ENHanced ANtenatal Care bundlE (ENHANCE) Protocol

STUDY TITLE:
Enhanced antenatal care bundle intervention to improve maternal and newborn outcomes in Malawi and Zambia: a multi-country parallel cluster-randomized controlled trial protocol

Study acronym: **ENH**anced **AN**tenatal **C**are bundl**E** study (ENHANCE)

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GLOSSARY

ANC	Antenatal Care
APH	Antepartum Haemorrhage
BCW	Behaviour Change Wheel
CI	Chief Investigator
CIOMS	Council for International Organisation of Medical Sciences
COM-B	Capability Opportunity Motivation-Behaviour
COMREC	College of Medicine Research Ethics Committee
CRF	Case Report Form
CTU	Clinical Trial Unit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ENHANCEs	ENHanced ANtenatal Care BundlE Study
ENHANCE	ENHanced ANtenatal Care BundlE
HAIs	Healthcare Associated Infections
HB	Haemoglobin
HCWs	Healthcare Workers
HRP	Human Reproduction Programme
IPD	Individual Participant Data
ISAC	International Scientific Advisory Committee
KMC	Kangaroo Mother Care
KUHeS	Kamuzu University of Health Sciences
LAMTs	Leadership and accountability, Mentorship and Task shifting
LMICs	Low Middle-Income Countries
MEIRU	Malawi Epidemiology and Intervention Research Unit
MLW	Malawi Liverpool Wellcome Research Programme
MoH	Ministry of Health
PHC	Primary Health Care
PI	Principal Investigator
PICF	Participant Information and Consent Form
PPI	Patient and Public Involvement
PPH	Postpartum haemorrhage
QMD	Quality Management Directorate
RCS	Research Capacity Strengthening
REC	Research Ethics Committee
RHD	Reproductive Health Directorate
SRHR	Sexual Reproductive Health and Rights
TDF	Theoretical Domains Framework
TMG	Trial Management Group
UoL	University of Liverpool
WHO	World Health Organization
WMA	World Medical Association

EXECUTIVE SUMMARY

Type of study

Non-blinded, multi-country parallel cluster-randomised controlled trial with baseline phase.

Setting

Public primary health centres in Malawi and Zambia

The problem

Despite high antenatal care (ANC) attendance and institutional delivery rates in Malawi and Zambia, women continue to die of maternal complications at 381 and 135 deaths per 100,000, respectively. These deaths are preventable with high quality healthcare aligned with evidence-based WHO guidelines. Both Malawi and Zambia have adopted the 2016 WHO recommendation for eight visits during ANC. However, just over half of pregnant women in Malawi and Zambia complete four ANC visits. Fewer visits has a significant impact on the pregnancy because crucial assessments and treatments are missed, and complications are not detected or acted upon. Even when women attend the ANC clinics, there may be poor compliance with recommended actions at each contact visit, which is compounded by fragmentation of health services. To improve services for pregnant women we will implement an ENHANCEd Antenatal Care Bundle (ENHANCE). ENHANCE will provide a comprehensive bundle of measures developed for primary health centres in resource limited settings, to support the consistent delivery of all aspects of antenatal care according to WHO 2016 guidelines. ENHANCE includes tools, leadership, mentorship, task shifting, and basic supplies to improve the quality of care and maternal and neonatal outcomes.

Broad Objective

To determine whether an ENHANCEd Antenatal Care Bundle compared with standard ANC care is acceptable and improves the antenatal care services, maternal,perinatal and neonatal outcomes in Malawi and Zambia.

Specific Objectives

Primary objective:

1) To measure the effectiveness of ENHANCE on reducing the composite outcome of, “maternal perinatal and neonatal mortality and morbidity and emergency referral”

Secondary objectives

1) To measure the effectiveness of ENHANCE on reducing maternal and newborn morbidity
2) To assess the effectiveness of ENHANCE on Health care workers’ practices related to detection, treatment and prevention of major related conditions
3) To determine the effectiveness of ENHANCE on improving knowledge, attitudes, and practices among healthcare professionals and women
4) To explore the perceptions of healthcare professionals and pregnant women on the effectiveness of ENHANCE
5) To assess fidelity and quality of implementation, acceptability and sustainability of ENHANCE across primary health care settings in Malawi and Zambia
6) To identify contextual factors associated with variation in the effect of ENHANCE across primary health care settings in Malawi and Zambia.

Methods
This is a multi-country, parallel cluster-randomised controlled trial with baseline period. There is an integrated implementation evaluation and health economic evaluation. The trial will include primary healthcare centres in Malawi and Zambia as clusters. During the first three months each cluster will provide standard care to establish weekly rates of maternal and newborn outcomes. After the baseline, the clusters will be randomly allocated in a 1:1 ratio to ENHANCE or standard care with provision of basic ANC supplies, using a minimisation algorithm to account for the imbalance in location, hospital deliveries volume and distance to referral facility. Both quantitative and qualitative approaches will gather the data required to meet the objectives. We will conduct an intention-to-treat analysis of the composite primary outcome. Descriptive statistics for continuous (mean and standard deviations), discrete (median and range or interquartile range) and categorical (frequency counts and percentages) variables will summarize baseline characteristics (demographic and clinical data) and outcome variables. Process evaluation surveys will be summarised using descriptive statistics as appropriate, and responses compared across PHCs and countries. Interviews will be analysed using combined deductive framework and inductive thematic analysis.

Expected findings
We will implement ENHANCE across 12 sites in Malawi and four in Zambia. We expect that staff and clients will improve adherence to WHO recommendations for antenatal care.

Dissemination
Research findings will be shared with local and global stakeholders ,COMREC and KUHes librarythrough reports, research dissemination conferences, peer reviewed publications, participant and public information groups, and via national and international forums.

1.0 INTRODUCTION

Maternal and newborn mortality and morbidity remain at unacceptable levels in many low-middle-income countries (1). A substantial proportion of these adverse outcomes are preventable as several interventions have been shown to be effective and supported by high-quality evidence. These interventions include antenatal care interventions to identify pregnancy related complications and prompt treatment(2), use of uterotonics, magnesium sulphate and antibiotics prophylaxis together with infection control measures to prevent and treat three major causes of maternal morbidity and mortality, namely postpartum haemorrhage (PPH), preeclampsia/eclampsia, and maternal sepsis, respectively(3). These preventive interventions are particularly relevant during the antenatal period, since in many low-resource settings antenatal care visits represent the only opportunity for providing pregnant women with health-care services. Thus, during ANC, pregnant women are informed and educated about pregnancy related complications, the advantages of skilled delivery care and birth spacing but also reached with several interventions such as anaemia, HIV, syphilis and malaria prevention, which are crucial for their health and the health of the unborn child (4,5).

ANC reduces maternal and perinatal morbidity and mortality directly through early detection and treatment of pregnancy-related illnesses, and indirectly through identification of women at high risk of delivery complications(6–9). Studies have shown an association between ANC utilisation and uptake of skilled delivery care; especially when skilled staff provides all necessary care for ANC clients, they are likely to come and deliver at the facility by skilled birth attendants, potentially reducing maternal and newborn morbidity and mortality (10,11).

Despite high antenatal care (ANC) and institutional delivery rates, both at 97% as of 2019 in Malawi and 97% and 84%, respectively for Zambia in 2018, women continue to die (12,13). Malawi and Zambia need to utilise these opportunities to provide quality of care to mothers during ANC and at birth. Besides, with a maternal mortality ratio of 381(Malawi) and 135 (Zambia) maternal deaths per 100 000 livebirths in 2019 (14), only 51% and 54% of pregnant women receive four antenatal care visits in Malawi and Zambia respectively. Almost half of pregnant women start ANC during fourth and fifth month of their pregnancy in both countries (12,13), Malawi and Zambia need to develop and prioritise strategies that increase contact of pregnant women with the health system and to improve the quality and integration of antenatal care services. However, in resource limited settings, many interventions aimed at improving care do not achieve their desired change, with few efficiently implemented and sustained due to health system constraints such as poor infrastructure, insufficient supply chain resulting in stockouts of essential resources, or poor organisation and leadership(15,16). However, evidence suggests that using care bundles to treat postpartum haemorrhage lowered the amount of resources used(16).

A care bundle is when a set of interventions are used together and significantly improve the patient or client outcomes compared to when implemented individually (17). Care bundles are used widely across healthcare settings to improve patient outcome(18). In high income setting, care bundles have been a basis of sepsis improvement, pressure ulcer care, prevention of ventilator associated pneumonia, health care quality improvement and reduction of perineal trauma during childbirth (19–

24). Similarly, a healthcare-associated infection (HAI) prevention bundles have been utilised in low middle income countries' (LMICs) neonatal units and reduced sepsis rates (25). While the elements of the bundle are essential, their interaction with health care system processes and staff behaviour need also to be targeted. We aim to implement the ENHANCE antenatal care bundle to support the consistent and comprehensive delivery of all aspects of antenatal care, according to current WHO guidelines.

The proposed bundle elements address client preparedness, assessment by the healthcare worker and the environment where the assessment is being conducted and include:

1. ANC tools like job aids for health workers, a revised health passport booklet, checklist reminders for both HCWs and women, an ANC education programme and referral thresholds.
2. Leadership & accountability, mentorship and task shifting to address local context and practical to PHC setting.
3. Basic ANC supplies, drugs and equipment including syphilis testing kits and treatment, blood pressure machines, fetal scopes, glucometer, pregnancy test kits, urine dipsticks, haemacue for checking HB and HIV testing kits (and treatment which is already in place).

While educating and counselling pregnant mothers on how to keep themselves and their unborn child healthy is crucial during ANC (26), evidence suggests that integrating a job aids-focused intervention into routine antenatal care results in good outcomes on provider communication and maternal knowledge and understanding(27). The updated health passport booklet will help to increase adherence to recently issued WHO ANC recommendations(28). Using checklists has helped healthcare professionals give high-quality necessary care during institutional deliveries (29,30).

Integrating leadership, management and governance interventions enhanced the performance of primary healthcare activities and maternal and child service uptake in Ethiopia, which contributed to the reduction of maternal and child deaths (31). Mentorship programmes are more appropriate in rural settings where midwives or nurses are geographically dispersed and have limited access to formal or informal education or training(32).Other studies have recommended use of champions to empower facility leadership to improve care delivery(33)(34). A healthcare champion is any health professional with the necessary expertise in a relevant field, respected by peers and backed by supervisors, who actively promotes or implements evidence-based practices to enhance care quality (33)(34). Use of champions has the ability to drive implementation outcomes by influencing the staff engagement in change and overcome organisational barriers to change(33). Task shifting is recommended in settings where the health work-force is disproportionate to population, to enable professional workers to focus on more technical, life-saving roles and to expand coverage of effective interventions(28,35). Finally, basic
supplies will ensure that WHO ANC recommended essential screenings are done at the right time and ensure timely recognition and treatment of risks and complications.

Partial formative work has been conducted to co-develop the intervention and tools. This includes ANC assessment reports through DIPLOMATIC ANC study (P.11/21/3461), which identified gaps in completing ANC assessment against WHO ANC guidance both in Malawi and Zambia. The well

documented areas in that study included weight, BP check, abdominal palpation, HIV and Syphilis testing, Insect treated nets, iron and antimalarial supplementation and scanning at times. The gaps identified in that study included number of visits/contacts, HB, urine test, breast examination, vulva inspection, nutrition assessment and supplementation and blood grouping and cross-matching. The same DIPLOMATIC study contributed the formative work of revising the health passport booklet (36), data verification of maternal deaths and near miss in DHIS 2 in Malawi, and an initial design workshop between Malawi and Zambia team to develop the proposed bundle. The proposed ENHANCE bundle will undergo review and possible modification during a final design workshop with diverse stakeholders and Patient and Public Involvement (PPI).

To understand the effect of ENHANCE in improving process outcomes and thereby reducing maternal and newborn morbidity and mortality, we will conduct an appropriately powered, cluster-randomised trial. Working with 32 health centres as clusters in Malawi and Zambia, we will collect baseline data before the implementation of ENHANCE for three months. The data to be collected will include outcomes of interest, resources availability and staffing. Then, 12 health centres (clusters) in Malawi and 4 in Zambia will be randomised to test ENHANCE, the remaining facilities will continue providing the standard of care but will only be provided with basic supplies.

Health centres (clusters) randomised to ENHANCE will receive the intervention which will include ANC tools and leadership, mentorship and task shifting components in addition to basic supplies. In PHCs randomised to ENHANCE two champions will be identified per cluster by the local management team in consultation with trial team. The champions will be either a midwife or other staff working within maternal health. The champions will be trained on the bundle and be willing to train, orient or mentor others. The champions will also be responsible for tracking additional activities of interventions implemented by other partners from both control and intervention that may potentially contaminate the intervention.
There will be a three-months transition period whilst these intervention components are well established and then a further 9 months during which time we will monitor and compare the outcomes in the health centres (clusters) randomised to ENHANCE and those where usual practice is continuing. We will conduct process evaluations to also examine in detail the way the bundle is implemented in practice, understanding the influence of modifying and contextual factors on this bundle. This part of the evaluation will involve monitoring what is happening in health centres, conducting survey, reviewing the processes of ANC, and detailed qualitative interviews to understand views and opinions of health centre facility staff and clients. Figure 1 summarises components of ENHANCE.

Finally, we will create a feedback mechanism between participating PHCs and their referring facility (the district hospital) to be implemented from the baseline phase to the end of cluster participation. This feedback mechanism will be developed during a wide stakeholder's design workshop in the formative phase.

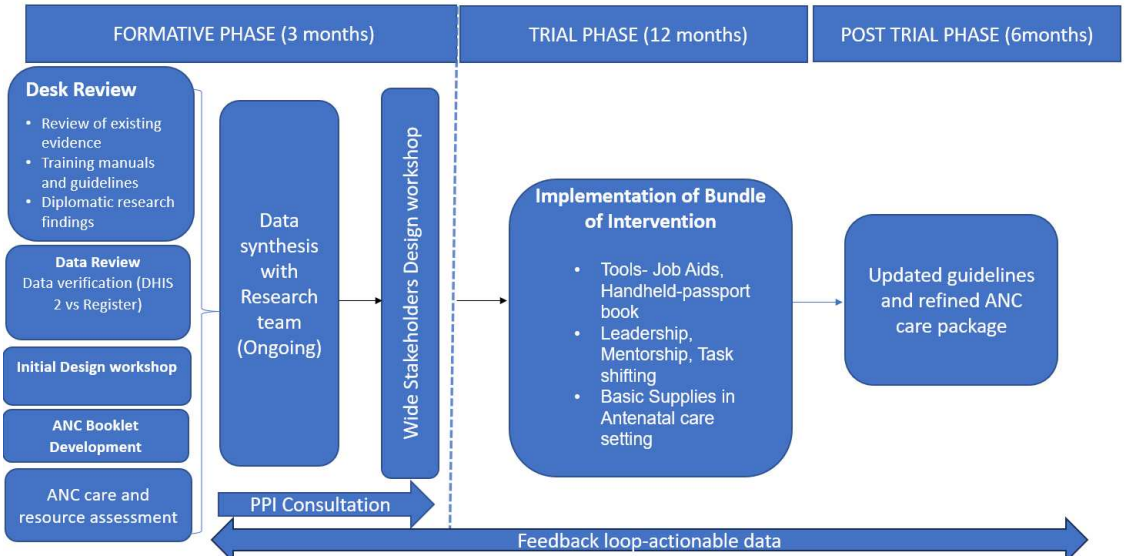

Figure 1: Enhanced Antenatal Care Bundle (ENHANCE)

2.0 RATIONALE

The "Enhanced Antenatal Care" bundle (ENHANCE) will be carefully developed for primary health care (PHC) settings in Malawi and Zambia where resources are limited. The bundle aims to maximise limited resource use and change healthcare workers behaviour to ensure that mothers using ANC services in health centres get the comprehensive care possible to improve prenatal health for both the mother and developing fetus, and potentially reducing maternal and newborn morbidity and mortality.

Malawi and Zambia have adopted the 2016 WHO guidelines on antenatal care (28). However, with only 51% (Malawi) and 54%(Zambia) of pregnant women completing four ANC visits, it still falls short of the current 2016 WHO ANC model recommendations of 8 care contacts during pregnancy (12,13,28). Yet, even when women attend ANC there is poor compliance with guidance on the recommended actions at each contact, for instance, in Malawi, only 29% of all pregnant women who received ANC, received all three key services, blood pressure measurement (84%), blood sample (94%) and urine testing (32%) in 2019 (12). Implementing ENHANCE will provide a detailed understanding of what works but also how and why it works. This serves to ensure that evidence-based practices of proven effectiveness can be successfully replicated and implemented in other settings.

3.0 OBJECTIVES

3.1 Broad Objective

To determine whether an ENHANCEd Antenatal Care Bundle compared with standard antenatal care is acceptable and improves the antenatal care services, maternal, perinatal and neonatal outcomes in Malawi and Zambia.

3.2 Specific Objectives

Primary objective:

1) 1) To measure the effectiveness of ENHANCE on reducing the composite outcome of, "maternal perinatal and neonatal mortality and morbidity and emergency referral"

Secondary objectives

1) To measure the effectiveness of ENHANCE on reducing maternal and newborn morbidity
2) To assess the effectiveness of ENHANCE on Health care workers' practices related to detection, treatment and prevention of major related conditions (anaemia, pre/eclampsia, congenital syphilis, risk for obstruction of labour)
3) To determine the effectiveness of ENHANCE on improving knowledge, attitudes, and practices among healthcare professionals and women
4) To explore the perceptions of healthcare professionals and pregnant women on the effectiveness of ENHANCE
5) To assess fidelity and quality of implementation, acceptability and sustainability of ENHANCE across primary health care setting in Malawi and Zambia
6) To identify contextual factors associated with variation in the effect of ENHANCE across primary health care setting in Malawi and Zambia

3.3 Hypothesis

The primary hypothesis is that the bundle will improve maternal, perinatal and neonatal outcomes in the intervention arm as compared with the control arm. Secondary hypotheses are: the intervention will improve the management of major pregnancy-related conditions; it will improve the knowledge, attitudes and practices of healthcare workers to provide the recommended practices as per WHO guidance; and contextual factors that affect the implementation of the bundle may also impact its effectiveness, acceptability and sustainability.

3.4 Implementation outcomes

Table 1 summarises the objectives, outcome measures and timepoint of evaluation.

Objectives	Level of evaluation	Outcome measure	Timepoint(s) of evaluation
Primary objective			
1) To measure the effectiveness of ENHANCE on reducing the composite outcome of, "maternal perinatal and neonatal mortality and morbidity and emergency referral"	Clinical health outcome	**A single composite primary outcome will be used. The components of the composite outcome will be:** • Maternal deaths • Stillbirths • Neonatal deaths • Eclampsia • Uterine rupture • Antepartum haemorrhage • Post-partum haemorrhage • Maternal sepsis • Birth asphyxia • Prematurity (born before 37 weeks gestation) • Low birthweight (weight less than 2500g) • Appropriate emergency referrals Each component of the composite will also be reported.	Monthly collection of routine health facility records for maternity ward records. From the baseline phase to the end of cluster participation
Secondary objectives			
1) To measure the effectiveness of ENHANCE on reducing maternal and newborn morbidity	Clinical health outcomes	• Proportion of women with the following obstetric complications: ○ (Pre)-eclampsia ○ Anaemia (Hb less than 7g/dl) ○ Syphilis	Monthly collection of routine health facility for maternity records and cohort records (6months prior) for ANC data records. From the baseline

Objectives	Level of evaluation	Outcome measure	Timepoint(s) of evaluation
		• Proportion of women referred out for any cause, or due to pre/eclampsia, anaemia and risk for obstruction of labour. • Proportion of newborns with the following complications: ○ Neonatal sepsis • Proportion of NNU admission for any cause • Proportion of newborn breastfeeding initiated within 60 minutes of birth • Proportion KMC admissions • Proportion of newborns resuscitated • Proportion of newborns received antibiotics	phase to the end of cluster participation Cohort records (6months prior to reporting month) for ANC data records. From the baseline phase to the end of cluster participation Monthly collection of routine health facility records for maternity and neonatal records. From the baseline phase to the end of cluster participation

2) To assess the effectiveness of ENHANCE on Health care workers' practices related to detection, treatment and prevention of major related conditions	Process outcomes	• Proportion of women starting ANC visit in first trimester (<12 weeks)
		• Average total ANC visits per woman
		• Proportion of women received required doses of the following (data from registers)
		  ○ TTV (≥2 doses)
		  ○ SP (≥3 doses
		  ○ Albendazole/Mebendazole (none or 1 dose)
		  ○ FeFol (≥120 tablets)
			Cohort (6 months prior to reporting month) data summary of routine health facility records for ANC. From the baseline phase to the end of cluster participation

Objectives	Level of evaluation	Outcome measure	Timepoint(s) of evaluation

		• Increased number of women receiving the following screenings during first or/and subsequent visits:
		  ○ Pregnancy test
		  ○ Syphilis test
		  ○ Anaemia (HB) check
		  ○ Blood pressure check
		  ○ Feta Heart Rate check
		• Proportion of women receiving:
		  ○ Pre/eclampsia treatment
		  ○ Syphilis treatment
		  ○ Anaemia treatment
		• ANC attendance
		• Postnatal check:
		  ○ Mother and baby at <48 hours
		  ○ Mother and baby at 1 week (from register)
		  ○ Mother and baby at 6 weeks (from register)
		  ○ Immunisation baby at birth (OPV 0 and BCG-(from register)
			Monthly collection of routine health facility records for maternity and neonatal records. From the baseline phase to the end of cluster participation
			
			Two months (prior to reporting month) postnatal outcome data. From the baseline phase to the end of cluster participation. From the baseline phase to the end of cluster participation

Objectives	Level of evaluation	Outcome measure	Timepoint(s) of evaluation
3) To determine the effectiveness of ENHANCE on improving knowledge, attitudes, and practices among healthcare professionals and women	Impact outcome	• HCWs reported change in awareness, knowledge, attitudes, behaviours, and/or practices with implementation of the bundle • Reported increase in ANC service responsiveness and utilisation • Women's reported change in awareness and behaviours in response to the WHO ANC guidance (more than 4 contacts) as well as changes in experience with and quality of care received • Staff trained in mentorship • Staff mentored • Support staff trained in task shifting • Task performed by support staff (task shifted)	From the implementation of the intervention to the end of cluster participation.
4) To explore the perceptions of healthcare professionals and pregnant women on the effectiveness of ENHANCE	Impact outcome	• Experience reported by HCWs and clients	Implementation of the intervention
5) To assess fidelity and quality of implementation, acceptability and sustainability of ENHANCE across primary health care settings in Malawi and Zambia	Process outcome	• Fidelity • Dose (coverage) • Appropriateness (sustainability)	From the implementation of the intervention to the end of cluster participation.

Objectives	Level of evaluation	Outcome measure	Timepoint(s) of evaluation
	Impact outcome	• Acceptability • Process mediators	
6) To identify contextual factors associated with variation in the effect of ENHANCE across primary health care settings in Malawi and Zambia	Impact outcome	**contextual factors**	From the implementation of the intervention to the end of cluster participation.

4.0 METHODS

4.1 Type of study

ENHanced ANtenatal Care bundlE (ENHANCE) is a non-blinded, multi-country, parallel cluster-randomised controlled trial in which health centres are the units of randomisation and clients/patients are units of analysis in low-resource primary health facility settings. The study includes a three months baseline period, a three months transition period and a nine months intervention period. Alongside the primary intervention trial, we will conduct an implementation study and an economic evaluation (depends on funds availability).

The proposed bundle will undergo wide stakeholders design workshop and Patient and Public Involvement (PPI) consultation for review and possible suggestion during formative stage. During this phase the stakeholders will also work on feedback mechanism to provide actionable data for the participating PHCs and for monitoring outcomes beyond PHCs.

During first three months each cluster will continue with their standard care and data will be collected to establish weekly rates of clinical and process outcomes which will act as a baseline period. After baseline, the cluster will be randomly allocated in a 1:1 ratio to ENHANCE or standard care with essential supplies provided too to control clusters. There will be a three-month transition period during which ENHANCE will be introduced to the clusters randomised to the intervention. Data collected during transition period will not form part of analysis.

The intervention will be delivered at a primary health centre (PHC) level and targets the health care providers, clients, and systems within the facility. The intervention seeks to change the behaviours of health care providers and clients to improve adherence to WHO ANC guidelines and best practices in preparedness, detection, treatment and prevention of major pregnancy related conditions. The intervention period will be for nine months excluding transition period. During this period process evaluation will be embedded to understand how the intervention is operationalising in practice.

In the final months of the study, we will complete data analysis and disseminate the information and also working on recommendations and guidelines.

4.2 Study setting

The study will be conducted in at least 24 public primary health centres in Malawi and 8 in Zambia. These health centres will be randomised into either intervention or control arm (12 in each arm from Malawi and 4 in each arm from Zambia. In Zambia the sites will be the ones where ultrasound scan is being conducted as part of maternal health services. The Zambian study sites were supported with ultrasound machines by the DIPLOMATIC study in 2021 and include Chisamba, Mumbwa and Chongwe districts. The 8 public primary health care centres in Zambia are summarised in Appendix 1A. The participating primary health care centres in Malawi have been identified from Mangochi district in the southeastern region and Lilongwe in the central region. Lilongwe and Mangochi were selected due to their high percentages of pregnant women attending antenatal care and delivering in healthcare facilities (37). Appendix 1B shows all eligible PHCs in Malawi.

4.3 Selection of participating facilities

The PHCs with between 700-2000 ANC attendants per year, provide the basic emergency obstetric care (Bemoc) and are willing to participate will be included in the study. Bemoc sites have been selected because many women first seek care in these sites. Sites will be identified and selected in collaboration with the study team, PI and Ministries of Health to ensure that the sites fulfil the requirements of the protocol including adequate participant numbers, representativeness, and equity.

After which identified PHCs will be visited and a "site readiness assessment" will be completed with the country study team, facility leadership and midwives. Human and physical resources available at the facilities will be assessed as part of site readiness, with the aim to ensure that the 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 and PHCs that are able to submit routine reports on time. Healthcare facilities that meet the selection criteria will then receive training in preparation for the baseline data collection. Site readiness assessment tool to be used is in Appendix 2.

The PHCs fulfilling the trial criteria will be selected to be a cluster for ENHANCE and will be opened once necessary approvals and documentations are met.

PHCs in Malawi and Zambia

Malawi's healthcare system is structured into four levels: community, primary, secondary, and tertiary (38). These levels are interconnected through a referral system. Primary Health centres in Malawi primarily offer outpatient services and basic maternity care, aiming to serve a population of 10,000. They are typically overseen by medical assistants, clinical technicians for outpatient departments, and nurse/midwife technicians for maternity care, with training periods averaging 2–3 years (38). However, Malawi faces a severe shortage of qualified healthcare workers, with only 0.488 doctors per 10,000 and just 5 midwifery and nursing staff per 10,000 (39). This is far below World Health Organization's recommended ratio of 4.45 health workers per 1000 population (40). Consequently, many primary healthcare staff, particularly nurses and midwives in maternity care, provide basic maternity services and are instructed to refer cases requiring higher-level care.

Zambia's healthcare system is organized into three main levels of care: First level (Primary care), Second level (Secondary care) and third level (Tertiary care). These levels are linked through a referral system. First Level (Primary Care) includes community-level health services such as health posts, rural health centres, and district hospitals. They provide primary healthcare (PHC) and preventive health services. At the District level PHC is overseen by medical Doctors, Medical licentiates, Clinical officers and Nurses, while Clinical officers and Nurses/midwives are in charge of most Health posts and health centres. Because more Doctors and Medical Licentiates managing complicated cases are found at District Hospitals, Health centres and health Posts consequently refer to these Hospitals. Like Malawi, Zambia faces a critical shortage of health care professionals with 2.6 medical doctors 2.6 per 10,000 and 21.5 nurse and midwifery staff per 10,000 (39).

4.4 Study period

The study period will be approximately 12 months.

Table 2: Study period

Activity	Year 1- 2024												Year 2- 2025												Year 3- 2026						
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
Trial planning and initial co-design																															
UOL sponsorship																															
COMREC ethics (Malawi) or APEX (Zambia)																															
UOL ethics submission																															
Site visitation																															
Final Co-design																															
Baseline Phase																															
Randomisation																															
Transition phase, trainings and resource allocation																															
Intervention phase																															
Process evaluation																															
Data analysis																															
Write Up and publication																															

5.0 CONCEPTUAL FRAMEWORK

The COM-B model is a representation of behaviour change theory; for our purposes, the model aims to understand behaviour in terms of the capability, opportunity, and motivation of actors to engage with and facilitate evidence based clinical practice during ANC (41,42). A range of co-interventions will address key aspects of the model. Briefly, capability will be addressed with enhanced education and training in leadership and mentorship delivered at the site and then reinforced by a local site champion providing ongoing feedback and refresher sessions. This will be supported by paper-based tools including visit specific checklists and aide memoires, which will also make it easier for providers to recall and complete all requirements consistently. ANC clients will be also provided with reminders to prompt them seeking care on time. Social opportunity will be enhanced through the peer-led collaborative learning approach (mentorship). Physical opportunity requires basic supplies to be available, and this will be enabled through physical supply monitoring and close linkages with the Ministry of Health. We will also employ task-shifting of key basic monitoring activities such as blood pressure checks and urinalysis. Motivation will be enhanced by supportive supervision, including feedback on site performance, oversight from the Ministry of Health Quality Management

Directorate and site launch events that fully engage site leadership. ENHANCE applies the COM-B model to health systems settings to facilitate evidence based clinical practice during antenatal care.

The targeted behaviours in this trial are shown in Figure 2, while approaches and components to facilitate achievement of targeted behaviours are summarised in Figure 3 below.

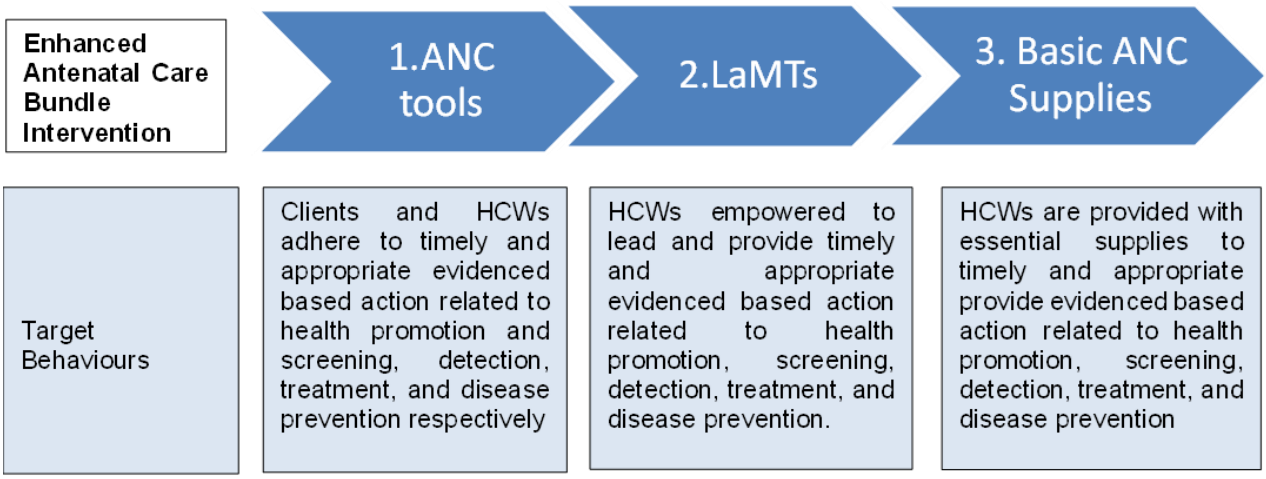

Figure 2: Enhanced Antenatal care Bundle Trial-target behaviours flowchart.

	CAPABILITY	OPPORTUNITY	MOTIVATION
FACILITY FOCUSED APPROACHES	• Site launch leadership training and education • Local leadership issue solving • Client education	• Local leadership engagement • Trial Champions	• Public dashboard of site performance • Site recognition • Actionable data feedback
FACILITY FOCUSED APPROACHES	• Champion network • Coaching by local champions • ANC tools, job aids, health passport booklet, checklist reminders, visit specific checklist, client reminders, education guides, referral threshold	• peer-led collaborative learning approach • Tracking sheet • Syphilis testing and treatment kits • Pregnancy test kits • Blood pressure machines • Heamacue • Fetal scopes • Task shifting	• Certification for completion of training • Locally conducted monitoring and feedback • Supportive site visits by national, district and study team

Figure 3: Summary of co-interventions that seek to support clients and Healthcare providers behavioural change

6.0 STUDY INTERVENTIONS

Control sites

1: Basic ANC supplies

The bundle containing necessary medicines, laboratory supplies, material and equipment will be provided at control sites during baseline phase to standardise the sites. The Ministry of Health will be responsible for continuous supply of medicine to all ANC clinics, with the project coming in if there will be anticipated stockouts in the sites. The project will supply control sites ANC clinics with kits for syphilis testing and treatment, blood pressure machines, fetal scopes, glucometer, pregnancy test kits, urine dipsticks, haemacue for checking HB and ensure that HIV testing and treatment which is already in place continues to function in the study sites. The study will continue to monitor such resource availability weekly in all clusters throughout the study. The tracking sheet will be introduced to monitor stock levels to avoid stockouts. 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.

There will be no ANC tools, training, mentorship and task shifting support that will be offered to control sites. The control sites will provide standard ANC.

Intervention sites

1: Basic ANC supplies

The basic ANC supplies will be same as for those provided to the control sites and all processes of monitoring and resupplying will also apply to the intervention sites.

2: ANC tools

A total of 6 tools (ANC card-booklet, job aids, checklist reminders, ANC education guide, referral guidelines, and tracking sheet) will be distributed to primary health care centres following WHO ANC guidelines. Training sessions for all maternity service staff will be conducted in partnership with MOH ensuring that health care providers are proficient in utilizing these resources effectively to enhance quality of ANC services. In addition, these sites will be supported with missing commodities and equipment. Practical aids that provide midwives and HCWs with step-by-step guidance on delivering essential care during ANC will be provided. The checklist reminders will guide midwives on what to check on each visit as well as clients when to seek ANC. We will provide ANC education platform that will ensure that mothers get the necessary information at each visit.

3: Leadership & accountability, mentorship and task shifting (LaMTs)

At start of intervention, during transition phase in each trial site, a training on leadership and accountability will be given to all HCWs working in maternity services. The leadership training manual and ANC guidelines will be used. We will adapt this training manual to suit the PHCs level. This leadership training will be specific for PHCs staff and equip them to take leadership roles when delivering care to ANC clients. We will train at least one midwife per cluster as a mentor who will be assisted by the study team in mentoring other HCWs during the study period. HCW will be responsible for taking vital signs observations to improve vital sign monitoring

compliance. Task shifting of vital signs observations to patient attendants or other cadres (with appropriate training and support) will be implemented to improve vital sign monitoring compliance.

7.0 STUDY IMPLEMENTATION PHASES

7.1 Formative work

During this phase the proposed ENHANCE bundle will undergo review from diverse stakeholders during a design workshop, which will include Patient and Public Involvement (PPI). Any suggested changes will be reviewed by both Malawi and Zambia study teams in collaboration with the Ministry of Health.

7.2 Baseline period

The Baseline period will last a total of three months during which comprehensive data collection will be undertaken. Initial analysis of baseline data to determine median cut points for the minimisation factors will take place after 2 months, with at least 2 months of data for all PHCs (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 PHC (cluster) being allocated during early month 3 of their baseline period. The baseline period will continue for the end of month 3 once allocation is known to allow facilities to prepare for implementation.

7.3 Transition period

Once the research team are made aware of the randomisation allocation, the PHCs (clusters) will be informed. Following the randomisation of clusters, the trial team will continue to collect data throughout the transition phase regardless of the treatment allocation. Data collected in this period will not be included in the final analysis.

7.4 Intervention Facilities

The Maternity staff from all PHCs randomised to the intervention will receive ENHANCE training that will enable them to implement the intervention effectively. The PHCs will be supported to roll out the intervention. During the bundle training, a champion will be identified from each PHC to oversee the day-to-day activities of the trial and to mentor others. The PHC facilities will be allowed a transition (set up) period of three months, to complete the delivery of training to all relevant staff, supplying of the tools, supplies and embedding improved practices into routine ANC care. The Champions will also provide performance monitoring and feedback and will be encouraged to share best practice and learning across their network. The task of midwives to check vital signs on ANC mothers will be task shifted to support staff (patient/hospital attendants and other cadres). The support staff who will implement task shifting of vital signs observations will receive appropriate training and being monitored by facility champions. Clusters will be launched with full engagement of the PHC staff. Provider motivation will be 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.

7.5 Control Facilities

Facilities not randomised to ENHANCE will continue with standard care but will be provided with basic ANC supplies. Monitoring of study outcomes will be conducted identically at the control PHCs. This will include understanding any contextual changes in facility practices or policies that could impact on the trial outcomes.

7.6 Monitoring of contamination

Monitoring for contamination of both the intervention and control sites will be conducted. The local team champions and trial team will monitor the introduction of any changes introduced and record their onset date. In control sites, this information will be collected by study team during monthly site assessment (section 13.2.2). 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 Zambia trial teams and recorded so that any impact on ENHANCE can be assessed. After randomisation, the commencement of a new study in the cluster should be discussed with the trial team, and Principal Investigator (PI) to consider study impact.

8.0 IMPLEMENTATION EVALUATION

Alongside the trial, we will conduct a process evaluation to assess the extent to which the interventions have been implemented as intended; key factors that may mediate their impact; why the interventions work or fail; and how different contextual factors influence success. This will be a mixed-methods approach to assess the processes, impact, and outcomes for ENHANCE. We will adopt the UK Medical Research Council guidance (figure 4) on process evaluations of complex interventions based on four main domains: context, description of the interventions and casual assumptions, implementation, and mechanisms of impact(43).

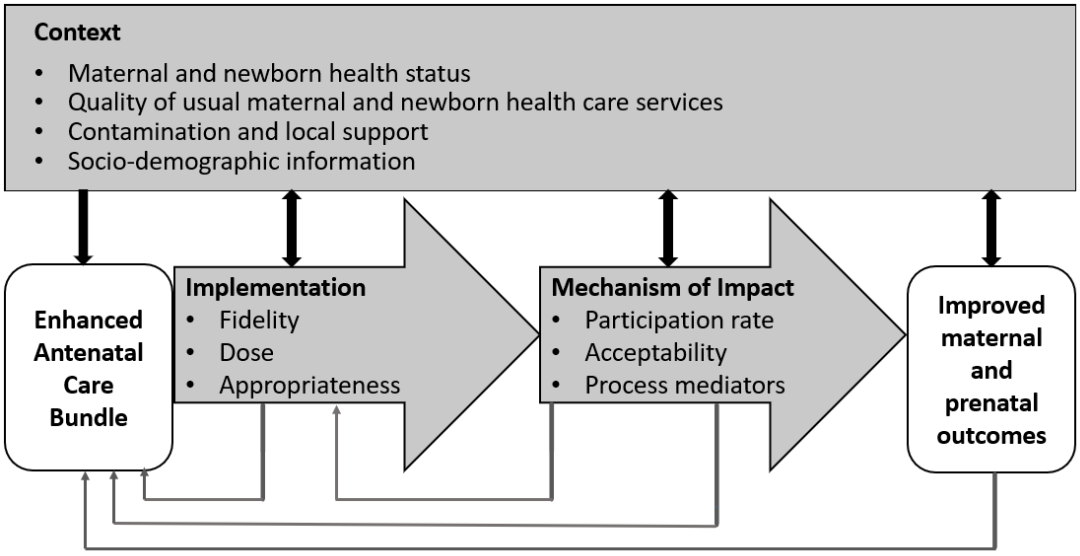

Figure 4: Process evaluation components

1) Context:

To assess inner and external contextual factors that may help or hinder implementation of ENHANCE, we will conduct surveys and interviews including items based on the Consolidated Framework of Implementation Research(CFIR) domains related to inner- and outer-setting (44).

2) Description of the intervention and casual assumptions:
Intervention activities will be documented and analysed for each site. Intervention components will be specified using Behaviour Change Technique Taxonomy. Hypothesised mechanism of change will be specified according to the COM-B model(45).

3) Implementation:

This domain will evaluate the implementation of ENHANCE in terms of the quality (fidelity), quantity (dose) and appropriateness for context, to ensure sustainability of the intervention. Bundle activities will be documented and analysed for each site. The activity documentation will include information on whether ENHANCE was delivered and engaged with as planned (fidelity), how much was delivered, frequency, duration and coverage (dose), how many healthcare workers (HCWs) used the bundle, and any information regarding modifications that were made to the bundle to adapt the study context and achieve the study protocol. These will be explored through multiple methods like facility assessments, in-depth interviews, and surveys with HCWs and clients, direct observations in ANC, and a review of relevant documents like bundle delivery checklist, training attendance and participation log. Data will be collected over the trial duration to explore possible loss of fidelity over time and extent to which implementation is sustained. Detailed sample size and data collection methods have been explained in section 13.0.

At the control facilities some assessments will be also conducted to understand the impact of providing resources alone and “contamination”. This will include interviews with HCWs and clients, direct observations in ANC, information of available projects and support, and review of relevant documents like resource delivery checklists and usage.

4) Mechanisms of Impact
The impact of ENHANCE on the experiences, perceptions and behaviours of healthcare staff and ANC clients will be explored through qualitative interviews. The qualitative research interviews will explore the social contexts within which the intervention is implemented, building a richer picture of intervention delivery and mechanisms of impact. We will also conduct a survey with HCW and clients to assess reach, exposure to, and acceptability of the intervention three months following the start of implementation. Finally, we will also conduct a survey of patient satisfaction with the services. We will aim to conduct this with an approximate ratio of 3:1 intervention to control women.

Process mediators, barriers, enablers to implementing the bundle, and sustainability will be explored using surveys in all ENHANCE PHCs; in-depth interviews will be based on COM-B model.

Surveys will be summarised using descriptive statistics as appropriate, and responses compared across PHCs and countries. Interviews will be analysed using combined deductive framework and inductive thematic analysis.

Figure 5 summaries the randomisation, implementation phases and evaluation.

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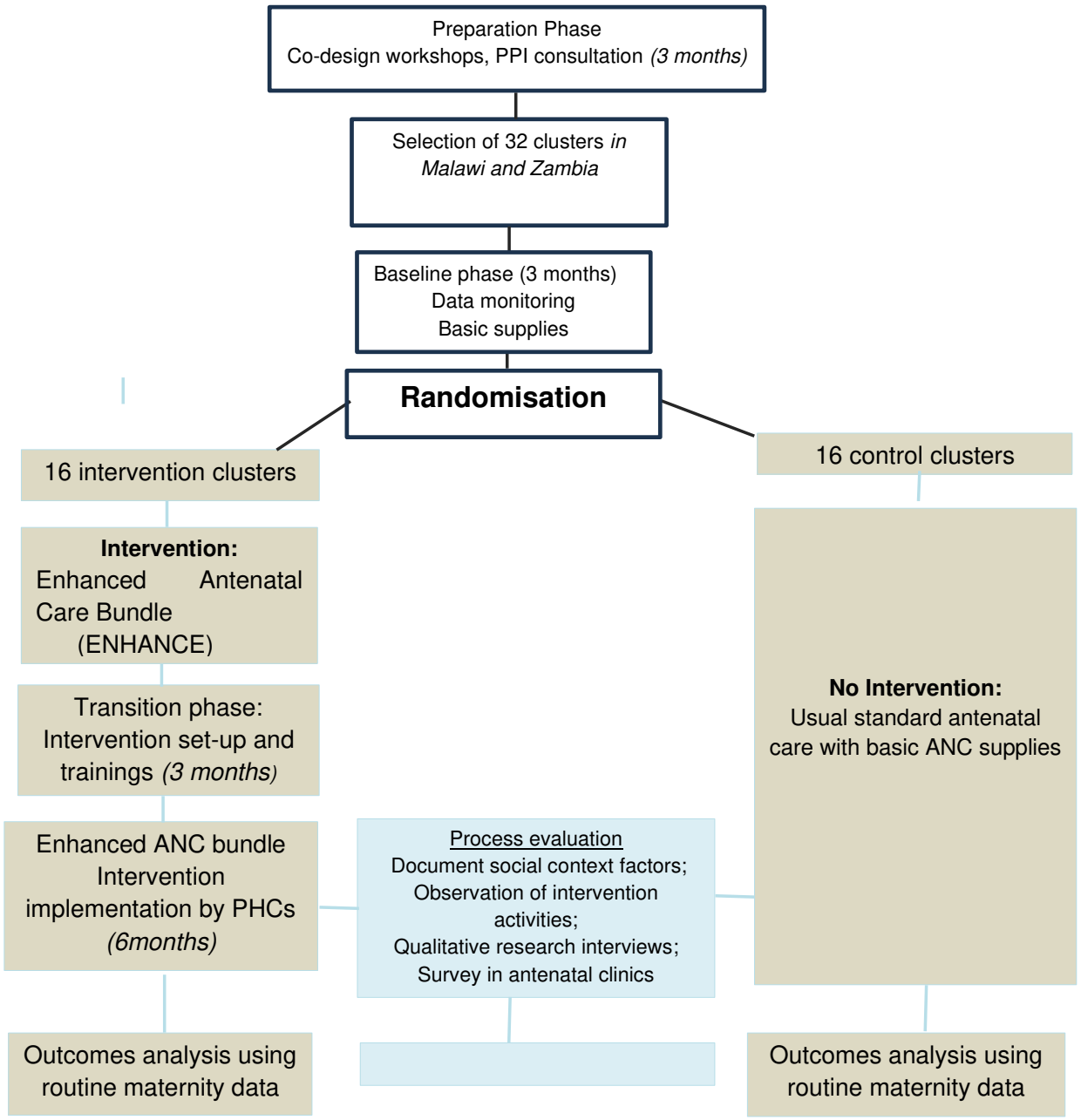

Figure 6 presents specific flow for Malawi site.

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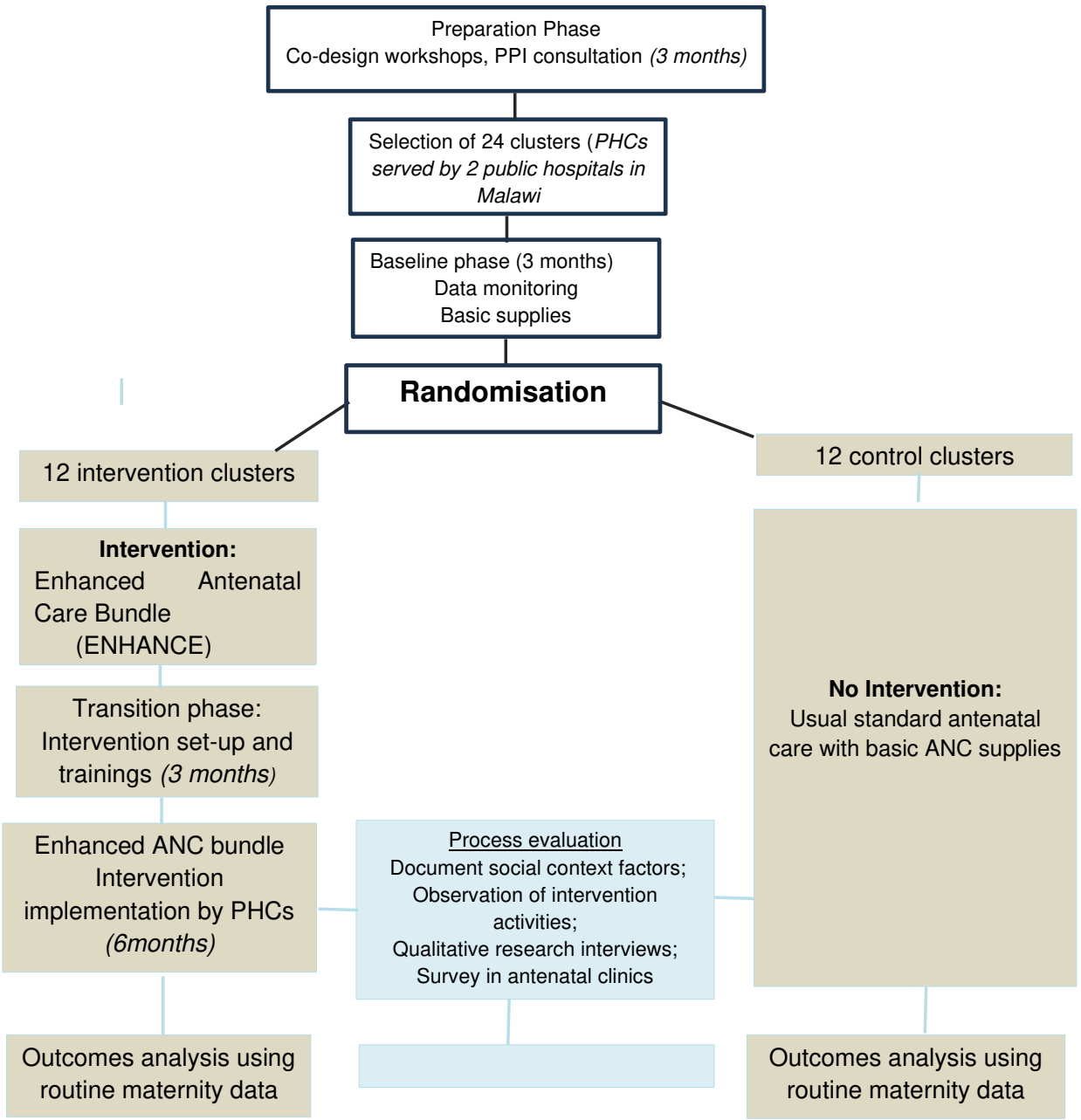

These figures are also representative of the study implementation for Zambia sites.

9.0 SAMPLE SIZE CALCULATION

WS7 sample size estimation and cluster randomisation

This parallel cluster-randomised trial (CRT) seeks to assess the impact of ENHANCE at the primary health facility level in Malawi and Zambia. Sample size was estimated to detect at least a 15% benefit of the bundle (measured by the absolute difference in the composite-primary-outcomes

between the intervention and control arm facilities). Assuming an intra-cluster (or within health facility) correlation (ICC) of 20%, at least twelve facilities (recruiting at least 100 participants per facility) are required in each arm to achieve a 90% statistical power at 5% significance level.

A total of thirty-two facilities (24 facilities from two districts in Malawi and 8 eligible facilities in Zambia) will be recruited (at least 1600 pregnant women per arm). To allocate the selected clusters (health facilities) into study arms (control or intervention), we will apply randomization by minimisation. This randomisation approach will account for any imbalances between the facilities in terms of geographical location (country and district), number of deliveries, and distance to the nearest referral hospital.

10.0 ELIGIBILITY CRITERIA

ENHANCE was developed to impact healthcare providers' and ANC clients' behaviour, to improve adherence to WHO ANC best practices guidelines in preparedness, detection, prevention and treatment of common related illness during antenatal care. ENHANCE will recruit 32 clusters (sites) based on sample size calculation described above. The facility data of all women who will attend maternity services during the trial will be collected and analysed following facility approval. Only women and health care workers who will participate in interviews or surveys during process evaluation will be required to provide informed consent.

10.1 Inclusion Criteria

Cluster

Primary Health Centre facilities offering maternity care will be included as a cluster following the completion of a successful feasibility report with the minimum prerequisites of:

1. A minimum of 700 ANC initial visits to a maximum of 2000 per year
2. Providers of basic emergency obstetric care
3. Public primary facility
4. Completed the site readiness assessment process

Participants-clients (in process evaluation-Interviews and survey)

1. ≤ 20 weeks of gestation at the initial visit to ANC
2. Able to provide informed consent
3. Willing to participate in the study
4. Aged 18 years and above

Participants-HCWs (in process evaluation-interviews and survey)

1. Healthcare Workers responsible for the care of women during pregnancy
2. Willing to participate in the study
3. Able to provide informed consent

10.2. Exclusion Criteria for Clusters

Cluster

1. PHC with less than 700 initial ANC visits per year-
2. PHCs with more than 2000 initial ANC visits per year-outliers to other facilities
3. PHCs not willing to participate in the study

4. High risk of contamination (geographically close to another participating centre or site where similar interventions are already taking place)

Participants-clients (in process evaluation-Interviews and survey)

1. > 20 weeks of gestation at the initial visit to ANC
2. Unable to provide informed consent
3. Medical and obstetric complications on the initial visit
4. Aged less than 18 years

Participants – HCWs (in process evaluation-Interviews and survey)

1. Not willing to participate in process evaluation
2. Unable to provide informed consent

11.0 DATA COLLECTION

11.1. Facility Sensitisation

Before any data collection, we will conduct facility sensitisation meetings to ensure that the facilities are aware of what the study is all about. This will involve a meeting with the health facility in-charges and MCH staff by the project management team. Ethical considerations explained in section 21 will be followed prior to any data collection.

11.2. Data collection methods

11.2.1 Qualitative Interviews

To understand implementation, we will conduct qualitative interviews and focus group discussions (FGDs) to explore the experiences of healthcare professionals and pregnant women with the intervention of enhanced antenatal care. We aim to capture the fidelity and quality of the implementation, the acceptability of the care bundle and client satisfaction. The qualitative inquiry will be informed by the theoretical Framework for Acceptability(46) and Framework for Implementation Fidelity(47) .

Health care worker interviews

Interview questions are structured to explore experiences, barriers, and enablers to delivering and sustaining ENHANCE. The interviews will also focus on broader areas of acceptability as well as identifying any unintended positive or negative effects of the intervention. Questions on barriers and enablers to delivering ENHANCE will be guided by COM-B and the Theoretical Domains Framework (TDF)(48). This approach allows for a rich data set on the contextual issues related to implementation (Appendix 3). Considering low numbers of staff in PHCs, especially from rural areas, at least two selected HCWs from PHCs involved in ENHANCE will be invited to the interviews. Approximately 32 interviews in the implementation clusters will be conducted, 24 interviews from Malawi and eight from Zambia. However, the final samples size will be based on data saturation and the richness of the information collected(49). We will also conduct at least 16 (1 per site) FGDs (minimum of 6 participants) to understand implementation impact from group perspective. The interviews will be conducted at least three months following implementation to ensure that new practice has been embedded. Appendix 4 is a FGD guide for HCWs.

We will also conduct 32 interviews (24 from Malawi and 8 from Zambia) (Appendix 5) and 16 FGDs to explore current ANC care management practice in control arm clusters (Appendix 6). This is to explore the differentiation between intervention and control arms and possible contamination.

Client interviews

We will also conduct 32 interviews (24 from Malawi and 8 from Zambia) (Appendix 7) with women accessing ANC services in the intervention sites to explore experiences, barriers, and enablers to accessing ANC services in the ENHANCE sites. We will also conduct 16 FGDs (Appendix 8) to explore acceptance, impact of ENHANCE and client's satisfaction with ANC services in the intervention site. The interviews will be conducted at least three months following implementation to ensure that new practices experiences are captured.

All personal identifying information (PII) will be stored on a password-protected server, and no PII will be shared beyond the research team. Following transcription, all recordings will be deleted from the recording devices. Transcript data will then be coded and analysed in NVivo 14.

If the diversity of sites and outcomes requires additional sites to be sampled to ensure a range of sites is represented in the sample, then the inclusion of additional sites for interviews will be considered. Analysis of the interviews will be undertaken by the Malawian and Zambian qualitative researchers, with support from the wider implementation evaluation team. Results of the qualitative evaluation will be provided to local project and facility staff to inform refinements to implementing ENHANCE.

11.2.2 Quantitative Surveys

Facility survey/site assessments

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 as well as core maternal and newborn quality of care indicators. This site assessment will be conducted before the baseline phase and then quarterly after baseline until the end of study (Appendix 2).

Weekly "facility forms" will be completed by the site champion to report facility level indicators, outcomes and other contextual changes. These include human and physical resource availability over time, any other critical policy or practice changes, any projects, trainings and interventions taking place at the sites (Appendices 9-11). The weekly forms will be also filled from control sites.

Client survey

Cross-sectional, electronic surveys for ANC clients will take place in all ENHANCE sites in each country (16 sites total, 10 per cluster, n=160) to explore change in awareness, knowledge and behaviours around receiving antenatal care in ENHANCE PHCs (Appendix 12) and client satisfaction survey in receiving care. This client survey will take place during the baseline phase and will be repeated near completion of ENHANCE to assess trial impact. We will aim to conduct this with an approximate ratio of 3:1 intervention to control women. Informed consent will be obtained as explained in section 21.7

Staff Surveys

Cross-sectional, electronic surveys will take place in all intervention sites in each country (16 sites total) with at least two HCWs per cluster (n=32). The surveys will include items based on COM-B/TDF models of behavioural change to explore barriers/enablers to implementing ENHANCE in the short- and longer-term. Process mediators, barriers, enablers to implementing the bundle, and sustainability will be explored using surveys in all ENHANCE PHCs (Appendix 13). The staff survey will also cover information on change in awareness, knowledge and, behaviours around providing ANC care to pregnant women (Appendix 14). This staff survey will take place during the baseline phase and will be repeated near completion of ENHANCE to assess trial impact. The survey will also assess reach, exposure to, and acceptability of the intervention three months following the start of implementation.

Primary and Secondary outcomes facility data

While the data for maternal and newborn outcomes that form part of primary composite outcomes and secondary outcomes on morbidity and ANC screening, detection and treatment services will be collected from District Health Information Software (DHIS2) on monthly basis using the form in Appendix 15. While other parameters that are not reported in DHIS2 but are available in facility registers or books will be collected using the form in Appendix 16. Appendix 17 summarises definitions of primary composite and secondary outcomes.

The identified champions will be required to track the intervention activities using the form in appendix 18 and to document their reflection on how the bundle is being implemented at their facilities using the champion log in appendix 19. Appendix 20 shows summary of outcomes, data methods and data collection tools as reflected in appendices.

Responses will be collected offline and uploaded by trial staff or champions. Responses will be pseudonymised – project champions will keep 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 MLW or Lusaka APEX Medical University (LAMU) data department. Informed consent procedure in section 21.7 will be followed prior to data collection.

12.0 DATA MANAGEMENT AND ANALYSIS

For ENHANCE the responsibilities for Data Management and monitoring are delegated to the MLW or LAMU data department. All data will be managed as per MLW or LAMU data management plans.

12.1. Source Documents

ENHANCE qualitative interviews and focus group discussions will generate data for qualitative data analysis. Qualitative data will be recorded in two forms – observational notes and digital audio recordings – and cross-referenced. A backup copy of the audio file will be saved, while another copy will be sent to the transcription and translation team. The audio file will be transcribed and translated directly into English by transcribers competent in both languages. All data will then be transferred to a qualitative data analysis software package (INVivo) and filed according to document type. Coded data will be transferred to a Microsoft Excel spreadsheet for broader thematic analysis. Following

transcription of audio files, all recordings will be deleted from the recording devices. Transcript data will then be coded and analysed in NVivo 14.

Paper-based and electronic quantitative surveys will be used to generate electronic data files for quantitative data analysis.

For facilities data, an ENHANCE source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes ENHANCE-specific source data. The trial team and champions in each facility will complete electronic case reporting forms (eCRFs) to aggregate anonymised data. Staff who are delegated to complete the eCRFs will be trained to ensure high quality data collection that adheres to all study requirements. MLW or LAMU data department and the study investigators will not have access to any identifiable information for the records entered into the eCRF database.

All electronic data will be kept in secure password protected databases housed on a secure network within MLW and LAMU. Strict access controls will apply both to the server and the databases. Database encryption is managed by the institutional IT departments using their rigorous SOPs.

All personal identifying information (PII) collected during interviews, focus groups and surveys will be stored on password-protected files stored on a secure network within MLW and at Lusaka Apex Medical University. No PII will be shared beyond the research team.

12.2. 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, tested and developed to prevent harms.

12.3 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 composite primary outcome. All observations will be included in the analysis. Descriptive statistics for continuous (mean and standard deviations), discrete (median and range or interquartile range) and categorical (frequency counts and percentages) variables will be applied to summarize baseline characteristics (demographic and clinical data) and outcome variables. Point estimates and 95% confidence intervals (95%CI) will be calculated for all outcomes. In the primary analysis, generalised linear mixed effects models (using a log link binomial distribution) will be applied to compare the risk of developing primary outcomes between the standard care and intervention groups using risk ratios (95%CI) and risk differences (95% CI), while adjusting for intra-cluster (hospital) clustering and potential residual confounding of minimization factors. Cluster and cluster by period will be included as random effects, and the minimisation factors (country, district, facility size and distance to referral facility) included as covariates. Exact P Values will be reported, and P-value<0.05 will be considered a significance association. If 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 composite 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 composite 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.

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

13.0. DATA MONITORING

13.1 TRIAL MONITORING

Monitoring is conducted to ensure the protection of patients participating in the trial and that 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 trial management group (TMG) and PIs 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.

13.1.1 Central Monitoring

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

13.1.2. Clinical Site Monitoring and auditing

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 PICF. 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.

14.0. RECORDS RETENTION

The retention period for ENHANCE 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 MLW data department or Lusaka Apex Medical University, 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.

The MLW data department and Lusaka Apex Medical University undertake 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. The closed database will have very controlled access as detailed in the MLW policy document. All paper records will be stored in the on-site temperature and pest-controlled archive (such as the MLW data archive) for a period indicated in the MLW Data archive policy document (10 years).

15.0. 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 trial 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 trial team at the MLW data department or Lusaka Apex Medical University 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 MLW data department or Lusaka Apex Medical University and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The independent members of the International Scientific Advisory Committee (ISAC) will provide oversight of the trial.
- The TMG will monitor trial progress and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan

16.0. SAFETY REPORTING

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

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.

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.

17.0. PUBLICATION AND DISSEMINATION

17.1. Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, always maintaining participant confidentiality. Individual HCWs 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 “ENHANCE 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/) and the requirements of the funder, NIHR UK, will be respected. The study registration number allocated will be attached to any publications resulting and members of the TMG 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. ENHANCE 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.

17.2. 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 ENHANCE Collaborative group which will also be named at the manuscript head. Named authors should include the study’s principal 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. Considerations for equitable authorship (ensuring local authors lead on local analyses, considerations for gender of authors) will be made throughout.

17.3. 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 MLW in Malawi and LAMU in Zambia communications team, and they will work collaboratively with the trial teams from Malawi-Liverpool-Wellcome Research Programme , the Kamuzu University of Health Sciences, Malawi, LAMU in Zambia 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.

Results from this study will be published in peer-reviewed journals, will be available via download on relevant websites, and will 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 national policy in Malawi and in Zambia and impact on practice globally. We will continue 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 Zambia to inform them of the research findings and implications for care, and other key international stakeholders such as the national professional organisations or active NGOs. A copy of the final report and any published paper(s) or abstracts of papers outlining research findings will be submitted to Kamuzu University of Health Sciences ethics committee formally COMREC, KuHeS and LAMU Library, and Research and Publication Committees (through the ethics board Secretariat).

17.4. Data Sharing

The funder of the research National Institute for Health Research (NIHR) 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 MLW and Zambia data department and discussed with the Principal Investigator in accordance with the data policy on data sharing.

18.0 RESEARCH CAPACITY STRENGTHENING

Capacity strengthening will focus both on individual support as well as institutional support. MLW, Lusaka Apex University and KUHeS staff will continue to benefit from opportunities for training and mentorship from the Safe Motherhood programme in collaboration with partner institutions and experts within the project. Two PhD students (Malawi and Zambia) have been appointed, with support from the University of Liverpool and Safe motherhood project and will benefit from the training opportunities as part of the Safe motherhood grant funded by NIHR. Seven master's students both in Malawi and Zambia have also been appointed.

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 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. We would ensure that individuals engaged in this study contribute to local research strengthening at their home institutions.

19.0 REGULATORY AND ETHICAL CONSIDERATIONS

19.1. Ethical Considerations

The protocol and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC) in each participating country (Malawi, Zambia) 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 as well as Sponsor before use.

ENHANCE 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 ENHANCE 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 NIHR guidance where appropriate.

19.2. Justifying the cluster-randomised design

The choice of cluster-randomised design must be justified, Ottawa statement, recommendation 1(50). The cluster-randomised design is required for ENHANCE as this intervention will seek to target health care providers and clients to improve the quality of care across a whole health facility. The intervention changes systems of care across a facility, and therefore it is not feasible to randomise individual practitioners or women to receive the intervention. Hence the cluster-randomised design is essential to evaluate ENHANCE and reduce the risk of cross contamination.

19.3. Research ethics committee review

In accordance with the Ottawa statement 2 (50), as ENHANCE involves human participants(staff and clients) then approval from research ethics committees in Malawi, Zambia and the UK will be sought.

19.4 Language Considerations

English is the designated language of healthcare teaching, provision and medical records in both Malawi and Zambia. 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. All tools for clients will be both in English and local language.
Participant information sheets and consent forms will be available in both English and appropriate local languages where required to be used in this study (Appendices 21-22).
Any other training materials where it is deemed by the country staff that understanding would be improved by also offering additional language versions then these may be translated from English into the most appropriate local language.

19.5. Identifying research participants

ENHANCE programme evaluates a behavioural change intervention that will seek to change the behaviour of healthcare facility staff and clients in the study to improve compliance with WHO recommendations for antenatal care. As per Ottawa Statement 3(50) the healthcare providers and clients will be targeted by the intervention, including receiving additional training or information and providing feedback on how their practice has changed. These healthcare providers and clients are the research participants. Provider and client data during the intervention period will also be used to assess trial outcomes.

19.6. Permission from Gatekeepers

“Gatekeepers” are individuals or bodies who protect the group-based interests that are affected by enrolment in a cluster-randomised trial. (Ottawa Statements 8-10)(50). ENHANCE trial will enrol a minimum of 16 PHCs in Malawi and eight in Zambia. In each case permission will be obtained from the institutional leadership and Ministry of Health. (Ottawa statement 9) (50)
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 trial team and copies also sent to ethics bodies.

19.7. Informed Consent Procedures

19.7.1. Individual clients

ENHANCE aims to improve staff and client compliance with best-practice, evidence-based care, as recommended by WHO. We anticipate that approximately more than 50 000 clients will receive care from staff with improved knowledge and understanding of best practices. Individual informed consent would only be required for those ANC clients who will be asked to provide feedback regarding their experience during the intervention period.

All data collected is routinely gathered and measures the impact of ENHANCE on health outcomes. Data will be reported at an aggregated facility and individual level. There are no commercial applications nor financial benefits resulting from the findings of this trial or the data collected.

19.7.2. Staff Training and engagement

Approval for trial conduct will be obtained from facility leadership teams prior to introduction of ENHANCE. This will include approval for staff training and other trial activity engagement with staff 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.

19.7.3. Staff and clients' interviews

Informed consent will be sought from healthcare facility workers and clients who agree to participate in individual interviews and suverys. They will be provided with ENHANCE information sheet and consent form if they are invited and the study team will ensure that they can review and consider the information and are aware that they can decline. They will be consented privately and without their supervisor or peers 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 appendices 21-22), and the opportunity for potential participants to ask questions and have these satisfactorily answered will be provided. All individuals will be free to either not participate or stop and withdraw at any time without their rights or opportunities being affected. Similarly, they will have the opportunity to attend the training or receive information but then may decline to provide any further feedback to the study team. Participants will be consented privately and without their supervisor or peers being present, and information about their participation, or not, in interviews will be kept confidential. Informed consent will be obtained, and interviews will be conducted in English or in the language considered appropriate for the participant by a local researcher, in a private location, or via video conference if COVID-19 restrictions require that at the time of interview.

Interviews will be recorded, transcribed and de-identified. Participants will also be given the option to withdraw themselves from the activities at any point during the interviews and for up to seven days after the interview has been completed and any conversations resulting from this activity will be destroyed.

19.7.4. Staff and clients Surveys

Consent information will be provided at the beginning of every electronic survey where the staff member or clients will have the opportunity to decline. The surveys will be completed pseudonymously on an electronic database provided to staff by members of the trial team using a tablet to enable them to complete the survey online. For clients, the research assistant will assist them filling the responses on the tablet. 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.

19.7.5. Champions

Champions will be invited to undertake the role following local selection by their facility leadership team. They will be trained and mentored by trial team. Champions who agree to take up this role 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 trial team throughout the programme, and for communication across the champion network. Champions will support local staff throughout the intervention to perform their required roles during trial implementation.

20.0. 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.

20.1. Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and MLW or Lusaka Apex University data department procedures as appropriate. They will be reported to trial oversight committees.

20.2. Serious breaches

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

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the MLW or Lusaka Apex University data department who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

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

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

Breaches confirmed as ‘serious’ will be reported to the REC within 7 days by the MLW data department on behalf of the Sponsor and notified to the TMG, and ISAC at their next meeting. Any requests for additional information from the Sponsor, TMG, ISAC, 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.

21.0. INDEMNITY

Malawi Liverpool Wellcome Programme and Lusaka APEX University will provide medical malpractice insurance cover for the in-country trial management while. The risks to clients 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 clients 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.

The University of Liverpool as study Sponsor also provides indemnity cover for this study.

22.0. POSSIBLE CONSTRAINTS

22.1. Covid-19

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

- Hand hygiene – all country research teams will avail sanitizers for handwashing, which will be used on research participants at the start and end of research activities.
- All participating health care workers will be encouraged to follow national guidelines for COVID 19 Prevention measures.
- Social distancing - research Participants will be stationed at least 1 meter apart during research activities and researchers will keep the same distance while collecting data through whichever methods
- Use of virtual data collection methods wherever that is possible and sensible.

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

22.2. Additional constraints – inconsistent flow of supplies

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

with facility teams for the smooth running of the study. We will provide basic resources for both control and intervention sites. Use of resources tracking records will ensure availability of resources during trial period.

22.3. Additional constraints – data quality

This study will use routinely collected data to evaluate outcomes of interest which might be delayed or incomplete. The Champions will be responsible for ensuring that the participating facilities submit complete data on time and data entry is done timely at district level. Both PHCs and district data officers will be oriented to ENHANCE and its requirements.

23.0 REQUIREMENTS FOR RESEARCHERS AND STUDY STAFF

The qualitative and quantitative research activities will be implemented by study team and the facility staff including nurses, clinician from which champions will be selected. All staff will be trained on the study. All site research staff involved in the study must be included on the site staff delegation log. The PI will sign off the delegation log for only those staff members s/he feels are able and competent to perform the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked against staff named on eCRF, and registration forms. The Research Manager will ensure that as a minimum the PI, research staff and site study data management staff have study-specific training. The study will need skilled researchers to collect qualitative data and analyse qualitative and quantitative data.

24.0 END OF STUDY

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. This is considered to be data lock, when all data are entered and cleaned and the final dataset is agreed. Following the end of study the only activities to take place are writing and dissemination activities.
The trial may be closed prematurely by the TMG, on the recommendation of an oversight committee. Facility closure activities will be centrally coordinated and conducted in accordance with MLW or LAMU data department 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

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25.0 BUDGET AND BUDGET JUSTIFICATION

Table 2 summaries the Trial budget for Malawi

Activity	Cost (GBP)	Cost (MWK)
Trial activities support (travel and trainings)	100,000	227,300,000
Trial supplies and equipment	50,000	113,650,000
Engagement and participant reimbursement	20,000	45,460,000
Data management support	50,000	113,650,000
Monitoring & Evaluation	7,000	15,911,000
Other Project Costs (Indirect cost)	30,000	68,190,000
Subtotal	**257,000**	**584, 161,100**
Contingency	**25,700**	**58,416,100**
Total	**282,700**	**642, 577,100**
COM Administrative contribution	**28,270**	**64,257,710**

25.1. Budget Justification

The National Institute of Health Research (NIHR) Global Health Research programme has funded the full resources for this study. The budgeted amount will be used to support research activities in the field and during data analysis. Participants compensation was calculated at $10 per participants according to COMREC guidelines. This amount will be given to study participants participating in either IDIs, FGD and surveys. The researcher allowances and other research support cost were calculated based on MLW guidelines.

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