and maternal death and near-miss reports. For study participants (healthcare workers trained in the APT-Sepsis intervention) it will also include diaries, responses to online surveys and interview transcripts. The APT-Sepsis case report form

(CRF) will be considered the source document for data where no prior record exists, and which is recorded directly in the bespoke electronic CRF.

Health facility staff will complete CRFs in each facility that will enable aggregate anonymised data to be reliably obtained from each facility. All data extracted will be entered onto the online database (REDCap) via the website or the REDCap app. Staff who are delegated to complete the CRFs will be trained to ensure high quality data collection that adheres to all study requirements. LCTC and the study investigators will not have access to any identifiable information for the records entered into the database.

15.1 Data collection methods

Data are to be entered into the database by members of the research team and project officers at site. Training will be provided prior to any data entry.

16 INTERIM ANALYSES

There are no planned formal interim analyses of outcomes or harms planned 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.

17 ANALYSIS PLAN

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

We will conduct an intention-to-treat analysis of the primary outcome. All observations (excluding those recruited in the transition phase) will be included in the analysis. Point estimates and 95% confidence intervals will be calculated for all outcomes. In the primary analysis, generalised linear mixed effects models incorporating a constrained baseline analysis, where both baseline and post-randomisation time points are included as outcomes, but with the treatment effect assumed to be zero in the baseline phase, will be used to calculate relative risk (using a log link binomial distribution) and risk differences. Cluster and cluster by period will be included as random effects, with country, and the 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). Significance will be set at $P<0.05$. Exact P Values will be reported. In the event that the mixed effects model fails to converge, we will consider excluding the random cluster by

period effect and/or the random cluster effect. Full details will be specified in the SAP. In the event of convergence issues, it will be made clear in the final report why these have occurred, and how this may affect the interpretation of the results.

A secondary analysis of the primary outcome will explore the effects of adjusting for additional covariates considered to be potentially associated with outcomes, such as urban/rural areas. These variables will be specified in the SAP. As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

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

17.1 Subgroup analyses

Pre-specified 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. Results of subgroup analyses will be interpreted cautiously. Subgroups will be detailed in the SAP and will include baseline factors such as country and facility size, as well as subgroups defined during the intervention phase such as high and low intervention fidelity.

Summary of study outcomes:

Primary Objective	**Primary Outcome Measures**	**Timepoint(s) of evaluation**
To examine if the APT-Sepsis programme is effective at reducing infection related maternal mortality and severe morbidity.	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).	Daily observation of the routine health facility records. From the Pre-implementation phase to the end of study. Outcomes will be collected from all women who are admitted* to the healthcare facility during pregnancy or within 42 days of delivery. Follow-up of events will occur for up to 28 days until death

Primary Objective	Primary Outcome Measures	Timepoint(s) of evaluation
	The primary outcome will be coded as 1 if any of these components occur, and 0 if none of them occur.	or discharge from a healthcare facility whichever is sooner

*Women who are dead on arrival at the facility (and therefore not admitted) will not be included in this study.

Secondary Objectives	Secondary Outcome Measures	Timepoint(s) of evaluation
To evaluate if the APT-Sepsis programme is effective at reducing secondary clinical outcomes of: Stillbirth, early neonatal death (infection related and total), maternal mortality (any cause), maternal near miss (any cause)	• Stillbirth, • Early neonatal death (infection related and total), • Maternal mortality (any cause), • Maternal near miss (any cause). • Maternal severe acute respiratory infections • Compliance with APT-Sepsis implementation	Daily observation of the routine health facility records. From the baseline phase to the end of cluster participation. Outcomes will be collected from all women who are admitted to the healthcare facility during pregnancy or within 42 days of delivery. Follow-up of events will occur for up to 28 days until death or discharge from a healthcare facility whichever is sooner.

Secondary Objectives	Secondary Outcome Measures	Timepoint(s) of evaluation
To explore differential or subgroup effects of the APT-Sepsis programme.	Sub-groups that have been specified are: a) country b) facility size (number of births) c) high v low performing facilities (defined by quantitative implementation fidelity assessment)	
Implementation: To understand the implementation of the APT-Sepsis programme in Malawi and Uganda, to facilitate interpretation of trial outcomes and development of a longer-term implementation strategy.	Implementation outcomes: Fidelity, Sustainability Acceptability, Understand the mediators of implementation including the impact of context	From the implementation of the intervention to the end of cluster participation.
Health economic analysis: To determine if the APT-Sepsis programme is cost effective.	The health economic analysis will be based on the principal outcome of the trial and be reported in terms of disaggregated costs and consequences and cost per major outcome averted where major outcome is defined as maternal infection related mortality and severe morbidity.	The data collection will be conducted during the period of study implementation. The economics analysis will take place in the last 13 months of the study.

18 TRIAL MONITORING

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g., enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities.

18.1 Central Monitoring

There are several monitoring features in place at the LCTC to ensure reliability and validity of the trial. Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

18.2 Clinical Site Monitoring

To perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g., patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol.
- discussing any emerging problems that may have been identified prior to the visit.
- checking CRF and query completion practices.

19 RECORDS RETENTION

The retention period for the APT-Sepsis data and information is 10 years from the official End of Trial date.

The PI in each country must arrange to store the essential trial documents (as defined by GCP guidelines) including the Investigator Site Files, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the LCTC on behalf of the Sponsor.

The PI is also responsible for archiving or noting the location of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g., in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

20 QUALITY ASSURANCE AND CONTROL

To assure protocol compliance, ethical standards, regulatory compliance, and data quality, as a minimum, the following will occur:

- The PI and all other country HUB staff, and site staff will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The independent members of the IDMC and TSC will provide oversight of the trial.
- The TMG will monitor trial progress and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan

21 SAFETY REPORTING

This trial seeks to implement recognised best practice at a health care setting level. The intervention seeks to improve compliance with WHO guidance and evidence based best practice around infection prevention and management, and therefore improve quality of care and health outcomes.

There are no novel treatments or medications being recommended in this study.

The basis of the intervention is to improve compliance with recognised best practice. These practices are already in use throughout the world, although they are unfortunately not consistently and reliably applied in all settings. Therefore, we do not anticipate adverse events as a direct consequence of the trial.

We recognise that in these settings there will be a range of important adverse outcomes as a consequence of infection and sepsis. Infection related adverse and non-infection specific outcomes (including death, near miss, severe morbidity and stillbirth and neonatal deaths) data will be measured throughout the study at every facility. Other outcomes, that may potentially be influenced by the intervention, such as caesarean section rates, will also be presented in the IDMC safety report. These outcomes will be monitored by the IDMC and reported by trial arm (the intervention is not blinded). The report content will be detailed in the IDMC charter.

Expedited reporting of individual events is not likely to provide any safety benefit as intervention effects are likely to be small compared to the background rate of such events and adjustment for clustering will be required to interpret if differences in death rates are due to the intervention.

22 PUBLICATION AND DISSEMINATION

The results from different participating sites will be analysed together and published as soon as possible, always maintaining participant confidentiality. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Study Trial Management Group (TMG).

We expect that at least the primary publication, implementation evaluation and health economic evaluation will be attributed to the "APT-Sepsis Collaborative Group". The TMG will advise on the basis of the writing committee, authorship details and the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The study registration number allocated will be attached to any publications resulting and members of the TOC will be acknowledged. Any

publications arising from this research will be reviewed internally by the TMG and peer reviewed by journals prior to publication.

Following the primary publications each participating site will be encouraged to conduct appropriate further analyses on their country data. The TMG should be informed of any planned additional analysis and publications that result. The APT-Sepsis collaborative group as well as the funder must be appropriately acknowledged. Study specific documents will be developed to ensure equitable and transparent plans for additional analysis that ensure inclusion of interested parties from the study team, with a special focus on leadership by junior researchers or PhD students supported through this study.

The PPI steering groups in each country will provide advice not only on trial design and materials but also, on how best to engage the public and on our messaging. In both countries we will establish peer support groups for women who have survived maternal sepsis. These will be facilitated by an experienced midwife and not only provide support for these women but also enable the trial team to maintain engagement with users at the sites and receive feedback on any concerns or issues. We have previously found Facebook to be an effective platform for engagement across the public and care providers in these settings and will again promote social media use to create a community who will act as advocates around maternal sepsis and an audience for the study findings.

We will give the sepsis survivors engaged through our PPI programme the opportunity to participate in sharing their sepsis. story in a video format, which with their explicit consent, will form part of a social media campaign to highlight the impact of maternal sepsis on mothers and their families.

23 AUTHORSHIP

As per ICJME guidance contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the APT-Sepsis Collaborative group which will also be named at the manuscript head. Named authors should include the study's Chief Investigator, country leads, Statisticians and study Managers and co-applicants involved as a minimum. Special considerations will be made to promote junior researchers and students, including those individuals identified for specific research capacity strengthening support, as lead authors in articles. Support for secondary analyses can be provided through institutions forming part of the HRP Alliance, including development of a research question and manuscript writing as well as statistical analysis. Considerations for equitable authorship (ensuring local authors lead on local analyses, considerations for gender of authors) will be made throughout.

24 DISSEMINATION TO KEY STAKEHOLDERS

Dissemination of the research findings is critical to maximise the benefits of the research and ensure findings reach the key stakeholders and change policy and practice if indicated.

Our communication strategy will be supported by the University of Liverpool communications team, and they will work collaboratively with the teams from Malawi-Liverpool-Wellcome Trust, the College of Medicine, Malawi, IDI, Uganda and WHO to maximise reach. This is supported by specific communication and dissemination funds. The PPI steering groups in each country will also provide advice on how best to engage the public.

Publications in peer-reviewed journals may result from this study. Results from this study will also be available via download on relevant websites and will also be shared with both local and global stakeholders through research dissemination conferences. To maximise the benefit from this research it is important that the findings inform policy, impact on practice globally. We are working closely with the World Health Organisation who have a vital role in determining health care policy worldwide. We will also ensure that we collaborate with the ministries of health in Malawi and Uganda to inform them of the research findings and implications for care and other key international stakeholders such as the Global Sepsis Alliance, FIGO and national professional organisations.

A copy of the final report and any published paper(s) or abstracts of papers outlining research findings will be submitted to The College of Medicine Research and Ethics Committee (COMREC), College of Medicine Library, and the College of Medicine and University of Malawi Research and Publication Committees (through the COMREC Secretariat).

25 DATA SHARING

The funder of the research Medical Research Council (MRC) also requires that open research data policy is applied this includes:

- Registering the trial on a public WHO-approved registry.
- Publishing the study protocol and statistical analysis plan.
- Publishing trial findings (within 12 months of completion).
- And sharing participant data (including individual-level data

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g., protocol, statistical analysis plan,

annotated blank CRF) will be prepared to be shared with external researchers. All requests for access to the IPD will be reviewed by an internal committee at the CTU and discussed with the Chief Investigator in accordance with the CTU policy on data sharing.

26 RESEARCH CAPACITY STRENGTHENING

Capacity strengthening is core to the planned proposal and to further solidify this we are collaborating with the Human Reproduction Programme (HRP) Alliance for Research Capacity Strengthening (RCS) at the World Health Organisation (WHO), a co-applicant in this proposal. By collaborating with the HRP Alliance for this study we are ensuring that RCS is integral to study conception and implementation. Working together with the large HRP Alliance network will provide opportunities for individual research strengthening as well as institutional strengthening. It will also provide opportunities for cost-sharing between institutions and networks, and opportunities for development for all collaborators. The linkage between implementing partners and the HRP Alliance are meant to exist beyond the timeframe of this study to ensure sustainable impact on RCS.

The HRP Alliance is comprised by a network of research institutions fostering research capacity strengthening globally. This is done primarily through seven RCS regional hubs located in different countries around the world (specific to this study there are three in Africa and one in South Asia), WHO Collaborating Centres, and HRP partners. HRP Alliance hubs are selected through a competitive process because of their experience in sexual and reproductive health and rights (SRHR) research as well as their expertise in building local research capabilities. One of the RCS regional hubs, catering the Eastern Mediterranean WHO region, is located at Aga Khan University. Additionally, the University of Liverpool is a WHO Collaborating Centre with a specific mandate to strengthen SRHR research capacity.

The HRP Alliance has experience supporting RCS through trainings, workshops, mentorship, fellowships led by the hubs and Collaborating Centres, while also providing financial support to doctoral and masters students to complete their studies in any of the RCS hubs. Similarly, the University of Liverpool, as a WHO Collaborating Centre, is also entrusted with supporting research capacity and can make resources available (via trainings, for example, or opportunities for fellowships) to individuals beyond this specific study team.

27 CAPACITY STRENGTHENING

Capacity strengthening will focus both on individual support as well as institutional support.

Dr Luis Gadama will continue to benefit from opportunities for training and mentorship from the HRP Alliance as his institution, Queen Elizabeth Central Hospital in Blantyre, Malawi, is already an HRP partner. Two Malawian PhD students have been appointed in Malawi, with fees fully supported by the University of Liverpool, and will benefit from the training opportunities as part of the HRP alliance.

Local study team members, especially junior researchers, will be encouraged and supported to conduct any further analysis of the data collected through this study or receive additional training through the HRP Alliance hubs in areas relating to maternal health research. A collaborative authorship model will be set in place, with priority given to local researchers and students using the data for their academic degrees. This will ensure that all collaborators can contribute fully and be recognised for their contribution at the publication stage.

Since institutional RCS is at the core of the HRP Alliance we would ensure that individuals engaged in this study contribute to local research strengthening at their home institutions. The link with the HRP Alliance will allow for institutional support by the hub in the Collaborating Centre at University of Liverpool, and other hubs located in Africa (African Population and Health Research Centre in Kenya and the University of Ghana School of Public Health in Ghana) and offer opportunities for future collaboration.

28 REGULATORY AND ETHICAL CONSIDERATIONS

28.1 Ethical Considerations

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC) in each participating country (Malawi, Uganda) and the United Kingdom where applicable for written approval. Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

APT-Sepsis will be conducted in accordance with the MRC guidance "MRC guidelines for management of global health trials (2017)" and the principles set out by the World Medical Association (WMA) in the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013) and Council for International Organisation of Medical Sciences (CIOMS) International Ethical Guidelines for Health-Related Research Involving Humans (2016). As APT-Sepsis is a cluster randomised trial, it will also be performed in accordance with the Ottawa Statement for the Ethical Design and Conduct of Cluster Randomised Trials (2012).

The Ottawa Statement sets out key ethical issues for cluster randomised trials. We use these to frame this section, with reference to the WMA Declaration of Helsinki), CIOMS and MRC guidance where appropriate.

28.2 Justifying the cluster randomised design

The choice of cluster randomised design must be justified, Ottawa statement, recommendation 1 (19). The cluster randomised design is required for APT-Sepsis as this intervention will seek to target health care providers to improve quality of care across a whole facility. The intervention changes systems of care that require changes across a facility and therefore it is not feasible to randomise individual practitioners or women to receive the intervention within a facility. Hence the cluster randomised design is essential in evaluation of the intervention and reduce the risk of cross contamination.

28.3 Research ethics committee review

In accordance with the Ottawa statement 2 (19), as the APT-Sepsis involves human participants (staff) then approval from research ethics committees in Malawi, and the UK will be sought in addition to WHO ethical approval.

28.4 Identifying research participants

The APT-Sepsis programme evaluates a behavioural change intervention that will seek to change the behaviour of healthcare facility staff in the study to improve compliance with WHO recommendations in infections prevention and management. As per Ottawa Statement 3 (19) the healthcare providers will be targeted by the intervention, including receiving additional training and providing feedback on how their practice has changed these healthcare providers are the research participants.

During this study the patients are not research participants. This is explained in the Ottawa statement that states, “simply being a patient or a professional participating in a cluster randomised trial of an educational, knowledge translation, or quality improvement intervention does not make one a research participant” (Ottawa statement 3 (19)). The CIOMS International Ethical Guidelines (20) agree: “In cluster randomised trials in which healthcare providers are the research subject, the intervention may not be targeted at patients, but aggregate data from patients’ records may be used to judge the effectiveness of the intervention…patients are not subjects in this type of study” (CIOMS 21) (20). This is the scenario in the APT-Sepsis trial in which there will not be researcher interaction with patients, with no additional information obtained specifically for the trial and no non-clinically indicated investigations, interventions or follow-up.

28.5 Obtaining informed consent

Informed consent will be sought from healthcare providers who participate in interviews, surveys, and complete diaries (Ottawa statement 7) (19). They will be given the APT-Sepsis information sheet and consent form if they are invited (detailed in section 21.6). Appropriately trained study staff will ensure that the staff can read and consider the information and ask any questions required to understand the implications of their involvement. This will include consent for their contact details to be collected. They will be free to either not participate or stop at any time without their rights or opportunities being affected. Similarly, they will have the opportunity to attend the training but then decline to provide any further feedback to the study team. They will be consented privately and without their supervisor being present and information about their participation, or not, in interviews will be kept confidential.

As patients are not research participants in the trial their informed consent in the APT-Sepsis study is not required. This is in accordance with the Ottawa statement, the CIOMS International ethical guidance and other multi-country trials studying similar health care worker behavioural change interventions.

28.6 Permission from "Gatekeepers"

"Gatekeepers" are individuals or bodies who may be called upon to protect the group-based interests that are affected by enrolment in a cluster randomised trial. (Ottawa Statements 8-10) (19). The APT-Sepsis trial will enrol a minimum of 64 health facilities in Malawi and Uganda. In each case permission will be obtained from the institutional leadership and Ministry of Health. (Ottawa statement 9; CIOMS 21) (19, 20).

These permissions will be obtained as part of the "site readiness" process. No activities will be carried out at the site until such written permissions are in place, and copies provided at the country HUB and copies also sent to LCTC.

28.7 Informed Consent Procedures

28.7.1 Individual patients

As patients are not research participants in the study, their informed consent is not required. The APT-Sepsis programme aims to improve staff compliance with best-practice, evidence-based care, as recommended by WHO and is optimising the care staff provide to patients. We anticipate that approximately 86,250 (total population 172,500) patients will receive care from staff with improved knowledge and understanding of best practices. Individual consent would therefore not be a practical and will not alter staff applying the knowledge and skills learnt to care for them.

All data collected is routinely gathered and measures the impact of the APT-Sepsis programme on health outcomes. Data will be reported at an aggregated facility level and the study will not

require individual patients to be interviewed or approached for study specific purposes. There are no commercial applications nor financial benefits resulting from the findings of this trial or the data collected.

28.7.2 Staff Training

Approval for trial conduct will be obtained from facility leadership teams prior to introduction of the APT-Sepsis study. This will include approval for staff training if the facility is randomised to receive the intervention. An attendance list of staff will be maintained to provide information about the numbers of staff who have received training. Information collected will include the date of training / Name of staff member / Job Role / Level of experience/ and contact information. This information will be held by the local facility team to keep track locally of staff trained and add aggregated numbers on to the database.

28.7.3 On site Staff Observations

Staff will be informed during the APT-Sepsis training that as part of the study evaluation on site observations will be undertaken by the HUB (Research) staff. They will gather data whilst observing staff during their daily activities, no personal identifying information will be recorded and any conversations resulting from these activities will not be documented or recorded.

28.7.4 Staff Interviews

Informed consent will be sought from healthcare facility workers or managers and research hub team staff, who agree to participate in individual interviews or focus groups. They will be provided with a consent form and the study team will ensure that they have the opportunity to review and consider the information and are aware that they can decline. They will be consented privately and without their supervisor being present and information about their participation, or not, in interviews will be kept confidential.

The process of informed consent will involve discussions between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g., information leaflet), and the opportunity for potential participants to ask questions and have these satisfactorily answered will be provided.

Informed consent will be obtained and interviews/ focus groups will be conducted in English or in the language considered appropriate for the participant by a local researcher, in a private location, or via telephone or video conference if preferred by participants or if restrictions require that at the time of interview. Interview/ focus group will be recorded, transcribed and de-identified. Participants will also be given the option to recuse themselves from the activities

at any point during the discussions and for up to seven days after the interview / focus group has been completed and any conversations resulting from this activity will be destroyed.

28.7.5 Staff Surveys

Consent information will be provided at the beginning of every electronic survey where the staff member will have the opportunity to decline. The surveys will be completed pseudonymously on an electronic database provided to staff by members of the HUB teams using a tablet to enable them to complete the survey online. Although staff will be encouraged to complete the survey by the Champions, the Champions will not be able to access the information entered by individuals. General information about the position and geographical location of the survey respondents will be collected. Names of respondents to the online survey will be kept in a confidential database to ascertain the number of times an individual has completed the survey. Only the research team if applicable to their role will have access to identifiers. Participants will be given the option to stop the survey at any point.

28.7.6 Champions

Champions will be invited to undertake the role following local selection by their facility leadership team. They will be trained by the HUB team. Champions who agree to attend the staff train the trainer events locally will verbally confirm their willingness to attend and undertake the role. A list of champions will be held so they can be contacted by the HUB team throughout the programme, and for communication across the champion network. Champions will support local staff throughout the intervention to perform their required roles to prevent maternal sepsis.

The Champions will also be given the option to complete a diary of their activities. Those who are willing to complete the diary will be provided with additional information on what this activity will involve and how the information will be used. A consent form will be completed by those taking part in this aspect and they will be advised they can stop diary activities at any point.

29 PROTOCOL DEVIATION AND SERIOUS BREACHES

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions, or principles of GCP, requirements are handled based on their nature and severity.

29.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

29.2 Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDMC and TSC) in determining whether the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting.

Breaches confirmed as 'serious' will be reported to the REC within 7 days by the LCTU on behalf of the Sponsor and notified to the TMG, IDMC and TSC at their next meeting. Any requests for additional information from the Sponsor, TMG, TSC, IDMC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented. Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

30 INDEMNITY

The University of Liverpool holds Indemnity and insurance cover with Griffiths and Armour, which apply to this study and provides indemnity for negligence in relation to the design or management of this trial. In addition, the Malawi Liverpool Welcome Programme will provide medical malpractice insurance cover for the in-country trial management.

The risks to patients who attend health care facilities that are participating in this study are no greater than would occur as part of their standard clinical care. Responsibility for patients care at health facilities participating in the trial remains the responsibility of the healthcare providers employed at that facility, and clinical practice at the facility would remain indemnified through their usual arrangements.

30.1 Possible constraints

30.2 Covid-19

Covid-19 health considerations: due to the prevailing COVID—19 threat all researchers or research assistants undertaking the study will practice COVID—19 prevention measures as per World Health Organization (WHO) protocols, and national guidance through:

- Hand hygiene – all country research teams will avail sanitizers for handwashing, which will be used on research participants at the start and end of research activities.

- All participating health care workers will be encouraged to follow national guidelines for COVID 19 Prevention measures.
- Social distancing - research Participants will be stationed at least 1 meter apart during research activities and researchers will keep the same distance while collecting data through whichever methods.
- Use of virtual data collection methods wherever that is possible and sensible.

To mitigate the impact of COVID-19 infections on the implementation of the study, particularly with regards to the collection of qualitative data through face-to-face interaction with participants, the study will be conducted to conform to the MLW Institutional Policy and MoH Policy for COVID-19 in Malawi, which include the continual use of face masks, social distancing and hand hygiene by both researchers and participants. In addition, qualitative interviews will be conducted outside or in well-ventilated open spaces, and, in the event of a change in guidance, face-to-face interviews will be replaced with online (MS Teams / Zoom) interviews. All individuals involved in the collection of quantitative data will be provided with the required personal protective equipment.

30.3 Additional constraints – inconsistent flow of supplies

Research targeting public health in low-income countries often experience intermittent supplies of resources. Meetings with District management teams will continue to ensure smooth flow of resources for patient management. Prior to study implementation, the study team will conduct site readiness assessment in potential facilities to their readiness to participate in the study. The sites will be informed that participation is voluntary. The study team will make every effort to collaborate with facility teams for the smooth running of the study.

30.4 Additional constraints – data quality

The Staff team including facility-based research officers will be trained in data collection technics, data collection instruments and confidentiality with routine data quality audits conducted for quality assurance purposes.

31 REQUIREMENTS

31.1 Researchers and Study staff

The qualitative and quantitative research activities will be implemented by study team and the facility staff including nurses, clinician from which research officers and possibly champions will be selected. All staff will be trained on the study. All site research staff involved in the study must be included on the site staff delegation log. The PI will sign off the delegation log for only those staff members s/he feels are able and competent the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked against staff named on eCRF, and registration forms.

The Research Manager will ensure that as a minimum the PI, research midwives and site study data management staff have study-specific training. The study will need skilled researchers to collect qualitative data and analyse qualitative and quantitative data.

32 END OF STUDY

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data Monitoring Committee (IDMC).

Facility closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC
- Study-related materials reconciled and returned/disposed of as appropriate.
- All facility data entered onto the study database, discrepancies raised and satisfactory responses received.
- Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

33 BUDGET AND BUDGET JUSTIFICATION

Item					Exchange rate MK1000
Personnel Cost	FTE	Quantity	Cost per unit item	Total Cost MK	£
Luis Gadama	100%	1*36	497,194.44	17,899,000.00	17899
Study Coordinator	100%	1*36	3,426,527.78	123,355,000.00	123355
Qualitative Researcher	0.5	1*12	1,807,500.00	21,690,000.00	21690
Project officers	3%	32*36	46,122.50	1,660,410.00	1660.41
Research Nurse	100%	3*36	1,107,569.44	39,872,500.00	39872.50
		Sub Total		**204,476,910.00**	**204476.91**
Direct costs					
Blood pressure machines		180	30,000.00	5,400,000.00	5400
Thermometers		300	5,000.00	1,500,000.00	1500
Tablets		32	300,000.00	9,600,000.00	9600
Site training		15	2,240,000.00	33,600,000.00	33600
Data Management				49,875,000.00	49875
Participant and Public Involvement (PP1)		4	2,625,000.00	10,500,000.00	10500
IT Support		4	1,725,000.00	6,900,000.00	14400
		Sub total		**117,375,000.00**	117375
Grant support and governance				2,000,000.00	2000
Other indirect costs				43,000,000.00	43000
COMREC Submission				125,000.00	125
		Sub total		**45,125,000.00**	45125
Total				**366,976,910.00**	
1O% KUHES Overheads				36,697,691.00	36698
		Sub total		**36,697,691.00**	36698
	Grand Total			**403,674,601.00**	**403675**

33.1 Budget Justification

33.1.1 Personnel costs

Staff with expertise and experience in clinical trials and qualitative and quantitative research methods and data analysis skills are required for the success of this project. Personnel costs includes Research Personnel, administrative support, and project officer. The unit cost for the staff is per month for the total period in the study.

33.1.2 Other direct costs

Other direct costs include all activities associated with recruitment, travel and subsistence, data collection stakeholder meeting, archiving costs, and ethics application fees.

33.1.3 Indirect costs

Research overheads are budgeted at 10% for the College of medicine as per established requirements.

34 REFERENCES

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APPENDIX 1 ADAPTED WHO NEAR MISS CRITERIA

Operational definitions:

Section I

The following criteria define a maternal near-miss if they occur during pregnancy, childbirth or within 42 days of pregnancy ending (including birth, abortion or miscarriage).

If one or more criteria are met and the woman survives the case will be counted as a near-miss event.

If the woman subsequently dies during the reporting period, then the case will be classified as a maternal death and not a near-miss event.

Medical events that are considered as near-miss:

Cardiac:

- Cardiac Arrest

(Sudden absence of pulse and loss of consciousness)

- Cardiopulmonary resuscitation

(A set of emergency procedures including chest compressions and lung ventilation applied in cardiac arrest victims)

Clotting:

- Failure to form clots

(The clinical inability to form clots/disseminated intravascular coagulation. Clinically, absence of clotting from the IV site or suture after 7–10 minutes.)

Respiratory:

- Gasping

(A terminal respiratory pattern. The breath is convulsively and audibly caught.)

- Cyanosis

(A bluish colour of the skin and mucous membranes due to hypoxaemia (insufficient oxygen being carried in the blood).

- Need for invasive ventilation (not due to anaesthesia)

(Requirement for invasive ventilation (mechanical ventilation in which positive pressure is applied to the patient's lungs via an artificial airway device), this does not include provision of oxygen or non-invasive ventilation alone)

Liver:

- Jaundice

(Clinically observed yellowing of the skin or sclera (whites of the eyes), raised bilirubin levels do not require laboratory confirmation)

Brain:

- Unconsciousness (not induced by anaesthesia/sedation)

(Any loss of consciousness lasting more than 12 hours, involving complete or almost complete lack of responsiveness to external stimuli. A state compatible with Coma Glasgow Scale <10)

- Stroke

(Rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours)

- Paralysis

(The complete or partial paralysis of both sides of the body)

- Uncontrollable fit

(Refractory, persistent convulsions. Status epilepticus).

Surgery:

- Hysterectomy

(In the maternal near-miss context, surgical removal of the uterus following infection or haemorrhage)

- Emergency laparotomy

(Requirement for an emergency surgical incision into the abdominal cavity, other than for a primary procedure to carry out a caesarean section (irrespective of fetal viability) or for treatment of suspected or confirmed ectopic pregnancy)

The near-miss criteria have been modified for the purposes of the APT-Sepsis trial to ensure their ascertainment will not be influenced by the intervention. Criteria which are reliant on appropriate completion of vital sign observations, diagnostic tests or treatments that are susceptible to variability based on site practices, performance and treatment thresholds have been excluded to reduce measurement bias.

Individuals in whom these signs / symptoms or outcomes are not identified or reported will be assumed not to have had a 'near miss'.

Section II

Severe infection-related morbidity

Deep surgical site or deep perineal/labial/vaginal tear infection

The event must occur within 30 days after the operative procedure or birth related injury (where day 1 = the procedure or birth date)

AND involve **deep** soft tissues of the incision or tear (for example, fascial and muscle layers)

AND the patient has at least one of the following:

- purulent drainage from the deep incision or wound.
- a deep incision or tear that spontaneously opens, or is deliberately opened or aspirated by a surgeon, physician or clinician/midwife

AND patient has at least one of the following signs or symptoms:

- fever or localized pain or tenderness.
- an abscess or other evidence of infection involving the deep incision or tear that is detected on gross anatomical or histopathologic exam, or imaging test

Deep reproductive tract or body cavity infection-related to birth

The event must occur within 30 days after the operative procedure or birth (where day 1 = the procedure or birth date)

AND
involve any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure, or is suspected to have been injured as a consequence of the birth process

AND

The patient has at least ***one*** of the following:

A) purulent drainage from a drain or aspiration procedure, or through the vagina or abdominal incision from the organ/space.

OR

b) an abscess or other evidence of infection involving the organ/space (including the ovaries, fallopian tubes or uterus or abdominal cavity) that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.

AND

Patient has at least ***two*** of the following signs or symptoms: fever or pain or tenderness (uterine or abdominal), or purulent vaginal discharge.

APPENDIX 2: CHAMPIONS (ROLES AND RESPONSIBILITIES)

A key component of the APT-Sepsis programme is the role of a Champion.

Champions promote and inspire others to take a more active role in healthcare. They will provide sources of information on maternal sepsis, signpost staff to materials, and support and train staff to make positive behavioural changes. The Champions will have several roles throughout the delivery and monitoring of the APT-Sepsis Programme. These include the following activities which and will be discussed during the training.

Individuals invited to become an APT-Sepsis Champions will ideally be someone who is passionate and enthusiastic about infection prevention and control and is willing to engage regularly with facility staff and organise activities to support the implementation of APT-Sepsis. Champions will act as a role model influencing colleagues' practice

Championship:

This refers to advocating for the practice and guidelines taught in the APT-Sepsis Programme including (but not limited to) the delivery of best clinical practice in Infection Prevention and Control (IPC). You will also demonstrate consistent and appropriate hand hygiene techniques and other IPC measures in your everyday practice.

Coaching:

It is important that Champions understand how to objectively assess others in carrying out safe IPC practice and to coach their colleagues, helping them to achieve their full potential through an individualised approachable and non-judgemental way.

Communication and coordination:

Champions are responsible for supporting and maintaining a strong communication link between the APT-Sepsis Research HUB Team and the healthcare staff members at their site.

Community:

APT-Sepsis Champions are vital to building a community at two important levels. The first level is intra-site community and the second level is inter-site community. These will be achieved through coaching sessions, local feedback, Champion network WhatsApp group, central training and Champion Network newsletters.

LIST OF SUPPORT DOCUMENTS

NB: Current versions, should be identified and confirmed with the trial co-coordinator prior to use.

Participant Information and Consent Forms

Appendix 1A English APT-Sepsis Champion Diary PISC
Appendix 1B Chichewa APT-Sepsis Champion Dairy PISC
Appendix 1C Tumbuka APT-Sepsis Champion Dairy PISC

Appendix 2A English APT-Sepsis Interview Intervention sites PISC _
Appendix 2B Chichewa APT-Sepsis Interview Intervention sites PISC
Appendix 2C Tumbuka APT-Sepsis Interview Intervention sites PISC

Appendix 3A English APT-Sepsis Interview Control Sites PISC
Appendix 3B Chichewa APT-Sepsis Interview Control Sites PISC
Appendix 3C Tumbuka APT-Sepsis Interview Control Sites PISC

Appendix 4A English APT-Sepsis Online Survey PISC
Appendix 4B Chichewa APT-Sepsis Online Survey PISC
Appendix 4C Tumbuka APT-Sepsis Online Survey PISC

Appendix 5A English APT-Sepsis Research Staff interview or Focus Group PISC
Appendix 5B Chichewa APT-Sepsis Research Staff interview or Focus Group PISC
Appendix 5C Tumbuka APT-Sepsis Research Staff interview or Focus Group PISC

Data collection tools

Appendix D Champions Dairy
Appendix E APT-Sepsis: Intervention site staff interview guide
Appendix F APT-Sepsis: Control site staff interview guide
Appendix f APT-Sepsis Interviews Or Focus group guide
Appendix Ga Quarterly site visit Control
Appendix Gb Quarterly visit Intervention sites
Appendix H Daily CRF
Appendix IA Weekly intervention and control site form
Appendix IB Weekly form intervention site form
Appendix J Hand hygiene Observation form
Appendix K Discharge form
Appendix L Enrolment form
Appendix M Follow up form
Appendix N APT - Weekly Form_ Intervention site
Appendix O Maternal death form

Appendix P Compliance form inpatients
Appendix Q Compliance form infection cases
Appendix S Staff survey form (intervention sites)