APT-Sepsis
The Active Prevention and Treatment of Maternal Sepsis

APT-Sepsis Protocol
V3.0, 07/11/2024

Study Sponsor:
Mrs Karen Jennings-Wilding Clinical Research, Sponsorship and Governance Manager Clinical Directorate 4th Floor Thompson Yates Building Faculty of Health and Life Sciences University of Liverpool L69 3GB Email: sponsor@liverpool.ac.uk

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Protocol Approval

We, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: Signed by: Professor David Lissauer
Signer Name: Professor David Lissauer
Signing Reason: I approve this document
Signing Time: 26 November 2024 | 1:58:43 PM GMT
EDDED0E8F74B44859497477A9ABF01938

Date: 26 November 2024

Full Name (Professor David Lissauer)
Job title, Chair in Global Maternal and Fetal Health, University of Liverpool, Sub-specialist in Maternal and Fetal Medicine (Department of Obstetrics and Gynaecology), Queen Elizabeth Central Hospital, Blantyre, Malawi

Authorised on behalf of Sponsor:

Signature: Signed by: Karen Jennings-Wilding
Signer Name: Karen Jennings-Wilding
Signing Reason: I approve this document
Signing Time: 26 November 2024 | 12:44:57 PM GMT
E0AD3C9FD9A84DEAA9365BA11703D062

Date: 26 November 2024

Title, Name
Mrs Karen Jennings-Wilding

Authorised on behalf of the Lead Statistician:

Signature: Signed by:
Signer Name: Dr Girvan Burnside
Signing Reason: I approve this document
Signing Time: 17 December 2024 | 1:49:49 PM GMT
6F9DE57B7291449190980B751D344F11

Date: 17 December 2024

Title, Name
Dr Girvan Burnside

Authorised on behalf of the Lead Country Investigator:

Signature: Signed by:
Signer Name: Professor Catriona Waitt
Signing Reason: I approve this document
Signing Time: 29 November 2024 | 4:26:07 PM GMT
B236292039D442F68724427E3B6E2C25

Date: 29 November 2024

Title, Name
Professor Catriona Waitt

General Information

This document describes the APT-Sepsis trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the study, but facilities are advised to contact the local team or the coordinating centre Liverpool Clinical Trials Centre (LCTC) to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the relevant Chief Investigator (CI), Professor David Lissauer, via the LCTC.

This protocol defines the facility and participant characteristics required for study entry and the schedule of follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted. Incidence of protocol non-compliance whether reported prospectively (e.g., because of central monitoring) are recorded as protocol deviations. These are monitored and reported to study oversight committees.

The protocol content is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is described elsewhere in this protocol.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse study portfolio underpinned by methodological rigour, a Good Clinical Practice (GCP) compliant data management system, and quality management system.

Contact Details:

Sponsor:	**Study Management, Monitoring and Analysis:**	**Statistics:**
Mrs Karen Jennings-Wilding Clinical Research, Sponsorship and Governance Manager Clinical Directorate 4th Floor Thompson Yates Building Faculty of Health and Life Sciences University of Liverpool Liverpool L69 3GB Tel: 07717 863747 Email: sponsor@liverpool.ac.uk	Liverpool Clinical Trials Centre 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL E-mail: apt-sepsis@liverpool.ac.uk;	Liverpool Clinical Trials Centre 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL E-mail: apt-sepsis@liverpool.ac.uk
Co-ordinating centres outside of the UK (1):	**Co-ordinating centres outside of the UK (2):**	
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Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**
Mrs Karen Jennings-Wilding Clinical Research, Sponsorship and Governance Manager Clinical Directorate 4th Floor Thompson Yates Building Faculty of Health and Life Sciences University of Liverpool Liverpool L69 3GB Tel: 07717 863747 Email: sponsor@liverpool.ac.uk	Professor David Lissauer MBChB, BMedSci, PhD, MRCOG NIHR Professor of Global Maternal and Fetal Health Sub-specialist in Maternal and Fetal Medicine University of Liverpool Malawi-Liverpool-Wellcome Trust Blantyre, Malawi Mobile: +265992892149 WhatsApp: +447866624534

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover: Sonia Whyte / Liu Yang **Email**: apt-sepsis@liverpool.ac.uk

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

Table of Contents

1 GLOSSARY

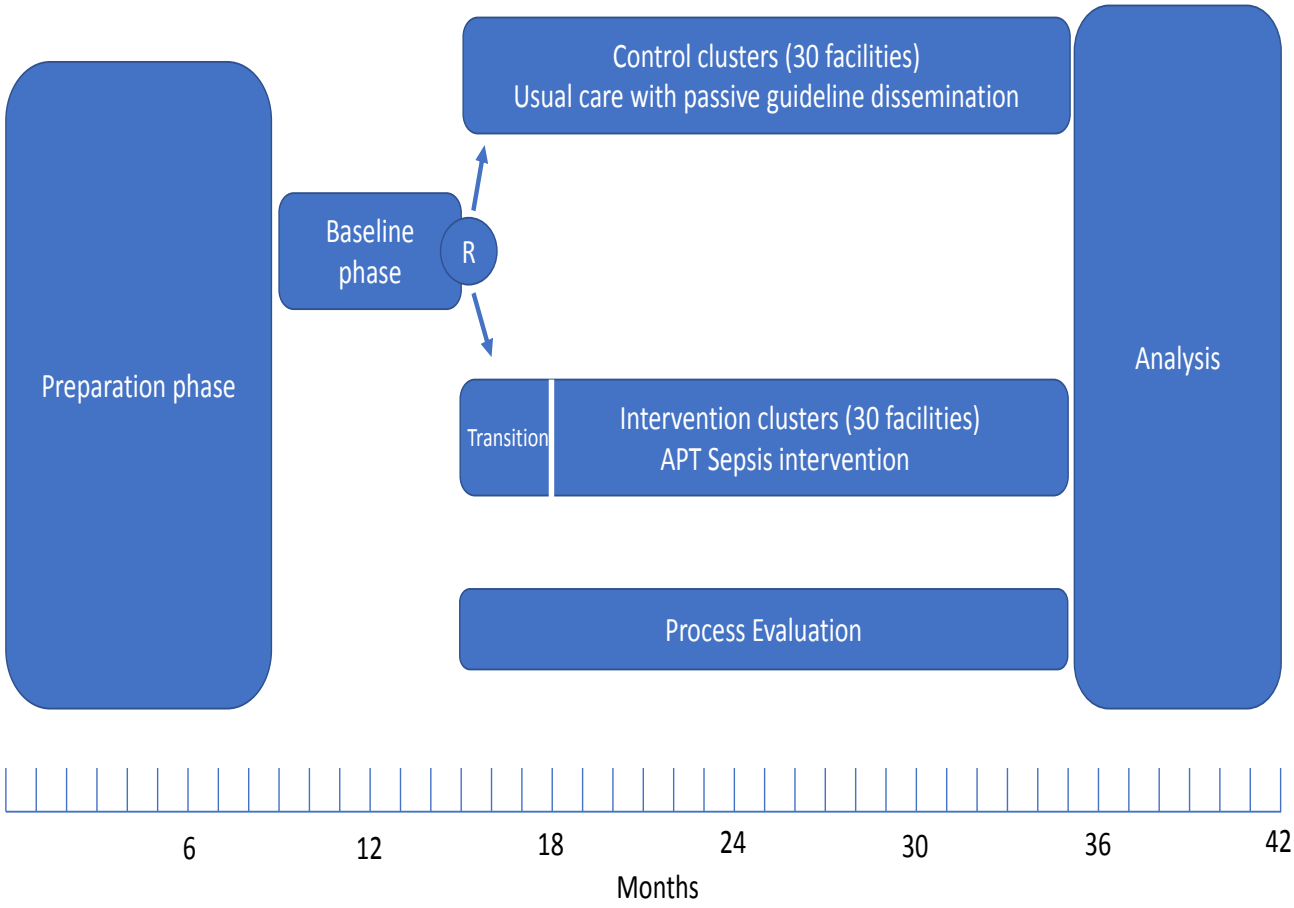
AE	Adverse Event
CI	Chief Investigator
COM-B	Capability, Opportunity, Motivation-Behaviour Model
CRF	Case Report Form
EDD	Expected Date of Delivery
FAST	Fluids, Antibiotics, Source identification and Transfer
FAST-M	Fluids, Antibiotics, Source identification and Transfer and Monitoring
GCP	Good Clinical 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
QC	Quality Control
REC	Research Ethics Committee
RM	Research Midwife (Registered)
RN	Research Nurse (Registered)
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

2 PROTOCOL OVERVIEW

Full Title:	The Active Prevention and Treatment of Maternal Sepsis
Acronym:	APT-Sepsis
Phase:	Multi-country, parallel cluster randomised trial with baseline phase
Population:	Cluster: Health facilities in Malawi and Uganda Research participants: All healthcare providers delivering care to women during pregnancy or up to 42 days after childbirth, including miscarriage or abortion in the study facilities
Sample size:	172,500 births
Inclusion Criteria:	Cluster inclusion criteria: Healthcare facilities with annual birth number ≥1500 offering comprehensive emergency obstetric care Completed site readiness assessment process Research participant inclusion criteria: Healthcare workers and managers responsible for provision of maternity care in the study facility
Exclusion Criteria:	Cluster exclusion criteria: Facilities not willing to participate in the study Research Participant exclusion criteria: Healthcare workers not willing to consent to participation
Study Centres and Distribution:	60 health care facilities (30 Malawi, 30 in Uganda) identifying women who are admitted with suspected sepsis whilst pregnant or within 42 days of delivery.
Intervention:	The APT-Sepsis intervention, which will change health care providers behaviours to improve deliver of care in 3 domains: 1) 5 moments of Hand hygiene, 2) Infection prevention and management, 3) Sepsis management.
Control:	Usual care with passive guideline dissemination
Study Duration:	57 Months

Objectives:	
Primary:	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. The primary outcome is maternal infection-related mortality or severe morbidity. This is a composite of infection-related maternal mortality, infection-related maternal near-miss (adapted WHO definition) or severe infection-related morbidity (adapted CDC definition of deep surgical site infection or body cavity infection). Outcomes will be collected from all women who are admitted to the healthcare facility during pregnancy or within 42 days of childbirth (including miscarriage or abortion). No follow-up of events occurring after discharge from a hospital care facility will be carried out.
Secondary:	To evaluate if the APT-Sepsis programme is effective at reducing other secondary clinical outcomes of: Stillbirth, early neonatal death (infection-related and total), maternal mortality (any cause), maternal near miss (any cause) To explore differential or subgroup effects of the APT-Sepsis programme by a) country b) facility size (number of births); country; high versus. 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 **Health economic analysis**: To determine if the APT-Sepsis programme is cost effective. To facilitate local **capacity building** in cluster randomised trials and maternal health implementation research To **disseminate the findings** in accordance with a well-developed dissemination and impact policy

3 SCHEMATIC OF STUDY DESIGN



4 ROLES AND RESPONSIBILITIES

4.1 Sponsor

The University of Liverpool is the Sponsoring organisation and is legally responsible for the study. They will formally delegate specific Sponsor's roles to the Chief Investigator (CI) and Liverpool Clinical Trials Centre (LCTC).

4.2 Funder

This project is supported by the Joint Global Health Scheme with funding from the UK Foreign, Commonwealth and Development Office, the UK Medical Research Council (MRC), The UK Department of Health and Social Care through the National Institute of Health Research (NIHR) and Wellcome (Grant ref: MRV005782/1). The role of the funder in this study is to monitor progress and may wish to attend the Trial Steering Committee as an observer, and/or audit individual studies.

Budget

APT-Sepsis summary budget(£)	
Personnel	690,965
Supplies	83,414
Travel	61,696
study activities	78,502
Operational costs	196,730
IDI indirect(8%)	88,905
Total	**1,200,213**

4.3 Study Team

Chief Investigator (CI): Professor David Lissauer is the Chief Investigator for the study and is responsible for overall design and conduct of the study in collaboration with other members of the study team.

Principal Investigators (PI): In each participating country a lead principal investigator will be identified to be responsible for identification of facilities, recruitment, data collection and completion of Case Report Form(s) (CRF(s)), along with follow up of study outcomes and adherence to study protocol. They will also be responsible for safety reporting and processing any applicable safety information to ethics and regulatory authorities. The Study Principal Investigators have relevant experience and commitment and the medical expertise necessary to conduct the study in accordance with the protocol and all regulatory and ethical requirements. A suitable deputy-PI should be identified to deputise in case of PI absence.

Liverpool Clinical Trials Centre (LCTC): at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for study management activities including (but not limited to) study planning, budget administration, Trial Master File management, safety reporting, data management and statistical analysis. They will provide support to local participating trial coordinators. There will be strong central trial group hosted at LCTC, who will provide trial management, Data Management, Administrative, Financial and Statistical support. The team will provide the day-to-day management of the study and support the TMG, HUBs, TSC, IDMC and PPI groups.

Study Country Hub (HUB): An internal management group (HUB) will be set up in Malawi and Uganda. Each HUB will employ a full-time trial coordinator, administrative support, and a team of clinicians for in-country implementation and monitoring. They will also be responsible for supporting the project officers at the clusters, who will receive additional salary to provide daily data collection of the clinical outcomes.

Health Economics Unit (HEU), Birmingham: Team will be a co-investigator and lead for Health Economics and will have oversight of data relevant to the health economics analysis. The specific case report forms (CRFs) pertinent to the economic data collection will be designed by HEU. The principal health economics researcher (to be appointed) will be employed for the last 13 months of the study to receive data, seek unit costs and carry out the analysis, liaise with other team members and write the analysis for the final report, supervised and overseen by the lead for health economics.

Integrated process evaluation team, a joint collaboration with University College London (UCL), University of Liverpool (UofL) and Liverpool School of Tropical Medicine (LSTM): Together the team will conduct a process evaluation will explore the implementation of the intervention in practice and will include quantitative survey data and qualitative data from interviews with practitioners.

4.4 Oversight committees

This study is subject to oversight from the following committees.

International Trial Management Group (TMG): A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

Trial Steering Committee (TSC): The Study Steering Committee will consist of an independent chair, and independent experts in the field of Maternal Health, a biostatistician, including the CI, a lay woman with previous experience of sepsis will participate and observers. The role of the TSC is to provide overall supervision for the study and provide advice through its independent Chair. The decision for the continuation of the study lies with the TSC and as such they will meet throughout the study (at least annually). Terms of reference for the TSC are set out in the TSC Charter.

Independent Data Monitoring Committee (IDMC): The Independent Data Monitoring Committee (IDMC) will consist of an independent chairperson, and independent members, who are experts in the field of Maternal Health and / or Sepsis, and an independent biostatistician. The IDMC will be responsible for reviewing and assessing study progress, conduct and review data. They will assess data quality, including completeness of data, and will review summary characteristics split by treatment group to allow assessment of potential selection bias. The IDMC will first convene prior to the start of recruitment and will then meet at least annually. The Terms of Reference are set out in the IDMC Charter.

4.5 Patient and Public Engagement Group (PPI)

An independent PPI group will be set up in Malawi and Uganda. Its role will be to contribute to all aspects of the study during preparation (design elements), delivery (conduct) and dissemination. A PPI WhatsApp group will be set up to allow communication between members. These PPI Group will also provide feedback (report) every 4 months to the TMG.

We will provide the training and support needed to enable a lay member to join and contribute to the Trial Steering Committee. We will also communicate with the public about the issues of maternal infection and sepsis and seek to raise understanding around this important problem. The members of the PPI group will also help identify future research priorities.

4.6 Maternal Sepsis Support Group

We recognise that women who have suffered from maternal sepsis, which may often also be accompanied by complications that effect their baby, do not currently have adequate support during their recovery. The project will establish peer support groups in Malawi and Uganda so that maternal sepsis survivors, with the support of an experienced midwife, can share their experiences. We hope these groups will also link with members of the PPI group and enable the study team to maintain engagement with users and receive

feedback on any concerns or issues. Members of the groups will also be given the opportunity to work with the study team to highlight this issue in their communities and the wider public in Malawi and Uganda.

5 PROTOCOL CONTRIBUTORS

Name	Affiliations	Contribution to protocol
Professor David Lissauer	University of Liverpool (UK)	Inception of study that led the writing of this. protocol, clinical and scientific arrangements, study design and conduct
Mrs Sonia Whyte	LCTC, University of Liverpool (UK)	Protocol development, governance arrangements and study conduct
Professor Carol Gamble	LCTC, University of Liverpool (UK)	Director LCTC oversight of trial arrangements
Dr Girvan Burnside	LCTC, University of Liverpool (UK)	Lead statistical arrangements, study design and conduct
Professor Andrew Weeks	University of Liverpool (UK)	Study design and conduct
Dr Luis Gadama	Kamuzu University of Health Sciences, Malawi	Clinical arrangements, study design and conduct
Professor Address Malata	Malawi University of Science and Technology (MUST)	Clinical arrangements, study design and conduct
Dr Mohammed Lamorde	Infectious Diseases Institute, Uganda	Clinical arrangements, study design and conduct
Dr Judith Nanyondo	Infectious Diseases Institute, Uganda	Clinical arrangements, study design and conduct
Professor Catriona Waitt	Infectious Diseases Institute, Uganda and University of Liverpool	Clinical arrangements, study design and conduct
Dr Peter Waitt	Infectious Diseases Institute, Uganda	Clinical arrangements, study design and conduct Capacity building lead, Uganda
Peace Okwaro	Infectious Diseases Institute, Uganda	Clinical arrangements, study design and conduct
Professor Arri Coomarasamy	University of Birmingham (UK)	Study design and conduct
Dr Ioannis Gallos	University of Birmingham (UK)	Study design and conduct
Mr James Martin	University of Birmingham (UK)	Study design and conduct
Professor Karla Hemming	University of Birmingham (UK)	Study design and conduct
Professor Tracy Roberts	University of Birmingham (UK)	Study design and conduct
Dr Jamie Rylance	Liverpool School of Tropical Medicine	Study design and conduct
Dr Mercedes Bonet	UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme HRP	Study design and conduct
Dr Fernando Althabe	UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme HRP	Study design and conduct
Dr Lou Atkins	University College London Centre for Behaviour Change	Study design and conduct
Dr Fabiana Lorencatto	University College London Centre for Behaviour Change	Study design and conduct
Dr Nicola Ann Desmond	Liverpool School of Tropical Medicine	Study design and conduct

Dr Catherine Dunlop	University of Birmingham (UK)	Study design and conduct

6 INTRODUCTION

6.1 Background

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). International organisations such as the World Health Organisation (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 behaviours 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 World Health Organisation 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".

6.2 Rationale

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. The first interventional domain is ‘hand hygiene’, ensuring compliance with the WHO 5 moments of hand hygiene. The second interventional domain is infection prevention and management and ensures adoption of evidence-based practices for infection prevention in maternity, including appropriate antibiotic prophylaxis for high-risk women and improved surgical practices. The third interventional domain is better sepsis management and consists of ensuring consistent measurement of patient vital signs and when there is suspected sepsis the triggering of the FAST-M maternal sepsis bundle. This bundle includes Fluids, Antibiotics, Source control, Transfer and Monitoring.

This approach helps provide local healthcare facility staff with the information, motivation and tools needed to reduced sepsis. We will provide training delivered by trained teams at the local facilities. We will provide paper-based checklists and reminders and create a network of Champions who can 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 60 health care facilities in Malawi and Uganda we will collect data prior to the implementation of APT-Sepsis and then 30 health care facilities (15 in each country) will be randomised to test the APT-Sepsis intervention the remaining facilities will continue their usual practices.

Facilities allocated to use 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 at least 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.

This research seeks to reduce death and severe morbidity due to sepsis that occurs during and after pregnancy, in low-income countries, in particular Malawi and Uganda. We anticipate it will also improve adherence to best practice in these facilities with improved hand hygiene, infection prevention and management, and sepsis detection and management. Through the study we will understand in detail how APT-Sepsis is applied in the clusters so that we can understand its implementation in practice and plan how it can be scaled if it is shown to be useful. We will also discover if the programme is cost effective.

The engagement of health care facilities with this study will provide additional training and understanding of how to better prevent and manage maternal sepsis for health care facility staff and we anticipate that these benefits will last beyond the life of the study itself. Working with the WHO Human Reproductive Programme (HRP) Alliance we will provide opportunities for junior researchers from Sub-Saharan Africa to use this study as a platform to enhance their research skills and knowledge.

To maximise the benefit from this research it is important that the findings inform policy and can therefore impact on practice globally. We are working closely with the WHO that has a vital role in determining health care policy worldwide. We are also collaborating closely 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, International Federation of Gynaecology and Obstetrics (FIGO), International Confederation of Midwives (ICM) and national professional organisations.

6.3 **Objectives**

We will evaluate if implementation of the APT-Sepsis programme is effective at reducing infection-related maternal mortality and severe morbidity through a cluster randomised trial in Malawi and Uganda. We will also conduct a rigorous process evaluation to understand the implementation of the programme and will determine its cost effectiveness.

6.3.1 Primary Objective

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 or 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). The primary outcome will be coded as 1 if any of these components occur, and 0 if none of them occur.	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 or discharge from a healthcare facility, whichever is sooner.

See Appendix 1 Near Miss criteria and severe infections definitions.

6.3.2 Secondary Objective(s)

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.
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 vs. 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.

Secondary Objectives	Secondary Outcome Measures	Timepoint(s) of evaluation
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.

7 STUDY DESIGN

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 60 clusters, each of which is a health facility (30 in Malawi and 30 in Uganda).

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.

7.1 Blinding

This is an open label study with no blinding requirements. All researchers and participants will know which intervention the cluster has been randomised to the APT-Sepsis programme.

8 STUDY SETTING

Participating health care facilities will be identified in Malawi and Uganda. 60 health care facilities will be selected following a suitability assessment process which will be performed by the Malawi or Uganda HUB teams.

There will be 32 facilities invited to commence the baseline data collection phase in each country, this enables a contingency of 2 facilities in each country in case any facilities chose to withdraw during the initiation or baseline phase.

8.1 Selection of Participating Facilities

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. The Malawi and Uganda HUB teams will conduct a site suitability assessment at all potential participating facilities.

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 ‘APT-Sepsis 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.

8.2 Project officers

Each participating healthcare facility will identify and assign a project officer(s) 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.

8.3 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.

9 ELIGIBILITY CRITERIA

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

APT-Sepsis will recruit 60 clusters (sites) and based on sample size calculations described below this has the potential to include data from 172,500 women.

9.1 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

9.2 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

9.3 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.

10 STUDY INTERVENTIONS

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

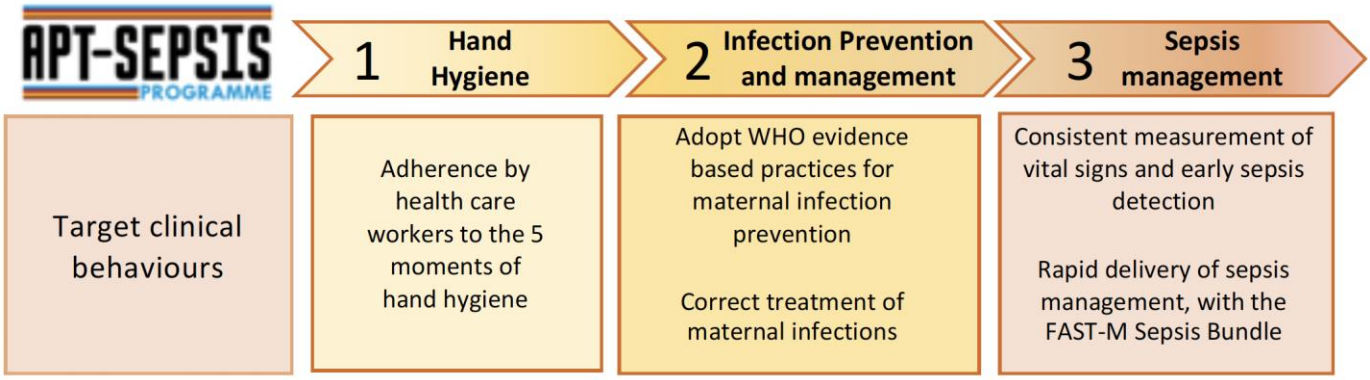


Figure 1. APT-Sepsis programme intervention overview

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.

10.1 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.

11 BASELINE PERIOD

The Baseline period will last a total of 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 (figure 2). 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.

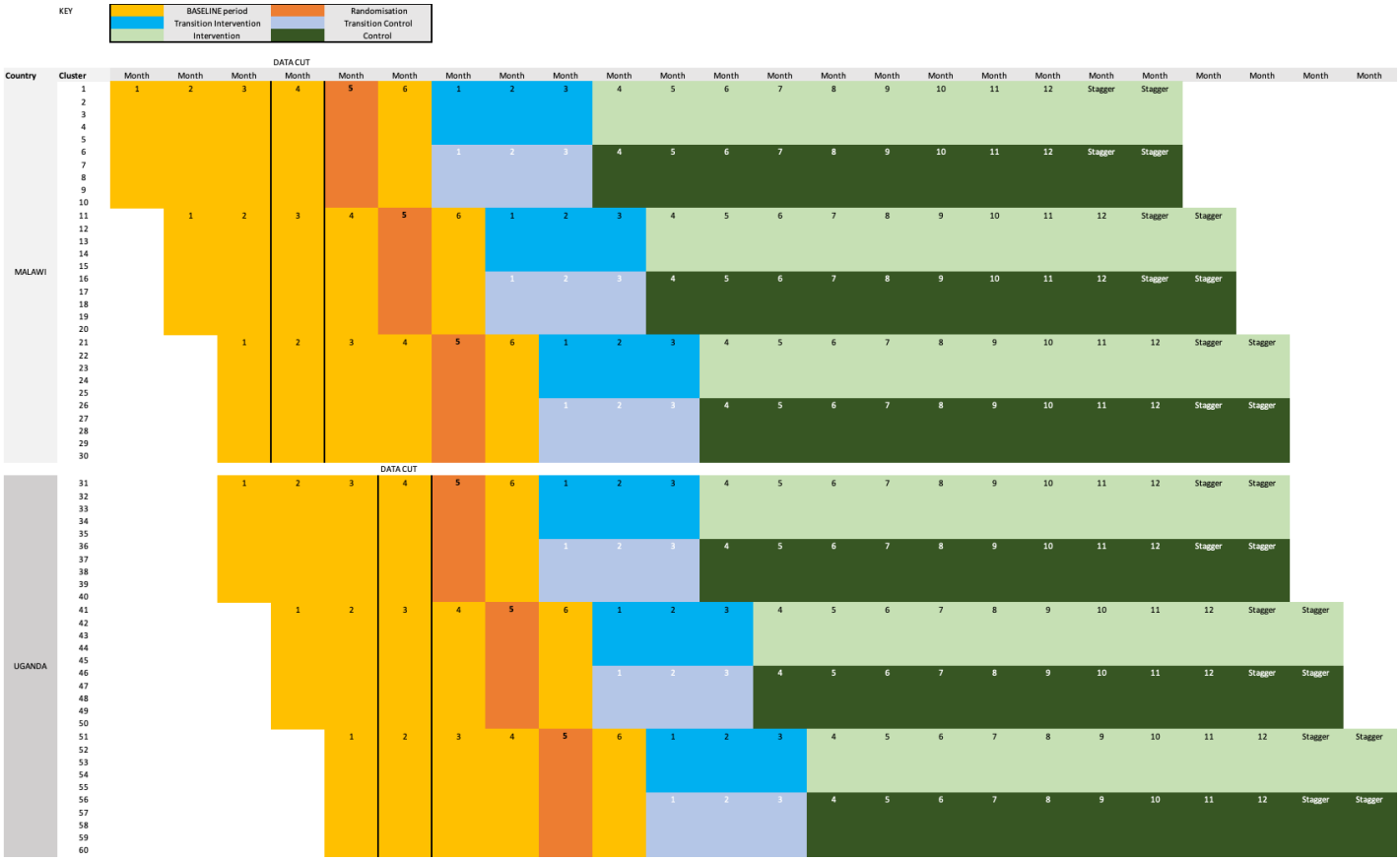


Figure 2 proposed stagger of clusters

12 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. It will also be based on logistics when a cluster is ready to be randomised, after they have been in the baseline phase for a sufficient length of time. The allocation will be displayed on screen, and sent by email to the study co-ordinator, and principal investigator.

13 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 3 month transition phase regardless of the treatment allocation.

14 IMPLEMENTATION PERIOD

14.1 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.

14.1.1 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.

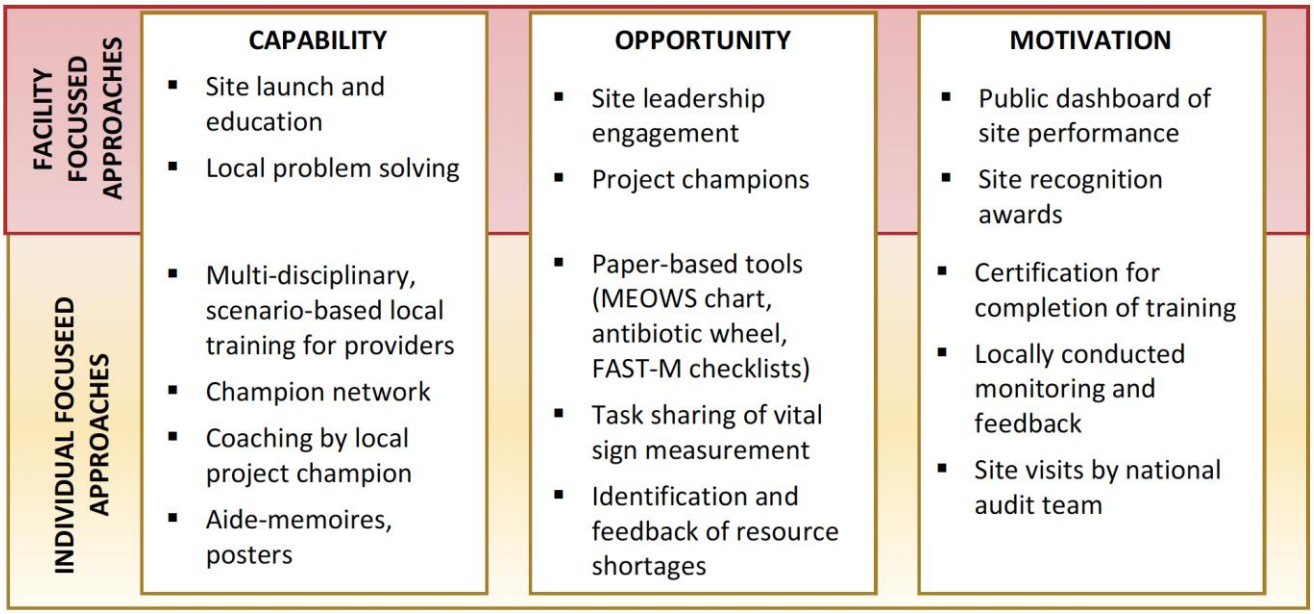


Figure 3. Summary of co-interventions that seek to support health care provider behavioural change

14.2 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.

14.3 Safeguarding

Local policies and procedure are expected to be in place to safeguard research participants, volunteers, research staff and associated personnel and their communities from all forms of violence, abuse or harm as a result of their association with the project. The study team are expected to behave ethically and responsibly.

All research staff who obtain consent should receive safeguarding training as per their local requirements. Participants (Healthcare facility staff) will be advised during the consent process that research staff must not ask for any financial, physical or sexual favours in return for taking part in this research. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Full details of the informed consent procedures that will be undertaken in the trial are in section 24

14.4 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 will be made available in both English and appropriate local languages where required.

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.

14.5 Health Economic Assessments

We will as part of the process evaluation prospectively record important resources use associate with the intervention until discharge. From the staff perspective resource use will include the additional time for delivery of the intervention and the training requirements. This will be assessed via random time and motion observations conducted in healthcare facilities (clusters) participating in the process evaluation in both arms of the study. We will also monitor additional resources e.g. soap, alcohol gel, paper-based tools and posters. From the patient perspective, we will record medications and procedures received by patients, as well as changes in facility supplies and procedures recorded at a facility level and information on the length of facility inpatient stay. Country specific unit costs will be sought from Malawi and Uganda.

15 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.

16 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.

17 STATISTICAL CONSIDERATIONS

17.1 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)

17.1.1 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.

17.1.2 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.

17.2 Method of Randomisation

17.2.1 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.

17.3 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.

17.4 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 timepoints 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.

17.5 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.

18 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 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.

19 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).

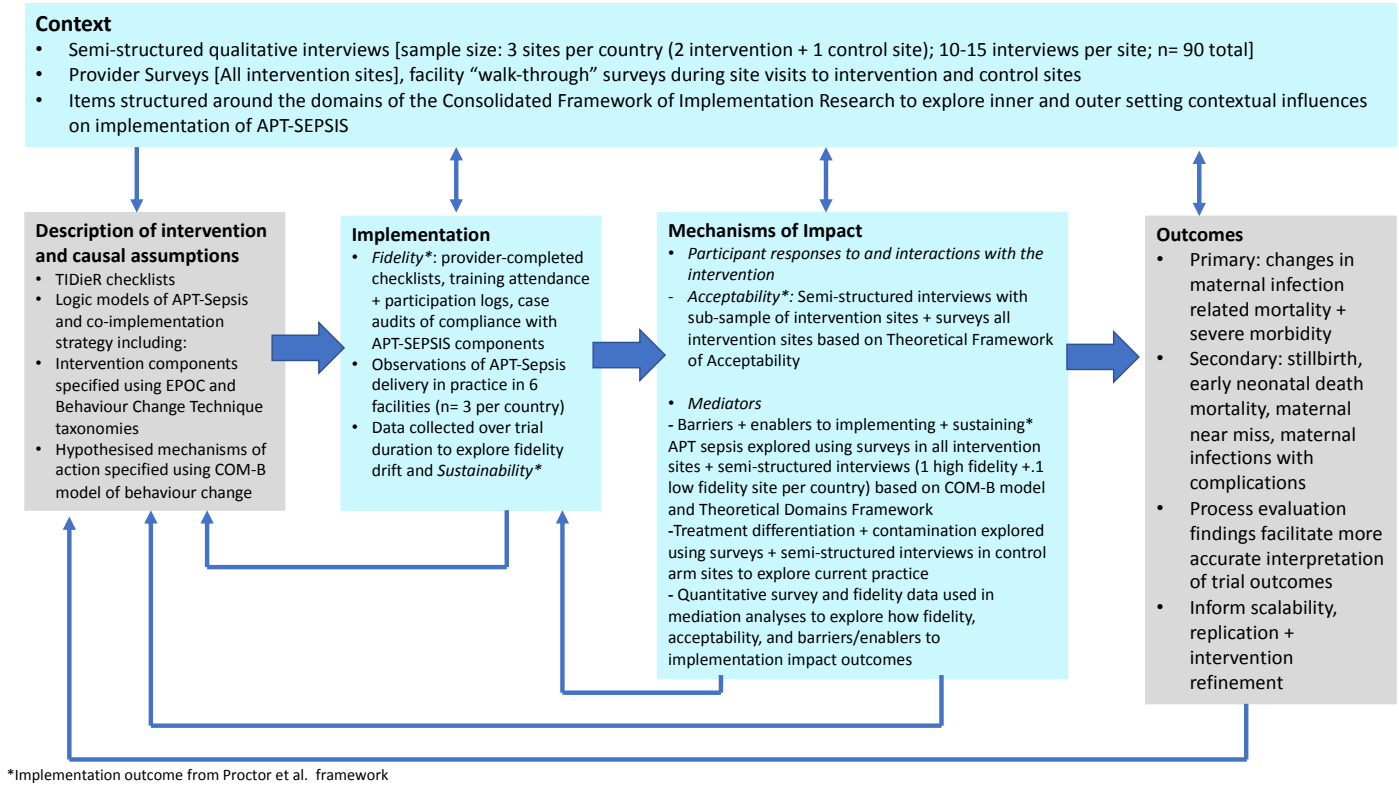


Figure 4 Implementation Outcome

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 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).

19.1 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, 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 (N=7 Uganda and N=7 Malawi) hub staff, 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 requires 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.

19.2 Surveys

19.2.1 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.

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.

19.2.2 Staff Surveys

Cross-sectional, electronic surveys will take place in all intervention clusters in each country (30 facilities total). We will engage the same purposive sample of participant roles 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 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. .

20 DATA MANAGEMENT AND TRIAL MONITORING

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.

20.1 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. 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.

20.2 Data Collection Methods

Data are to be entered into the REDCap database using a laptop or tablet by members of the research team and project officers at site. Staff may access the secure database using a website or mobile app. Training will be provided prior to any data entry.

20.3 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.

20.3.1 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.

20.3.2 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.

20.4 Risk Assessment

A full LCTC risk assessment will be conducted prior to trial commencement according to the LCTC Risk assessment SOP and will be kept updated by the trial manager throughout the trial.

20.5 Confidentiality

This trial will collect personal data (e.g., participant names of healthcare staff who are trained), and staff who participate in the interviews this will be handled in accordance with all applicable data protection legislation. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by HUB teams. This transfer of identifiable data is disclosed in the participant information leaflet.

Consent forms will be transferred separately to any other trial documentation to ensure the pseudonymisation of data is maintained.

The country HUB teams will be responsible for administering surveys to the healthcare staff participating in the study to understand the implementation of the APT-Sepsis intervention.

For the ascertainment of the trial primary and secondary outcomes aggregated anonymised data will be used.

Data (including special category) will only be collected, used and stored, if necessary, for the trial (e.g., evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial cluster number indicating the date and site of completion.

Site-specific information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

21 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 DMC and independent members of the TSC will provide independent 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.

22 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.

23 REGULATORY AND ETHICAL CONSIDERATIONS

23.1 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.

23.2 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 to evaluation the intervention and reduce the risk of cross contamination.

23.3 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, Uganda and the UK will be sought in addition to WHO ethical approval.

23.4 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.

23.5 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 24). Appropriately trained study staff will ensure that the staff have the opportunity to 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 .

23.6 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 60 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.

24 INFORMED CONSENT PROCEDURES

24.1 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.

24.2 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.

24.3 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.

24.4 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. Interviews/focus groups 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.

24.5 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.

24.6 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.

25 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.

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.

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 (IDSMC 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.

26 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.

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.

27 PUBLICATION AND DISSEMINATION

27.1 Publication Policy

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 establishing 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

27.2 **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.

27.3 **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 each of the following:

MALAWI: The College of Medicine Research and Ethics Committee (COMREC), College of Medicine Library, The National Health Sciences Research Committee (through the COMREC Secretariat), and the College of Medicine and University of Malawi Research and Publication Committees (through the COMREC Secretariat).

UGANDA: Uganda National Council for Science and Technology.

The results of APT-Sepsis will be published regardless of the findings.

27.4 **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.

28 GENDER AND EQUITY CONSIDERATIONS

A better understanding of effective strategies for identification and prompt management of maternal and sepsis will directly address the needs of pregnant and recently pregnant women affected by infections and its complications. This is particularly challenging in settings where women have limited access to health services, related to their socioeconomic or cultural context.

The project management and organisation will promote gender equality. In the context of our study, we will be sensitive to gender balance within our research consortium.

29 ENVIRONMENTAL IMPACT OF THE PROJECT

The direct environmental impact of the project is minimal to achieve this, we will:

- Minimise travel for meetings conducting them using video conferencing as a first choice.
- Minimise the use of paper during the study and related activities.
- The participating sites are responsible of appropriate disposal and destruction of waste related to the study according to local healthcare facility standards.
- By providing the basis for the development of intervention strategies to improve the management of maternal infections and their complications, this study will contribute to a better use of antimicrobials and efforts to control antimicrobial resistance.

30 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 master's 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.

30.1 Capacity strengthening

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

At the individual level, we have identified people from the participating countries Malawi and Uganda will receive support to develop research capacity.

Uganda: We will strengthen linkages between the HRP and the IDI research unit and participate in regional trainings to develop capacity in quantitative and qualitative research skills including systematic reviews and meta-analysis.

Two PhD and two master's students in Uganda will be supported. One of the Masters students will focus on data science and will access facilities at IDI African centre of Excellence for bioinformatic and data science. These students will leverage resources at IDI including the IDI research forum and education opportunities with IDI's capacity building unit.

The capacity building specialist, Dr Peter Waitt , will provide mentorship to students as well as the facility champions using face to face and virtual platforms.

Malawi: 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.

31 CHRONOLOGY OF PROTOCOL AMENDMENTS

Version	Date	Clarification of Changes
1.0	28/10/2022	Original approved version
2.0	09/10/2023	PI change in Uganda, clarification of follow up duration period up to 28 days, process evaluation clarification of text and typographic errors corrected.
3,0	07/11/2024	Revision of the intervention period from 17 months to 9 months (paragraph 11) and statistical calculations revision to account for reduction in the intervention phase (Paragraph 17.1.2). Inclusion of Research (HUB) team interviews / focus groups (paragraph 19.1)

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34 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to ethical review are submitted as separate version-controlled documents.

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.

Annex 1: 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.