E-MOTIVE TRIAL PROTOCOL

Early detection of postpartum haemorrhage and treatment using the World Health Organization MOTIVE 'first response' bundle: a cluster randomised trial with health economic analysis and mixed-methods evaluation

Version Number:	V6.0
Version Date:	24-Jul-2023

INSERT COUNTRY INSTITUTION LOGO

Protocol development

Protocol Amendments
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	16/07/2020	2.0	Substantial	Addition of clinical trials.gov number, change of DMC member, edit to list of ITMG members, addition of definition for 'spoke', removal of India as a participating country, clarification of health facility eligibility criteria (section 3.3), edit to outcomes (section 6), change in number of facilities used for adaptive cycles (section 5.3), removal of PPH rate per health facility as minimisation criteria (section 3.4), clarification regarding randomisation of health facilities (section 3.4), addition of option for qualitative interviews to be completed via video/teleconference (section 5.3 and 6.3), addition of sections regarding measurement of blood loss and Blinded Endpoint Review Committee (section 6.1), changes to list of secondary clinical and implementation outcomes (section 6.2), change to aims and objectives of process evaluation (section 6.3), change to observations for process evaluation (section 6.3), clarification that DMC will monitor maternal deaths and ICU admissions (section 7), clarification regarding source data (section 8.1) and clarification regarding statistical analysis (section 11)

2	18/06/2021	3.0	Substantial	Change of logo for UCL Centre for Behaviour Change, changes to trial team – Rachel Lillywhite has replaced Adam Devall as Team Leader and Kristie-Marie Mammoliti added as Programmer Manager, E-MOTIVE kit changed to trolley or carry case for intervention, Quality of oxytocin added as minimisation variable for randomisation, amendment to statement regarding consent to confirm consent for observations will not be sought in a separate consent form (section 4), change to objectives for adaptive cycle process evaluation, change to timeframe for adaptive cycles – adaptive cycles to last between 3-5 months rather than 4-5 months (section 5.3), change to procedures for adaptive cycles to confirm baseline data will be collected for first month and online surveys will not be conducted (section 5.3), change to primary and secondary outcomes to specify timeframes for measurement of some outcomes (section 6.1-6.2), change to additional outcomes to confirm that number of vaginal births and number of caesarean sections will be extracted weekly rather than monthly (section 6.2), clarification that minimisation will be stratified in each country and will be performed by an independent statistician from BCTU (section 3.4)
3	30/09/2021	4.0	Minor	Addition of Pakistan as a participating country

4	25/10/2022	5.0	Substantial	In the initial months of the baseline period, we had concerns about data veracity from a pilot site and after consultation with the funder, the independent TSC and DMC committees, we decided to drop all the initial main trial data and adopted a complete source data verification approach for all births. As a result, the duration of study data collection was reduced from 24 months (11-month baseline phase, 2-month transition phase and 11-month intervention phase) to 16 months (7-month baseline phase, 2-month transition phase and 7-month intervention phase). This decision was made in conjunction with updated sample size simulations, because of the following changes to the assumptions: a) increased numbers of study sites as 80 sites were successfully enrolled, and b) increased rates of the primary outcome based on accruing baseline data. Hence, we were confident the study could be conducted in a shorter length of time without unduly impacting on our ability to detect the same size of difference as originally planned (sample size updated in section 11.1). Changes to trial team - Dr Sindhu Kulandaipalayam Natarajan has replaced Kristie-Marie Mammoliti as Programme Manager and Marcelina Podesek and Isobelle Horne have replaced Rebecca Timms as Data Manager. Removal of Sri Lanka as a participating country (Sri Lanka formally withdrew from the study) and change in number of countries from 6 to 5. Change in number of adaptive cycle sites from 3-4 to 2-3 and change in approximate timeframe for adaptive cycles from 3-5 to 2-5 months. Changes to randomisation (section 3.4) including data used for randomisation changed from first 6 months to first 5 months baseline data and number of facilities added as minimisation variable. Details added to treatment supply and storage (section 5.1). Changes made to measurement of blood loss (section 6.1), changes made to secondary implementation outcomes (section 6.2), changes made to process evaluation (section 6.3), changes made to on-site monitoring (section 9.2), changes made to

				analysis of outcomes measures (section 11.2) including addition of section on source verified data. Update to reference list
5	24/07/2023	6.0	Substantial	Change to Dr Adam Devall job title, change in QA Manager, clarification regarding patient eligibility criteria for the study (section 3.3), additional details added to randomisation section (section 3.4), clarification regarding measurement of blood loss process (section 6.1), clarification made to secondary clinical and implementation outcomes section (section 6.2), clarification made to analysis of outcome measures section (section 11.2), update to reference list (section 18) and addition of appendix for Pakistan before-and-after study

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Disclaimer: The views expressed are those of the authors.	

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	The E-MOTIVE trial
Protocol Version Number:	Version: 6.0
Protocol Version Date:	24-Jul-2023
CI Name:	Prof Arri Coomarasamy
Trial Role:	Chief Investigator
Signature and date:	 29-Jul-2023
Team Leader Name:	Rachel Lillywhite
Signature and date:	 24-Jul-2023
Senior Statistician Name:	Mr Lee Middleton
Signature and date:	 25-Jul-2023

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, a formal signed letter will be issued by the sponsor to serve as confirmation of approval of this protocol.

Compliance statement:

This protocol describes the E-MOTIVE trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the E-MOTIVE trial.

The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the General Data Protection Regulations (GDPR) 2018, as well as the ethical research frameworks of all participating countries. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Reference Numbers	
Sponsor number	RG_19-231
Clinicaltrials.gov reference number:	NCT04341662
Country level reference number (if applicable):	TBC

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	The E-MOTIVE trial
Protocol Version Number: Protocol Version Date:	Version: 6.0 24-Jul-2023
PI Name:	Professor Lumaan Shaikh
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ABBREVIATIONS	
Abbreviation	**Term**
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
CIOMS	Council for International Organization of Medical Science
COM-B	Capabilities, Opportunities and Motivations for Behaviour Change
CRF	Case Report Form
DMC	Data Monitoring Committee
GDPR	General Data Protection Regulation
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICU	Intensive Care Unit
ISF	Investigator Site File
ITMG	International Trial Management Group
ITMS	Integrated Trial Management System
LMIC	Low- and Middle-Income Countries
MRC	Medical Research Council
NC	National Coordinator
NPI	National Principal Investigator
PI	Principal Investigator
PIS	Participant Information Sheet
PPH	Postpartum Haemorrhage
REC	Research Ethics Committee
TAG	Technical Advisory Group
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic Acid
UoB	University of Birmingham
WHO	World Health Organization
WMA	World Medical Association

DEFINITIONS	
Term	**Description**
Hub	A country-specific collaborating institute acting as a central, coordinating centre.
Spoke	A health facility within a participating country

TRIAL SUMMARY

Title Early detection of postpartum haemorrhage and treatment using the World Health Organisation MOTIVE 'first response' bundle: a cluster randomised trial with health economic analysis and mixed-methods evaluation.

Aim To evaluate the implementation of early detection and the use of the World Health Organisation (WHO) MOTIVE 'first response' treatment bundle for postpartum haemorrhage (PPH) on clinical, implementation and resource use outcomes. We will evaluate the implementation through mixed-methods and carry out a health economic evaluation from the public healthcare system perspective.

Study Design Multi-country, parallel cluster randomised trial with a baseline control phase, along with mixed-methods and health economic evaluations.

Setting: Secondary level health facilities in Kenya, Tanzania, Nigeria, South Africa, and Pakistan.

Population *Cluster*: Health facility is the randomisation unit. Health facilities are eligible for inclusion if they have 1000 to 5000 births a year and provide comprehensive obstetric care with ability to perform surgery for PPH. *Research participants*: All healthcare providers attending vaginal births in the study facilities.

Intervention The E-MOTIVE intervention consists of three elements: 1) a strategy for early detection of PPH, which allows triggering of the 'first response' treatment bundle; 2) a 'first response' bundle called "MOTIVE", based on the WHO guideline recommendations and consisting of uterine **M**assage, **O**xytocic drugs, **T**ranexamic acid, **IV** fluids and **E**xamination & Escalation; and 3) an implementation strategy, focusing on simulation-based training with peer-assisted learning, local E-MOTIVE champions, feedback of actionable data to providers, calibrated drape with trigger line, and MOTIVE emergency trolley and/or carry case.

Control Usual care with dissemination of the current guidelines.

Outcomes *Primary*: Composite of the following three clinical outcomes: severe PPH defined as blood loss ≥1000 ml or postpartum laparotomy for bleeding or postpartum maternal death from bleeding. *Key Secondary:* 1) postpartum haemorrhage detection, and 2) compliance with MOTIVE bundle. *Secondary:* blood transfusion, uterine tamponade, Intensive Care Unit admissions or higher-level facility transfers, and new-born deaths along with implementation and resource use outcomes.

Randomisation and sample size 80 health facilities will take part in the study. Initially, all health facilities will enter a 7-month baseline period in which they will be following usual care. After this, we will randomise 40 of the 80 health facilities to the E-MOTIVE intervention for 7 months, allowing two months for transition. The other 40 health facilities will continue to follow usual care as per the baseline period for the entire trial duration (16 months). The anticipated sample size for the study will be 215,040 women. This sample size is expected to have over 90% power to detect a 25% relative reduction in the primary outcome from 4% to 3% after allowing for clustering. The number of clusters has been inflated by 10% to allow for drop out of health facilities and for varying cluster sizes. Randomisation will use a minimisation algorithm to balance the intervention and control facilities by the number of vaginal births per health facility, the health facility rate of the composite primary outcome during the baseline phase, the quality of oxytocin used per health facility, and the number of facilities in each arm.

Mixed methods work During the 7-month baseline phase, we will refine and optimise the E-MOTIVE implementation strategy by piloting it in two to three facilities per country over up to two adaptive cycles for addressing barriers and enablers to delivery and implementation, ahead of the intervention phase.

Process evaluation during the intervention phase We will conduct a mixed-methods process evaluation to assess the extent to which the E-MOTIVE intervention has been implemented as intended. The implementation outcomes of interest are fidelity, adoption, adaptation, acceptability, and sustainability, as well as contextual influences and barriers and enablers to implementation.

Health economics We plan to assess the cost-effectiveness of the E-MOTIVE intervention compared with usual care from a public healthcare system perspective for each country, as measured by incremental cost-effectiveness ratios for a) severe PPH prevented, b) laparotomy for PPH prevented, c) death from PPH avoided, and (d) quality-adjusted life-years prevented.

Figure 1 *Study flowchart*

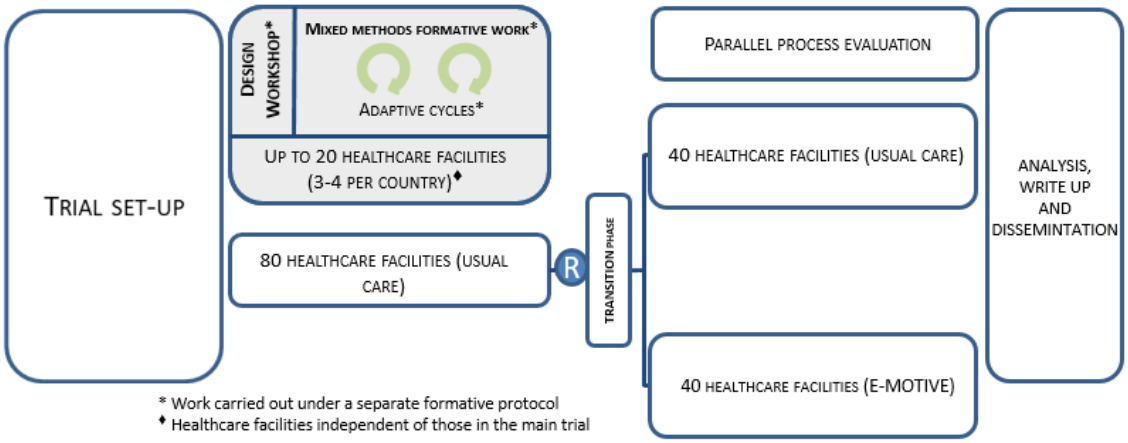


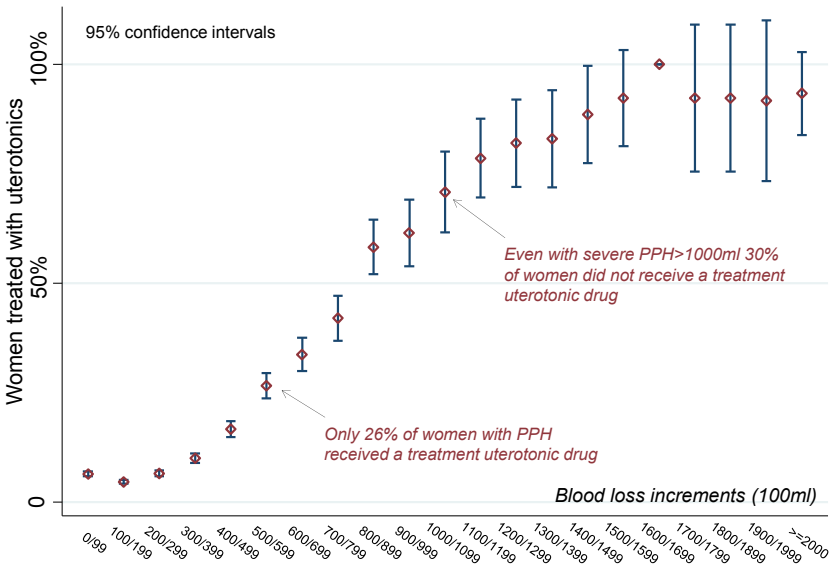
TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1. Background

Every six minutes a mother dies from PPH in low-resource countries, in the prime of her life and often leaving behind a young family.[1] In many settings, when a mother dies in childbirth, her infant has less than a 20% chance of surviving past the first month.[1] PPH, defined as a blood loss of more than 500 ml, is the leading cause of maternal death worldwide, accounting for 27% of maternal deaths.[2] The WHO published "Recommendations for the Prevention and Treatment of Postpartum Hemorrhage" in 2012 to provide evidence-informed recommendations for managing PPH.[3] However, adherence to these recommendations is currently limited by a number of challenges.

Figure 2 *Treatment of PPH from the multicountry WHO CHAMPION trial*

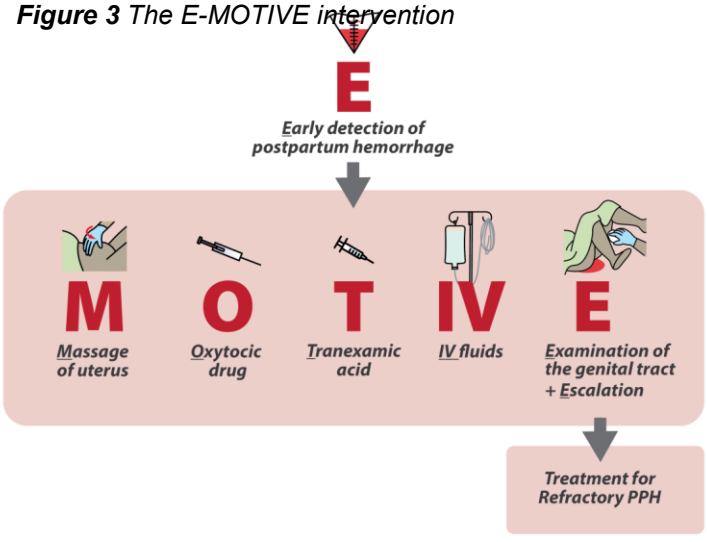


Challenges → proposed solutions

1) PPH is often not detected early; thus life-saving treatment is not promptly initiated → Solution: Early detection and treatment of PPH

Data from multiple LMICs show that most women with PPH do not receive life-saving treatment.[4] Analysis of the WHO CHAMPION (Carbetocin HAeMorrhage PreventION trial) trial data (n=29,645; 10 countries) showed that only 26% (235/886) of women with a blood loss between 500 – 600 ml received a uterotonic drug for PPH treatment (***Figure 2***).[4] Even with a blood loss of 1000 – 1100 ml, only 70% (68/96) of women received a uterotonic drug for treatment of PPH.[4] Published data from 42 Nigerian and 61 Tanzanian hospitals as well as audit data from 5 Kenyan hospitals show that the real-world PPH detection rates are low (Nigeria 2.2%, Tanzania 2.5%, and Kenya 1.8%).[5,6] Such low detection rates would mean low or delayed usage of a 'first response' PPH treatment bundle. These facilities currently rely on visual estimation of blood loss, widely

Figure 3 *The E-MOTIVE intervention*



recognised as inaccurate, and can result in underestimation.[7] Therefore, we will implement an early PPH detection strategy with objective measurements of blood loss to ensure that a 'first response PPH treatment bundle' is promptly triggered for maximum benefit.

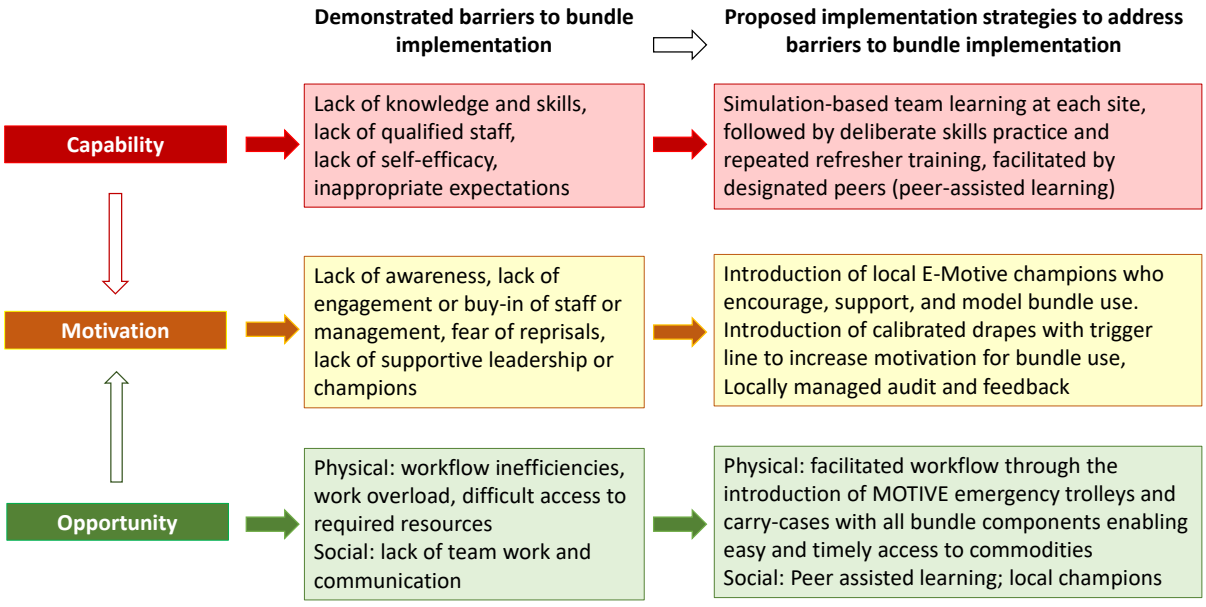
2) Delayed or inconsistent use of interventions for PPH management → Solution: the bundle

PPH is often detected late; a sequential approach to administering life-saving interventions could mean more time – and lives – are lost. Furthermore, some treatment interventions recommended by WHO, may not be used at all. Survey data from the participating facilities in Kenya and Nigeria show that tranexamic acid (TXA) is used late and most often only for women requiring surgery for PPH. Other easy-to-implement interventions of standard PPH care, e.g., uterine massage and IV fluids, that could be critical are inconsistently used and may be considered optional by doctors and midwives. We aim to change provider behaviours so that they detect PPH early and rapidly implement all recommended interventions of the MOTIVE bundle (***Figure 3***) simultaneously, without waiting for response to individual components (sequential implementation).

3) Despite guideline dissemination, many care providers do not provide effective care → Solution: Implementation strategy targeting Capabilities, Opportunities and Motivations for Behaviour change (COM-B)

An extensive body of implementation research based in high income countries has identified that passive dissemination of new clinical guidelines, including care bundles, alone is unlikely to result in sustained behaviour changes and improved quality of care.[8] We will design an implementation strategy to address known barriers and enablers for improving bundle implementation. This will be based on a model of behaviour change (COM-B), which recognises that individuals must have Capability, Motivation, and both physical and social Opportunity to perform the behaviour(s) of interest.[8] Our implementation strategy and rationale are given in ***Figure 4***.

Figure 4 *E-MOTIVE implementation strategy and rationale.*



4) Limited scale-up and coverage →Solution: Engagement of strong implementation partners: WHO/HRP, Jhpiego, UCL Centre for Behaviour Change, and Concept Foundation

WHO/HRP is a leading collaborator in our program (***Box 1***). Jhpiego has deep knowledge in building resilient and self-reliant implementation programmes; Jhpiego functions in over 40 countries, with strong presence in Africa and Asia. The University College London (UCL) Centre for Behaviour Change is credited with the development of the well-recognised and used COM-B model for behaviour change;[10] the Centre will use behavioural theory and frameworks to develop behavioural change interventions to improve PPH bundle use and outcomes. The Concept Foundation (Executive Director: Metin Gulmezoglu) will contribute by providing data and information on availability, quality, and access issues for the PPH commodities in the bundle.

Box 1: What WHO/HRP partnership brings to the program?

WHO/HRP (F Althabe) led the development of the Gates Foundation sponsored first response PPH treatment bundle (MOTIVE).[9] Since then, the WHO has worked with the University of Birmingham to map out the E-MOTIVE programme on its Evidence to Decision framework, with particular emphasis on desirable and undesirable effects, values, required resources, equity, acceptability, and feasibility. This collaboration includes formative work, evidence synthesis, policy formulation, and stakeholder engagement. If E-MOTIVE is found to be effective, WHO/HRP will consolidate the research results by issuing normative guidance for the programmatic implementation of E-MOTIVE for global impact.

2. AIMS AND OBJECTIVES

Primary objective:

Evaluate the implementation of the E-MOTIVE intervention compared with usual care on clinical, implementation and resource use outcomes.

Secondary objectives:

1. Assess the cost-effectiveness of the E-MOTIVE intervention compared with usual care from a public healthcare system perspective.

2. Develop, optimise and manualise an implementation strategy, with parallel process evaluation alongside the trial, ready for scaling-up of the E-MOTIVE intervention if found to be effective.

Our purpose is to integrate the evidence into WHO guidance for programmatic implementation of the E-MOTIVE intervention, if found to be effective, for global impact.

3. TRIAL DESIGN AND SETTING

3.1. Justification for Trial Design

This is a multi-country, parallel cluster randomised trial with a baseline control phase, along with mixed-methods pilot, process evaluation and health economic evaluations. A cluster design is necessary as the intervention is delivered at the health facility level, targeting the healthcare providers within them, and so it would not be feasible to randomise individual participants.

3.2. Trial Setting

Secondary-level health facilities across 5 countries (Kenya, Tanzania, Nigeria, South Africa, and Pakistan).

3.3. Eligibility

Cluster: Health facility is the randomisation unit. Health facilities are eligible for inclusion if they have 1000 to 5000 births a year and provide comprehensive obstetric care with ability to perform surgery

for PPH. Health facilities are selected based on being administratively and geographically distinct from each other. Pre-existing implementation of early detection or bundled approach for PPH management are exclusion criteria.

Research participants: All healthcare providers attending vaginal births at the study facilities.

Patients: All verified vaginal births in the study facilities

3.4. Randomisation

After regulatory approvals, all 80 health facilities will enter an 7-month baseline period in which they will be following usual care with dissemination of the current guidelines. After this 7-month baseline period, we will randomise in a staggered fashion 40 of the 80 health facilities (1:1 ratio) to the E-MOTIVE intervention for 7 months, allowing two months for full implementation and embedding of the intervention. The other 40 health facilities will continue to follow usual care as per the baseline period for the remainder of the intervention phase ***(Figure 1).*** To allow us to perform the randomisation sequentially, a minimisation algorithm will ensure a balance of the intervention and control facilities for the following measured at the level of the health facility during the first 5 months of the baseline phase:

1. Number of vaginal births;

2. Proportion of births with the composite primary outcome;

3. Quality of oxytocin

4. Number of intervention and control clusters in each country

Details of how these are calculated are presented below. The minimisation will be stratified in each country (separate minimisations) to increase the balance in all of the above covariates within a country.

Number of vaginal births

After the first five months of the baseline phase has completed, for each cluster, we will gather the total number of births and the number of months of data collection to calculate the cluster's monthly birth rate. We will then use the cluster's monthly birth rate to determine the country's median birth rate. The clusters above and below the country median will form the categories for the minimisation algorithm.

The proportion of births with the composite primary outcome before randomisation

After the first five months of the baseline phase has completed, for each cluster, we will gather the total number of births and the total number of events. The ratio of the number of events to the number of births will give us the proportion of births with the composite outcome for that cluster. We will then use the cluster's primary outcome proportion to determine the country's median primary outcome proportion. The clusters above and below the country median will form the categories for the minimisation algorithm.

Oxytocin Quality

The quality of oxytocin (measured during the baseline phase) will be dichotomised as ≤90% and >90% to form the categories for the minimisation algorithm.

Number of intervention and control clusters in each country

In an attempt to balance the number of clusters allocated to each arm, we will include a covariate that represents the number of clusters assigned to intervention and control, as there is evidence that this improves balance in the number of clusters in each arm[11].

The randomisation of health facilities will be performed using a validated minimisation algorithm that follows the Pocock and Simon range method[12] using the "rct_minim" command in Stata 16. The first cluster in each country will be allocated completely at random. All further clusters will be allocated using the minimisation algorithm. To reduce the predictability of allocation and to ensure a balance in covariates across arms, a small random element (10%) will be included in the algorithm. A random element is typically included to better protect the blinding of treatment allocations when recruiting new facilities. A random element of 10% would mean we expect 90% of clusters to be allocated using the minimisation algorithm to the arm that minimises covariate imbalance, and 10% are not.

The randomisation of health facilities will be performed using a validated minimisation algorithm and implemented by an independent statistician from the University of Birmingham Clinical Trials Unit (BCTU). Full details of the randomisation specification will be stored in a confidential document at the University of Birmingham Clinical Trials Unit (BCTU).

4. CONSENT

The E-MOTIVE intervention aims to change local healthcare providers' behaviour for management of PPH and increase compliance with WHO recommendations for PPH treatment. All the interventions in the bundle are already recommended for all women with PPH and represent life saving measures administered to women in an emergency setting. The leadership at each facility will provide facility-level permission for participation in the study and permission for staff employed at the health facility to extract anonymised routinely collected data on clinical outcomes. All healthcare providers will provide written informed consent before trial-specific training. A separate written informed consent will be obtained from healthcare providers during the adaptive cycles and process evaluation for trial specific data collection including interviews and surveys. Individual-level consent from women for participation in this evaluation is not required as women are not the direct target of the intervention; nor are they interacted with for the purpose of data collection; and no identifiable information on women will be held by the E-MOTIVE study investigators or BCTU (please see section 13 for details).

5. TRIAL INTERVENTION

Intervention: The E-MOTIVE intervention targets healthcare providers and consists of an implementation strategy for early detection of PPH, which allows the initiation of the 'first response' treatment bundle, which is called MOTIVE, consisting of uterine **M**assage, **O**xytocic drug, **T**ranexamic acid, **IV** fluids and **E**xamination & **E**scalation (***Box 2***). The timing, dosing and manner with which these interventions will be implemented will be in line with WHO recommendations and local protocols where available.[2,9] The implementation strategy focuses on simulation-based training on site with peer-assisted learning, local E-MOTIVE champions, feedback of actionable data to providers, calibrated drape with trigger line, and MOTIVE emergency trolley and/or carry case.

Control: Usual care with dissemination of the current guidelines. In usual care, 'first response' treatment may include some or all of the components of the MOTIVE treatment bundle. All components are routinely available in all facilities, recommended for all women with PPH, but currently are used inconsistently by healthcare providers.

Box 2: Insights from members of the PPH Bundles Expert Advisory Group

Four of this project's collaborators (F Althabe, S Miller, GJ Hofmeyr, and D Lissauer) were among the WHO/HRP technical advisory group (TAG) that developed the PPH bundles as a way of implementing the WHO PPH recommendations.[9] The set of four interventions included in the PPH First Response care bundle (uterotonic drugs, IV isotonic crystalloids, tranexamic acid, and uterine massage) was accepted by consensus by the 21 advisors as being highly relevant and able to be used across all facility levels.[9] The group agreed that the next phase for this bundle should be the development of an implementation strategy culminating in a model for use at the facility level in LMICs. At a minimum the TAG suggested that the strategy should include: training, teamwork, packaging the bundle elements in an easy-to-use trolley or kit and on-going monitoring and evaluation. However, a full implementation strategy was not developed during TAG process. The group advised undertaking implementation research.[9]

5.1. Treatment Supply and Storage

Medicinal supplies used in the trial (oxytocic drugs, tranexamic acid and IV fluids) will be sourced from local stocks at the health facilities. Most health facilities do not require additional medicinal supplies, based on our facility surveys and discussions. However, where required, the BCTU will work with Hubs to provide supplies to both the intervention and the control facilities. The BCTU will centrally provide blood collection drapes (both non-calibrated and calibrated) and digital weighing scales to the Hubs. The Hubs will arrange for distribution of these supplies to the health facilities. The Hubs will request a report from individual health facilities for availability of interventions.

The quality of oxytocin and tranexamic acid products used at individual health facilities across all participating countries will be evaluated by the Concept Foundation. This work is outlined in a separate protocol.

5.2. Standardisation of labour care

All other aspects of labour care will be as per the local protocols and determined by the attending obstetrician and healthcare team. The intervention health facilities will change their local protocols to implement the E-MOTIVE intervention. The individual components will not be enforced and compliance with the E-MOTIVE intervention will be measured.

5.3. Design of the E-MOTIVE implementation strategy: Adaptive cycles

Aims

The overall aim is to conduct a small-scale, mixed-methods process evaluation in each country to explore two key implementation outcomes, which need to be optimised before progressing to trial: fidelity (extent to which the intervention is delivered and engaged with as intended) and acceptability.

Objectives

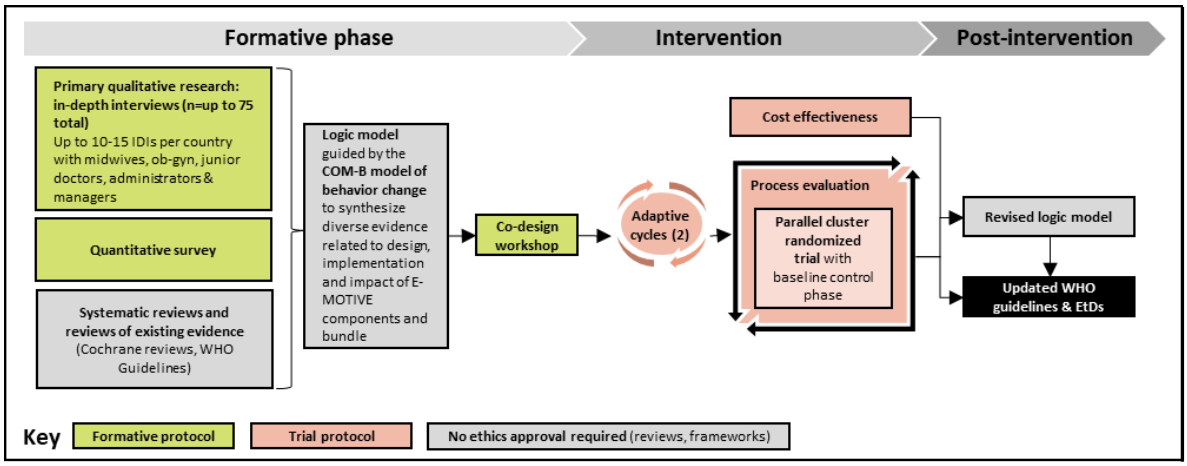
1. To pilot the E-MOTIVE intervention and co-implementation strategy and assess: fidelity of delivery and enactment, acceptability, change in implementation outcomes, and barriers and enablers to implementing the interventions as intended.

2. To refine and optimise the E-MOTIVE co-implementation strategy to address barriers and enablers to delivery and implementation, ahead of the intervention phase.

Design

We plan to use the 7-month baseline trial data collection period to pilot the feasibility of the provisional implementation strategy and tools in health facilities in each of the 5 countries over up to two adaptive cycles (***Figure 5***). Each adaptive cycle will last approximately between 2 and 5 months.

Figure 5 *The E-MOTIVE study adaptive cycles, parallel cluster randomised trial, process evaluation and cost-effectiveness. The formative components of the project (qualitative research, quantitative survey, and co-design workshop) are outlined in a separate protocol.*



Sample

Field-testing will be carried out in at least two, but up to three, facilities per country. These will be purposively sampled to ensure representativeness of the facilities participating in the trial. To maintain internal validity of the trial, facilities taking part in the pilot adaptive cycles will be excluded from the main trial.

Procedure

The clinician in charge of the labour ward will organise an E-MOTIVE team that includes senior clinicians and midwives, obstetric anaesthetists, a project officer for training and implementation support, another project officer for qualitative and quantitative evaluations, and a representative from a women's group (e.g., White Ribbon Alliance).

For the first adaptive cycle, in Month 1, the facility will collect baseline data. After approximately one month, we will implement the E-MOTIVE intervention and deliver the implementation co-intervention on site [simulation-based with peer-assisted training, establish local champions, MOTIVE trolley and/or carry case, and establish procedures for ongoing audit and feedback].

Following a one to two month embedding and implementation period, we will then collect a mixture of qualitative and quantitative data to explore fidelity, acceptability, and barriers and enablers to implementation. In line with the Medical Research Council (MRC) guidance for process evaluations of complex interventions, we will combine basic quantitative measures of implementation with in-depth qualitative data to provide detailed understanding of intervention functioning on a small scale.[13] Therefore, fidelity and adoption may be explored via a combination of: quantitative 'site implementation logs' and checklists completed by the local facilitators to document extent of implementation. We will also conduct in-depth qualitative interviews based on behavioural science theories and frameworks (e.g., COM-B model, Theoretical Domains Framework, and Theoretical Framework of Acceptability) to explore barriers and enablers to implementation.

Semi-structured interviews will be conducted with healthcare providers, including nurses, midwives, and doctors of different levels of seniority and experience. We will aim to interview approximately five healthcare providers from each facility taking part in the adaptive cycle. We will identify and recruit healthcare providers to participate in the semi-structured interviews who have had a real experience in using the E-MOTIVE intervention in clinical care, so that their responses are guided by practice challenges rather than hypothetical. Interviews will explore self-reported adoption and perceived barriers and enablers to implementing the E-MOTIVE intervention with fidelity. Potential modifications and enhancements to the interventions will also be explored.

We will obtain informed consent from participants prior to them taking part in interviews. The local clinical collaborator will identify eligible participants to take part in the interviews and will send the study information sheet to potential participants. Participants will then have the option to contact the local research coordinator to arrange an interview.

Interviews will be conducted by a trained researcher from the local team in each country. This is likely to be a research midwife or social scientist. Interviews will be conducted in a private location in the participating facility or via video/teleconference (according to participant preference), audio-recorded and transcribed verbatim. Transcripts will be de-identified so that no individual or organisation may be identified from the data. Study materials

Information sheets, consent forms and draft interview topic guides are available on request.

Analysis

Quantitative data will be summarised descriptively and qualitative data analysed using rapid qualitative analysis approaches, such as framework analysis. We will triangulate the quantitative and qualitative feasibility data to identify areas or specific intervention components for which there is low fidelity or acceptability, and themes around barriers to implementation. We will convene a meeting involving multidisciplinary research team members and local clinical collaborators from each participating country to agree which issues identified need to be addressed and how best to refine or add to the existing intervention materials and components. The interview questions to explore barriers and enablers will be based on the COM-B model, which is mapped onto two behavioural and implementation science frameworks that specify different types of behaviour change strategies: Behaviour Change Wheel and Behaviour Change Technique Taxonomy.[10] Therefore, if we find that Capability, Opportunity, and Motivation are key barriers during the adaptive field-testing phase, we can consult these frameworks to identify additional intervention strategies to consider including in the refined intervention.

If adaptations to the intervention are made following the first adaptive cycle which require testing, we will progress to a second cycle of piloting to test the adapted intervention, collecting the same

qualitative and quantitative measures on fidelity and adaptation. Following analysis of feasibility data from Cycle 2, we will further discuss and adapt the intervention as needed, prior to finalising the intervention materials ahead of randomisation and the intervention phase of the trial.

6. OUTCOME MEASURES AND STUDY PROCEDURES

6.1. Primary outcome

The primary outcome is a composite of the following three clinical outcomes: 1) primary severe PPH defined as blood loss ≥1000 ml following a vaginal birth in the facility measured up to 2 hours postpartum; 2) postpartum laparotomy for bleeding until discharge from the health facility*; and 3) postpartum maternal death from bleeding until discharge from the health facility*. If any of the components occur, this will be deemed as positive for the primary outcome.

Measurement of blood loss

Blood loss will be collected using blood collection drapes for all women after vaginal birth. All facilities will use non-calibrated drapes during the baseline phase. During the intervention phase, facilities allocated to the control arm will continue to use non-calibrated drapes and facilities allocated to the intervention arm will use calibrated drapes containing measurement and trigger lines. The calibrated drapes are identical to the non-calibrated drapes with the only difference of having measurement and trigger lines to aid healthcare providers detect and treat PPH early. Blood loss will be measured for all women by weighing the blood collection drapes at the first hour postpartum or if bleeding continues, the blood collection will be extended to the second hour postpartum. The weight of the blood collection drape containing the blood will be recorded using digital weighing scales. If there is excessive, additional blood loss beyond the second hour postpartum up to 24 hours postpartum a visual estimation of blood loss will also be provided, and this will be included in the overall blood loss measurement as a secondary clinical outcome.

Only blood loss data that has been source verified will be included in the primary analysis – see section 11.2 for details. Blood loss data that has not been source verified is included in a sensitivity analysis.

Blinded Endpoint Review Committee

A Blinded Endpoint Review Committee (BERC) will assess incoming data relevant to the primary outcome to confirm if any postpartum laparotomy was performed for bleeding and if any maternal death was due to bleeding. Initially, two central independent reviewers (identified by the ITMG) will review de-identified data via the online E-MOTIVE database where there is a case of postpartum laparotomy and/or maternal death. The reviewers will not be able to view the facility's responses as to whether the postpartum laparotomy was for bleeding and/or the maternal death was due to bleeding. Each reviewer will be prompted to log in to the E-MOTIVE database and record their assessment on an electronic case report form (e-CRF) following receipt of an automated notification. If there is discordance between the assessments of the two reviewers or if their assessment conflicts with the assessment provided by the facility then a further assessment will be required by a central independent arbitration committee of five members convened by the ITMG. The committee will meet as frequently as required and a decision will be made by a majority vote. The arbitration committee will have access to the facility assessment (on the Discharge Outcome form) and the two reviewer assessments in order to make their decision. The Programme Manager (or delegate) will minute committee discussions and enter a summary of the discussions along with their decision on

to the e-CRF. The review by the BERC members will be undertaken blinded to the randomised allocation of the health facility. Members of the BERC are required to formally register their assent to join the committee by signing a separate charter. Further details of the BERC can be found in their charter.

Components of the primary composite outcome

The three components of the primary composite outcome will be measured individually and are:

1) Primary severe PPH defined as blood loss ≥1000 ml following a vaginal birth in the facility measured up to 2 hours postpartum;
2) Postpartum laparotomy for bleeding until discharge from the health facility*;
3) Postpartum maternal death from bleeding until discharge from the health facility*

6.2 Secondary clinical and implementation outcomes

Secondary clinical outcomes

These include the three individual components of the composite primary outcome. The secondary clinical outcomes (where we expect to see a reduction if E-MOTIVE is effective) are based on the Core Outcome Set for PPH treatment[14], and are the following:

1. Laparotomy postpartum until discharge from the health facility*;
2. Laparotomy with compression sutures postpartum until discharge from the health facility*;
3. Laparotomy with arterial ligation postpartum until discharge from the health facility*;
4. Hysterectomy postpartum until discharge from the health facility*;
5. Hysterectomy postpartum for bleeding until discharge from the health facility*;
6. All cause maternal mortality postpartum until discharge from the health facility*;
7. Blood loss (reported in ml) up to 24 hours postpartum;
8. Primary PPH defined as blood loss ≥500 ml up to 24 hours postpartum†;
9. Duration of hospitalisation postpartum;
10. Duration of ICU hospitalisation postpartum until discharge from the health facility*;
11. Transfers to higher-level facility postpartum until discharge from the health facility;
12. All cause neonatal mortality postpartum until discharge from the health facility*;
13. Use of Non-pneumatic anti-shock garment (NASG) postpartum†;
14. Use of uterine balloon tamponade postpartum until discharge from the health facility †*;
15. Blood transfusion postpartum until discharge from the health facility†*;
16. Blood transfusion for postpartum haemorrhage until discharge from the health facility†*;
17. Intensive Care Unit (ICU) admissions postpartum until discharge from the health facility†*;
18. Primary severe PPH (defined as blood loss ≥1000 ml) following a vaginal birth in the facility measured up to 2 hours postpartum†;
19. Postpartum laparotomy for bleeding until discharge from the health facility*;
20. Postpartum maternal death from bleeding until discharge from the health facility*;

†*Combined clinical and quality of care exploratory outcomes where we may observe an increase or a reduction if E-MOTIVE is effective.*

**In cases where a woman is transferred to another facility postpartum, discharge from the health facility relates to the facility the woman is transferred to [and the relevant outcomes will be obtained from the facility to which the woman was referred].*

Secondary implementation outcomes

The key secondary implementation outcomes of special interest are 1) PPH detection (with the following numerator and denominator: women who objectively had PPH (source-verified blood loss ≥ 500 mL after weighing the drape) and were diagnosed with PPH by the birth attendants divided by the total number of women who objectively had PPH (source verified blood loss ≥ 500 mL after weighing the drape), and 2) compliance with MOTIVE bundle (with the following numerator and denominator: women who objectively had PPH and were treated with the PPH bundle following a diagnosis of PPH by the birth attendants divided by the total number of women who objectively had PPH (blood loss ≥ 500 mL after weighing of the drape). Compliance with the MOTIVE bundle is defined as adherence to three core elements of the bundle: administration of oxytocic drugs, TXA and IV fluids. If all three core elements are administered when a PPH is diagnosed, this will be deemed positive for bundle compliance. If any of the three core elements are not administered when a PPH is diagnosed, then this will be deemed negative for bundle compliance. It is hypothesised that the causal mechanism underpinning the intervention is that it will increase the rate at which PPH is diagnosed; and that an increase in awareness of women suffering from PPH will subsequently lead to an increase in uptake in the interventions to stop PPH from progressing to severe consequences. This will ultimately lead to a reduction in the proportion of women suffering adverse outcomes from PPH.

Other implementation outcomes are:

1. PPH treatment (with the following numerator and denominator: women diagnosed with PPH by the birth attendants divided by the total of women having a vaginal birth in the health facility)
2. Bundle usage (with the following numerator and denominator: women treated with the PPH bundle following a diagnosis of PPH by the birth attendants divided by the total of women having a vaginal birth in the health facility)
3. Bundle usage for PPH (with the following numerator and denominator: women treated with the PPH bundle following a diagnosis of PPH by the birth attendant divided by the total of women diagnosed with PPH by the birth attendants);
4. Uterine massage;
5. Oxytocin use;
6. Misoprostol use;
7. TXA use;
8. Intravenous fluids use;
9. Examination of the genital tract;
10. Number of women receiving any treatment uterotonic;
11. Number of women requiring additional treatment interventions (not responding to the MOTIVE bundle).

All secondary implementation outcomes will be reported with three denominators: the total study population; women diagnosed with PPH by the birth; and women who objectively had PPH (blood loss ≥ 500 mL after weighing the drape) unless otherwise specified.

The data are routinely collected as part of normal clinical practice and women will not be approached for additional trial-specific data or follow up at any point.

From each participating health facility, we will extract the following additional outcomes weekly:

1. Vaginal births (number);
2. Caesarean sections (number);

From each participating health facility, we will extract the following additional outcomes monthly:

3. Availability of bundle components;
4. Availability of NASG;
5. Availability of UBT;
6. Availability of blood transfusion;
7. Availability of surgical theatre for obstetrics;
8. Availability of ICU;
9. Availability of skilled birth attendants.

6.3. Process evaluation

Aims and objectives

Alongside the trial, we plan to conduct a process evaluation to assess the extent to which the E-MOTIVE interventions have been implemented as intended. We will adopt the UK-MRC guidance on process evaluations of complex interventions to evaluate E-MOTIVE based on three main domains: context, implementation, and mechanisms of impact. We will also be guided by the implementation outcomes framework.[13] The implementation outcomes of interest are:

- Fidelity and Dose: To what extent was the E-MOTIVE intervention and the implementation strategies delivered and engaged with as planned?

- Adaptation: what modifications were made to the E-MOTIVE intervention to adapt to the study context, and achieve the study protocol?

- Contamination and treatment differentiation: To what extent did the clinical actions taken to detect and treat PPH in the usual care control arm differ from those in the E-MOTIVE intervention arm? Is there evidence of cross-contamination between trial arms?

We plan to assess mechanisms of impact as:

- Acceptability and Participant responses: how did healthcare providers respond to and interact with the E-MOTIVE intervention? To what extent were the E-MOTIVE interventions considered acceptable?

- Mediators: what were intermediate processes which explain subsequent changes in implementation outcomes, and what are the barriers and enablers to implementing E-MOTIVE interventions as intended?

- Unanticipated consequences: what are the unintended consequences of the E-MOTIVE intervention?

Design

To answer these questions, we will use a range of methods, theoretical, and analytical approaches similar to those described earlier for the formative and adaptive phases of the programme of research. In line with MRC process evaluation guidance, we will balance in-depth qualitative data collection with a feasible, small sample of participants in each country, alongside quantitative measures across the full trial sample.[9] Methods may include a combination of observations, checklists, document analyses, in-depth interviews, and surveys.

Qualitative interviews with healthcare providers

We will first conduct in-depth interviews with a purposive sub-sample of healthcare providers, including nurses, midwives, and doctors of different levels of experience and management responsibilities. We will do interviews in a sub-sample of both intervention and control arms to explore implementation as intended in the intervention arm, but also what current usual care is in control arm facilities so we can monitor for the extent of treatment differentiation and possible contamination.

We will purposively sample up to three facilities per country (2 intervention arm, 1 control). In each facility, we will interview up to 4 healthcare providers, giving a total sample size of up to 60 participants (i.e., 4 per facility x 3 facilities per country x 5 countries). These facilities will be purposively sampled based on facility size (number of births) and high vs low performing facility. Facilities may also be sampled based on PPH burden and geographical location/country specific factors, to ensure diversity and representation.

Intervention arm interviews will explore self-reported fidelity of delivery, adoption and enactment of the E-MOTIVE intervention, perceived acceptability of the interventions, and barriers and enablers to implementation in practice. We will also explore any other ongoing quality improvement initiatives and factors external to E-MOTIVE that may have influenced practice. Control arm interviews will explore current practice around detection and management of PPH, replicating the interviews done in the formative phase of the study (separate protocol). The interview topic guides will be based on behavioural science frameworks used to explore acceptability, clinical practice, mechanisms of change and barriers and enablers. Both topic guides will be semi-structured, that is, whilst we will have a fixed number of open-ended questions we will ask of all participants, there will be flexibility in the precise wording of the questions in order to adapt and reflect on earlier responses, and these questions will be followed up with open-ended, flexible prompts, to allow the researcher to respond to and further unpack participants' views and responses to the initial questions.

Intervention arm interviews will be done at 6-7 months at selected sites, to allow time for initial intervention delivery and embedding of the intervention in clinical practice. Control arm interviews will be done at 6-7 months in specific facilities if any areas require further exploration following the survey. Potentially eligible participants will be identified by a local collaborator, who will provide participants with a study information sheet. Participants will be asked to sign a consent form prior to taking part. Interviews will be conducted by a local trained researcher (i.e., research midwife, social scientist), in a private location at the participating facility or via video/teleconference- according to participant preference. Interviews will be audio-recorded, transcribed verbatim, and de-identified. These will then be analysed by post-doctoral researchers at UCL and the University of Melbourne, using a combined deductive framework and inductive thematic analysis approach.

Surveys

To balance the in-depth qualitative interviews, we will conduct a cross-sectional survey with a larger, more representative sample of healthcare providers across all participating facilities and countries. Like the interviews, the surveys will explore the perceived intervention acceptability, barriers and enablers to implementing E-MOTIVE and the co-interventions during the trial, and potentially sustaining implementation longer term. The survey will also be structured around the aforementioned behavioural science frameworks around acceptability and influences on implementation. It will include items to mirror the interview questions, but with a mixture of response formats (Likert-type scales, dichotomous yes/no questions). It will include a brief demographics section (e.g., role, years of experience), questions on general knowledge of PPH, how PPH is detected and managed in that facility, extent of implementation of the E-MOTIVE intervention components, and perceived acceptability and barriers and enablers to implementing the E-MOTIVE interventions (MOTIVE bundle and co-implementation strategy). We will also administer a survey to the control arm facilities to explore current practice and possible contamination. This will be the same current practice survey as administered in the formative research phase (separate protocol). The survey for control arm facilities will be administered at 6-7 months.

The survey for intervention arm facilities will be administered at one time point: at 6-7 months (to explore sustainability of implementation). Local collaborators will identify potentially eligible participants and email a study information sheet and link to the electronic survey. Eligible participants are those who work in the labour wards at the facilities recruited for E-MOTIVE. We aim to recruit 1-2 obstetricians, 3 medical officers/residents/junior doctors, and 5 midwives/nurses per facility. This is the information that will be given to the local collaborators. The first two screens of the digital survey will include a study information sheet and consent form, which participants must complete prior to progressing to the survey. No identifiable data will be collected and stored via the survey.

Survey data will be summarised using descriptive statistics. We will compare responses according to participant role, across facilities, and countries.

Quantitative fidelity of delivery assessment

As part of data collection for the trial outcomes, we are collecting data on which E-MOTIVE intervention components were delivered when a PPH was detected. This will enable us to quantitatively assess fidelity of delivery of the E-MOTIVE intervention for all participating facilities. This will be calculated as a proportion of bundle components delivered for treating a PPH. General consensus criterion suggests less than 50% delivery = poor fidelity, 51-79% moderate fidelity, and 80-100% high fidelity. We will compare proportions of bundle component delivery over the duration of the trial to explore sustainability and fidelity drift. We will also explore the potential to use such quantitative process evaluation data, including survey responses, to explore associations with observed outcomes.

Observations

We will also conduct structured observations of PPH detection and management. These observations will be simulations, led by Jhpiego using Objective Structured Clinical Examinations (OSCEs). OSCEs may be conducted at each intervention facility at different time points including pre-training, immediately post-training, post-training when all practice sessions are complete and between 3-6 months following training. The OSCEs will be conducted using an adapted version of an existing Jhpiego OSCE checklist for PPH (i.e., adapted to reflect bundled approach of the E-MOTIVE

intervention). Medical records and facility logbooks may be evaluated to understand the broader context of maternity care, as well as any meeting notes from workshops, trainings, and meetings about the process of implementation. As appropriate, other documents will be included, for example, media coverage about the study or process during the time of implementation to understand how the intervention is viewed by communities and stakeholders involved and affected. These will be collected by local researchers of the E-MOTIVE team (i.e., research midwives, social scientists).

Implications

Findings from the process evaluation will also be fed back into the final iteration of the logic model, to provide a better understanding of the pathways to successful design of the E-MOTIVE intervention. The process evaluation will ultimately help to identify any threats to the internal validity of the trial, as well as to understand issues around equity, transferability, scalability, and sustainability of the intervention. Findings from the process evaluation will facilitate more accurate interpretation of observed outcomes, and inform future scalability and implementation of the E-MOTIVE and co-interventions if shown to be effective.

7. ADVERSE EVENT REPORTING

As the interventions being tested as a bundle in this trial are recommended and used throughout the world, there are no adverse events which would be anticipated as a unique consequence of participation in the trial. No expedited reporting of adverse events is proposed. We are anticipating that there will be deaths in this trial. However, most of these deaths will be a consequence of the PPH or other postpartum complications. It is possible that there may be a difference in the rate of death between the two arms of the trial if the E-MOTIVE intervention reduces deaths in the intervention arm. However, this will not be detected by expedited reporting because (i) the proportion of deaths due to the trial intervention will be small compared to the background risk of death and differences will be difficult, if not impossible, to detect by reporting of individual deaths, and (ii) this is a cluster randomised trial so adjustment for the clustering will be required to explore whether crude differences in death rates are due to the intervention. Maternal deaths and ICU admissions will be collected for all participants in the trial and these outcomes will be monitored by the independent Data Monitoring and Ethics Committee.

8. DATA HANDLING AND RECORD KEEPING

8.1. Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). In order to allow for the accurate collection of the data, source data will be accessible and maintained by health facility staff. Source data are generally kept as part of the medical records generated and maintained at site, but some data variables may be entered directly onto the CRF. The source data for the E-MOTIVE trial will also include birth registries, staff records, and for participants (healthcare providers) their responses to online surveys and interview transcripts. Health facility staff will fill in the CRFs in each facility and all data extracted will be entered onto the online E-MOTIVE database (https://bctu-redcap.bham.ac.uk/). BCTU and investigators will not have access to any identifiable information for any of the records entered onto the database.

8.2. Case Report Form (CRF) Completion

Data reported within the CRFs will be consistent with the source data and any discrepancies will be explained. In the cases where the CRF constitutes source data, this will be filed in the medical records as detailed above and entered into the online E-MOTIVE trial database. All missing and ambiguous data will be queried with health facility staff. Staff delegated to complete CRFs will be trained to adhere to the requirements of data capture as explained in the E-MOTIVE training slides. In all cases, it remains the responsibility of the health facility's local champion to ensure that the CRF has been completed correctly and that the data are accurate. This may be evidenced by the signature of the health facility's local champion, or delegate(s), on the paper CRF (if completed).

For the E-MOTIVE trial this will be in the form of an electronic or paper CRF. The data held on the completed original electronic CRFs are the sole property of the respective local champions whilst the data set as a whole is the property of the BCTU and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the sponsor. Appropriate data sharing requests will be considered by the International Trial Management Group (ITMG) and the BCTU data sharing committee.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the electronic CRFs and confirm accordingly. The **E-MOTIVE Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection.

Staff delegated to complete the electronic CRFs will be trained to adhere to online completion of the CRFs in the trial database from source data. Online data entry is achieved via unique passwords and usernames, which must not be shared amongst the team. All time formats, where applicable, should be in accordance with the 24-hour clock. Rounding of numbers, where applicable, should be in the normal way (i.e., ≥*x*.5 is rounded up to the nearest whole number). Protocol non-compliances should be added to a Protocol Deviation Log, held by the site, and reported to the Trials Office on discovery.

8.3. Data Management

Data must be entered on paper via the CRF booklet or directly on the online E-MOTIVE database (https://bctu-redcap.bham.ac.uk/). Where Paper Case Report Forms (CRFs) are completed, these will be signed and dated, filed in the medical records, and data will be entered on to the online E-MOTIVE database by a member of the research team at the local spoke health facilities.

Participating health facility teams should transfer all data from paper CRF booklets into the online E-MOTIVE database. E-MOTIVE Hub research staff will check all electronic CRFs for completeness, data consistency and compliance with the protocol. If discrepancies or missing data are identified, the Hub will raise queries with the research team at the spoke facility via the E-MOTIVE database.

The central E-MOTIVE trial office at BCTU will liaise directly with each Hub to resolve any inconsistencies in data, identified centrally.

8.4. Data Security and data protection

The security of the Trial Database System is governed by the policies of the University of Birmingham. Data management and data security within BCTU will abide by the requirements of the General Data Protection Regulations (GDPR) and any subsequent amendments. The trial will be conducted at collaborating sites in accordance with the country-specific data protection requirements. Data will be acquired and stored on the REDCap platform. Access to data will be

restricted by usernames and passwords, at participating health facilities, Hubs, and BCTU. Each record on the database will be allocated a unique trial number at entry in the database. All documents will use this as the identifier. All data will be analysed and reported in summary format. No individual will be identifiable.

8.5. Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived. Archiving will be authorised by the BCTU on behalf of the Sponsor following submission of the end of trial report. It is the responsibility of the National Principal Investigator and Local Champion to ensure all essential trial documentation and source documents at their site are securely retained in line with the relevant national laws and regulations. The final dataset will be stored for at least 10 years in accordance with UK Policy Framework for Health and Social Care Research 2017. No documents should be destroyed without prior approval from the BCTU.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. Site Set-up and Initiation

Staff at participating health facilities will undergo a standardised site set-up training package. This will include:

● Online training modules (set-up, control, intervention). Templates will be provided and stored in the Investigator Site Files. Ongoing training will be documented and monitored throughout the study to ensure the intervention is delivered optimally.

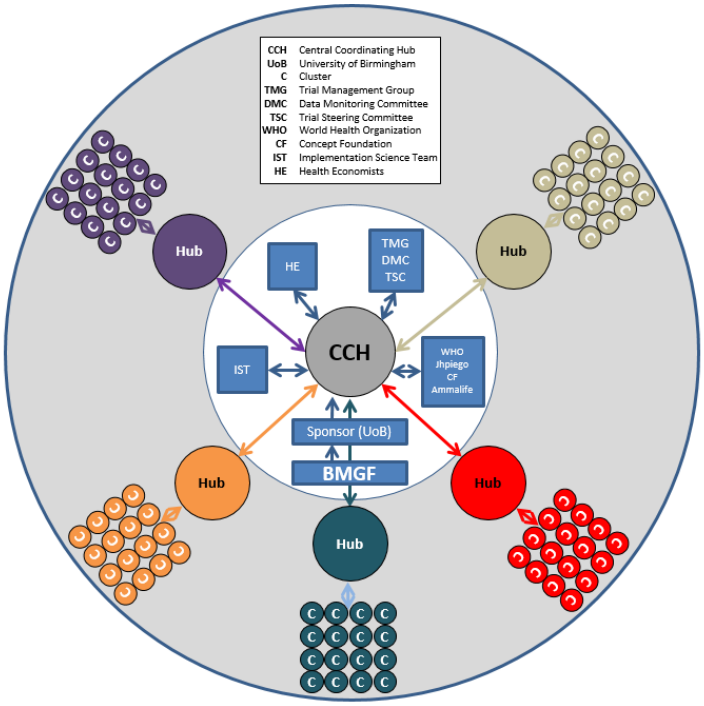
● Site initiation visit: from either BCTU or local Hub. Key members of the health facility research team will be required to attend either a meeting or video/teleconference covering aspects of the trial design, protocol procedures, data reporting and record keeping. The BCTU must be informed immediately of any change in the Site research team.

● A two-month E-MOTIVE 'transition phase' to allow health facilities to adjust to change clinical practice for the delivery of the interventions.

Site opening

Hubs - Hubs are the central, country-specific coordinating centres (***Figure 6***). The Hubs will take responsibility for the management of the health facilities in the country called the Spoke facilities; will provide administrative services for the country network; will provide training for Spokes and will maintain regular communication with the University of Birmingham. Hubs will sign a contract with the University of Birmingham delineating the responsibilities of the Hub as lead site for the E-MOTIVE trial. Hubs should subsequently put agreements in place with each of the Spoke facilities (if required) and ensure that the necessary approvals are in place prior to commencing the trial at each health facility.

Figure 6 *Hub and spoke organization model for the E-MOTIVE study.*



All participating Local Champions will provide evidence of trial specific training to their national Hub. All members of the research team at health facilities will also be required to sign the E-MOTIVE Site Signature and Delegation Log, which details which tasks have been delegated to them by the Local Champion.

9.2. Monitoring

On-site Monitoring

Monitoring visits and observations of healthcare providers managing real life vaginal births will also be conducted in health facilities during the baseline and intervention phases (both in sites randomised to the intervention and control groups) and in health facilities participating in the adaptive cycles. These will include observing the facility readiness for managing PPH and healthcare provider's treatment of postpartum haemorrhage if PPH occurs. An observation guide has been developed for use in health facilities participating in the adaptive cycles and health facilities randomised to the intervention group. A separate observation guide has been developed for use in health facilities during the baseline phase and in health facilities randomised to the control group. Observations of vaginal births will be conducted in intervention and control facilities at 1 or 2 time points during the study.

Additional on-site monitoring is carried out as required following trial specific risk assessment and as documented in the monitoring plan. The monitoring of spoke facilities will be conducted by the Hubs; the Hubs will be monitored by BCTU.

Any monitoring activities will be reported to the central trials team at BCTU and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, or poor compliance with the E-MOTIVE intervention.

If an on-site monitoring visit is planned, the Hub trial team will contact the health facility to arrange a date for the proposed visit and will provide the health facility with written confirmation.

Investigators will allow the Hub staff access to source documents as requested. During on-site monitoring visits the source data contained in source documents e.g., patient notes will be checked by the Hub team to ensure data are legible, original, accurate and well maintained.

Central Monitoring

E-MOTIVE trial staff from BCTU will be in regular contact with the Hub research teams to check on progress and address any queries that they may have.

Hub trial staff will check CRFs from the spoke facilities for compliance with the protocol, data consistency, missing data and timing. Hubs will send spoke facilities data queries for missing data or clarification of inconsistencies or discrepancies. BCTU will centrally monitor data received from the Hubs. More detailed monitoring processes will be detailed in the Monitoring Plan.

9.3. Audit and Inspection

National Principal Investigators and Local Champions will permit trial-related monitoring, regulatory inspections, audits, and ethical review at their site. The investigator will comply with these visits and any required follow up. If there are any externally-conducted inspections, Hubs are requested to notify BCTU in advance of any relevant inspections of the Hub site.

9.4. Notification of Serious Breaches

The Sponsor of the trial is responsible for notifying the regulatory bodies in writing of any serious breach of the conditions of the trial protocol, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the women giving birth in the study facilities;

- the scientific value of the trial.

Hubs must notify the BCTU and Spokes are therefore requested to notify the Hub, of any suspected trial-related serious breach of the trial protocol. Where BCTU is investigating whether or not a serious breach has occurred, sites are requested to provide sufficient information to report the breach to the regulatory bodies where required and in undertaking any corrective and/or preventive action.

Any major problems identified during monitoring may be reported to BCTU, the TSC and the relevant regulatory bodies.

10. END OF TRIAL DEFINITION

The end of trial is defined as the final data capture from all participating health facilities. This will ensure completion of data collection, data input and analysis. The E-MOTIVE Trials Office at BCTU will notify each Hub that the trial has ended within 90 days of the end of trial and it will be their responsibility to notify the regulatory bodies of that country as relevant. A summary report will be sent to each Hub for submission to the regulatory bodies within 12 months of the end of the trial (if required).

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size

Following issues around study data collection, and in discussion with the funder and the independent TSC and DMC committees, the study was reduced from 24 months to 16 months. Below, we outline the original sample size calculation and present the updated sample size calculation.

Original sample size calculation

Assuming there are 80 health facilities in the trial, evenly split across the intervention and control groups, with an average number of 192 births per health facility per month, the anticipated total sample size for the study (running for 22 months) would be 337,920 (=80*192*22). The number of health facilities (80) has been inflated by 10% to allow for drop out from the number of health facilities required (72). This sample size is expected to be sufficient to provide approximately 90% power at 5% significance (two-sided) to detect a change from 2% to 1.5% (25% relative reduction) in the primary outcome, after allowing for clustering and for varying cluster sizes and across most realistic scenarios. Below, we describe this calculation in more detail, firstly providing the rationale for the choice of these key values, and then outlining the methodology used to calculate the sample size. We provide details of the sensitivity of power to any changes in these key design parameters.

In the control condition, we expect the prevalence of the primary composite outcome to be around 2%. This prevalence is informed by the prevalence of a similar outcome based on analysis of the CHAMPION trial[4] and we have considered sensitivity to this prevalence between 1.5% and 4%.

A relative risk reduction of 25% was considered to be a clinically meaningful difference to detect, though smaller reductions could also be worthwhile. Under some scenarios (such as a high value of the ICC) this target effect size might not be detectable at 90% power, and so we therefore consider a larger target effect size to demonstrate the size of effect size that can be demonstrated under these less conservative other scenarios. We have thus considered sensitivity to the power for a relative reduction of 20% and 30%.

Sample size calculations have allowed for the clustered nature of the design through the intra-cluster correlation (ICC). As recommended, values for the ICC have been informed through a combination of the literature and analysis of available data on a similar set of outcomes. Analysis of the CHAMPION trial[4] found an ICC of 0.03 (95% CI: 0.02 to 0.05) for a similar composite outcome of PPH ≥1000 ml, laparotomy and maternal death. This ICC was estimated using a linear mixed regression model and so is on the proportions scale as is appropriate for a sample size calculation. As the literature suggests, rare clinical outcomes tend to have small ICCs, for this reason we have considered an extended range for the ICC, from 0.001 to 0.05, with an expected ICC of 0.02.

To allow for variations in clustering over time, we have allowed for a cluster by period random effect. This has been incorporated in the sample size calculations using the cluster autocorrelation (CAC).[15,16] There is limited information from the literature on likely values of the CAC. Using data from the CHAMPION trial[4], we created two 11-month periods, which match the planned study design. From this, we estimated a CAC of 0.97. No current methodology exists to calculate a confidence interval for this value. We have chosen to consider sensitivity to the CAC between the values of 0.95 and 1.0.

Survey data from health facilities that was collected to obtain information on the number of births per health facility. From this survey data, we calculated an average number of births per health

facility per month of 192. The health facilities varied in size. We have estimated a coefficient of variation of cluster sizes of 0.5 and have allowed for this in our sample size calculations using a conservative correction. [17] [Rutterford 2015].

The methods to calculate the sample size in a parallel CRT with a baseline period have been described fully by Hooper and Bourke.[15,16] These methods have been implemented in an RShiny App (https://clusterrcts.shinyapps.io/rshinyapp/), used to inform the sample size for this trial.

Table 1 provides information on the expected level of power across the range of parameters outlined above. These suggest that the study has at least 80% power in almost all likely scenarios to detect a 25% relative risk reduction in the composite primary outcome from 2% to 1.5% (***Table 1***). If the ICC is at the upper limit (0.05), the study would have more than 80% power to detect a relative risk reduction of 30% in the composite primary outcome from 2% to 1.5% under every scenario considered except one (ICC=0.05 and CAC=0.95).

Table 1*: Original estimates of the power with changes to key design parameters.*

			RR = 20%			RR = 25%			RR = 30%		
			Control Prevalence								
			1.5 %	2.0 %	4.0 %	1.5%	2.0%	4.0%	1.5%	2.0%	4.0%
CAC = 0.95	ICC	0.001	96.4	99.2	99.9	99.6	99.9	99.9	99.9	99.9	99.9
		0.02	54.6	67.1	92.9	68.1	80.3	98.0	84.1	92.8	99.8
		0.05	30.8	39.2	67.3	38.9	49.3	79.1	53.3	65.7	92.1
CAC = 0.97		0.001	96.8	99.3	99.9	99.7	99.9	99.9	99.9	99.9	99.9
		0.02	67.8	80.1	97.9	81.9	91.4	99.7	93.8	98.2	99.9
		0.05	43.0	54.2	83.8	54.4	66.8	92.8	71.2	83.0	98.6
CAC = 1.00		0.001	97.4	99.9	99.9	99.6	99.9	99.9	99.9	99.9	99.9
		0.02	95.8	98.9	99.9	99.7	99.9	99.9	99.9	99.9	99.9
		0.05	95.4	98.8	99.9	99.9	99.9	99.9	99.9	99.9	99.9

Note: Power has been calculated assuming 72 health facilities, with an average number of 192 births per month (22 month study), and a coefficient of variation of cluster sizes of 0.5. CAC: Cluster autocorrelation; ICC: Intra cluster correlation. RR = Risk reduction

Updated Sample Size Calculation

In October 2021, a revised sample size calculation was performed, based on the study shortening from 24 months to 16 months (allowing for a 2-month transition period). As part of this, we evaluated some of the parameters made in the earlier calculation using estimates from the accrued baseline data (collected from October 2020 to September 2021) in sites with high quality data.

Assuming there are 80 health facilities in the trial, evenly split across the intervention and control groups, with an average number of 192 births per health facility per month, the anticipated total sample size for the study (running for 14 months) would be 215,040 (=80*192*14). The number of health facilities (80) has been inflated by 10% to allow for dropout from the number of health facilities required (72).

Table 2 provides information on the expected levels of power for a 16-month study (two 7-month periods and a 2-month transition period) across the range of parameters described earlier. These suggest that the study has at least 90% power at 5% significance (two-sided) to detect a 30% RRR for most scenarios after allowing for clustering and for varying cluster size. The study will have over 90% power to detect smaller RRR if the ICC is close to the lower bound (0.001), the CAC is at the upper bound (1.0), or the prevalence of the study is relatively large (4.0%).

***Table 2**: Estimates of the power with changes to key design parameters.*

			RR = 20%			RR = 25%			RR = 30%		
			Control Prevalence								
			1.50 %	2.00 %	4.00 %	1.50 %	2.00 %	4.00 %	1.50 %	2.00 %	4.00 %
CAC = 0.95	ICC	0.001	86.8	94.5	99.9	97.4	99.5	99.9	99.7	99.9	99.9
		0.02	43.2	54.4	84	62	74.6	96.3	78.8	89.1	99.5
		0.05	24.8	31.6	56.1	36.8	46.7	76.4	50.6	62.7	90.3
CAC = 0.97		0.001	87.5	95	99.9	97.6	99.5	99.9	99.8	99.9	99.9
		0.02	53.9	66.3	92.5	74.1	85.5	99.1	88.8	95.7	99.9
		0.05	34.1	43.4	72.7	50.2	62.4	90.1	66.8	79.1	97.7
CAC = 1.00		0.001	89.7	96.2	99.9	98.3	99.7	99.9	99.9	99.9	99.9
		0.02	83.7	92.1	99.9	95.9	99	99.9	99.5	99.9	99.9
		0.05	83	92.6	99.9	96.2	99.1	99.9	99.4	99.9	99.9

Note: Power has been calculated assuming 72 health facilities, with an average number of 192 births per month (14-month study), and a coefficient of variation of cluster sizes of 0.5. CAC: Cluster autocorrelation; ICC: Intra cluster correlation. RR = Risk reduction

Analysis of the baseline data found a prevalence of the primary outcome of 3.6% (95% CI: 3.4% to 3.8%) and an ICC of 0.018 (95% CI: 0.01 to 0.034). With large prevalence (4.0%), the study would have over 90% power to detect a 20% RRR for most likely scenarios (Table 2). A re-estimation of the CAC using two 7-month periods in CHAMPION data found a CAC of 0.99. With a CAC of 1.00, the study would have over 90% power to detect a 20% RRR for most likely scenarios.

11.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. All analyses will be by intention to treat, which means that health facilities will be analysed according to their randomised allocation. The baseline characteristics, for example age, number of previous births, and pregnancy type, will be summarised as means and standard deviations, medians and inter-quartile ranges, or numbers and percentages, as appropriate, stratified by trial arm and time-period. A flowchart will be constructed to show the flow of both health facilities and patients throughout the trial.

The primary comparison will be composed of those health facilities randomised to the E-MOTIVE intervention versus those randomised to the usual care. For the primary outcome, our aim is to fit a mixed-effect logistic model incorporating a constrained baseline analysis to calculate relative risks

and risk differences. We will use marginal standardisation to obtain the risk difference and risk ratio. Under a constrained baseline analysis, each observation has a binary indicator for time – indicating whether the observation was made during the baseline phase or the post-randomisation phase (which represents the change in the control arm over time) – and a binary indicator for treatment – indicating whether the observation was allocated to the usual care or E-MOTIVE (which represents the treatment effect). The constrained part of the model assumes no differences at baseline as is appropriate under a randomised design. This approach is recommended in cluster randomised trials with a baseline assessment of outcome.[18] No small sample correction will be used as there are expected to be in the region of 70 health facilities in the analysis and the mixed model is expected to have appropriate estimation of the standard errors in this situation.[19] Clustering will be allowed for in all analyses through the use of random effects. Recent developments in the methodological literature for the design and analysis of multiple-period cluster randomised trials suggest that a simple exchangeable correlation structure is not sufficient to depict the correlation structure in multiple-period cluster randomised trials.[15,16] We will explore including a random cluster by period interaction in addition to a random cluster effect to allow for the decay in correlation between observations made in the same cluster, but at different time periods. If models with complex correlation structures do not converge, we will fit models with a simpler correlation structure. Other secondary outcomes will be modelled similarly, using appropriate link and distribution function in the generalised linear mixed model family.

The primary analysis will be unadjusted, except for factors used in the randomisation method (number of vaginal births per health facility, country, and quality of oxytocin per health facility during the baseline phase). As a sensitivity analysis, we will perform a propensity score (PS) based method – the direct PS adjustment as recommended by Leyrat et al[20] [Leyrat 2013]. Under this method, the PS is obtained by fitting a multivariable logistic model with potential confounders (age; parity; multiple pregnancy; mode of birth; and birth weight). The potential confounders have been proposed by the E-MOTIVE TMG following a consensus meeting.

The primary composite outcome (severe PPH, postpartum laparotomy for bleeding, and maternal mortality from bleeding) will be considered significant at the 5% level, and effect sizes and 95% CIs will be reported. Treatment effect measures with confidence intervals will be presented for the individual components of the primary composite (severe PPH, postpartum laparotomy for bleeding, and maternal mortality from bleeding), but it is not expected that there will be sufficient power to make definitive conclusions about any of them.

Results on secondary clinical and implementation outcomes (listed in section 6.2), will be interpreted with caution. To this end, treatment effect measures with confidence intervals will be presented as supporting evidence only.

All analysis will be carried out using Stata.

Subgroup Analyses

Tests for statistical heterogeneity (e.g., by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. The subgroup analyses will be performed on the primary and key secondary implementation outcomes only.

Planned subgroup analyses include A) *Population subgroups:* age (three levels categorised by tertiles of the distribution), previous birth (none vs any), type of pregnancy (singleton vs multiple), gestational age (term vs preterm), type of birth (e.g. spontaneous versus assisted), risk factors for

PPH (diagnosis of preeclampsia, induction or augmentation of labour, previous caesarean, previous postpartum haemorrhage, antepartum haemorrhage, episiotomy, vaginal tears, retained placenta), baseline period PPH rate (low vs high PPH rate as objectively diagnosed by blood collection drape using data from the baseline period), country, number of vaginal births (above median vs below median as calculated using data from the baseline period); and B) *Intervention subgroups:* compliance with the E-MOTIVE intervention (defined as a minimum of administration of oxytocic drugs, TXA and IV fluids for objectively diagnosed PPHs; over the median and below the median; and time since intervention exposure (defined as number of months since cluster began post-randomisation phase).

Missing Data

Every attempt will be made to collect routine clinical details on all women giving birth vaginally in the facilities using an efficient and pragmatic approach; it is thus anticipated that missing data will be minimal. Women with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this may include simulating missing responses using a multiple imputation approach. Full details will be included in the Statistical Analysis Plan.

Source-verified Data

Analyses of outcomes with blood loss data will only include blood loss that has been source-verified. Blood loss measured using the blood collection drape, which is source-verified will have a corresponding photograph, which is uploaded to a secure portal, of the drape on the E-MOTIVE digital weighing scale displaying the drape weight. The photograph should also display the drape weight documented on the E-MOTIVE stickers before being placed in the patient notes. The drape weight value entered on to the E-MOTIVE REDCap database is verified against the drape weight in the photograph and the photograph is linked to the patient record on the database using the E-MOTIVE patient I.D number.

11.3. Planned Interim Assessments

The DMC will be tasked with reviewing the main effectiveness outcomes and ensuring that the trial is proceeding as planned (in particular does not exhibit any clear indicators of bias or large amounts of missing data). To this end, we expect the DMC to monitor the quality of the data; the pooled estimate of prevalence and within-period intra-cluster correlations (as a flag to indicate if the estimates used in the power calculation were accurate); and most importantly to monitor the characteristics of the participants in the control and intervention arms, so as to have some way of determining if any selection bias was occurring. The exact format and frequency of this monitoring will be determined with the DMC. Formal interim assessment of effectiveness is not anticipated due to the nature of the intervention and timing of the intervention period; however, the DMC will reserve the right to request a formal comparison if they see fit. Details of the agreed plan will be written into the Statistical Analysis Plan and DMC Charter. Further details of DMC arrangements are given in section 12.6.

11.4. Planned Final Analyses

The primary analysis for the study will be carried out once all outcome data have been entered onto the study database and validated as being ready for analysis.

11.5. Health Economic Evaluation

We plan to assess the cost-effectiveness of the E-MOTIVE intervention compared with usual care from a public healthcare system perspective, as measured by ICERs for a) severe PPH prevented, b) laparotomy for PPH prevented, c) death from PPH avoided, and (d) quality-adjusted life-years prevented.

Base case analyses will be conducted from a public healthcare system perspective and we will undertake sensitivity analyses to assess the robustness of the results and explore their generalisability. We will record important resource use, including: staff time, meetings and training, clinical and administrative supplies, hospital inpatient days, medications, investigations, and other follow-on impacts associated with potential complications and additional treatments incurred relating to PPH. We will collect the resource use data for hospital inpatients stay for all women giving birth in both intervention and control facilities. We will attach unit costs to resource use to estimate the additional cost of the E-MOTIVE program. Country specific unit costs will be sought from the International Drug Price indicator guide, relevant WHO datasets (e.g., WHO-CHOICE), and participating countries. Cost data will be presented in US dollars.

12. TRIAL ORGANISATIONAL STRUCTURE

12.1. The Birmingham Clinical Trials Unit

The BCTU is the International Coordinating Centre for the trial. Each country will appoint a National Principal Investigator (NPI), a National Coordinator (NC) and a National Coordinating Centre – the Hub – who will take responsibility for the study.

12.2. Sponsor

The University of Birmingham is the Sponsor of the E-MOTIVE trial in all collaborating countries. Sponsorship will be provided by the University of Birmingham upon signing of the Clinical Trial Agreement with the Hub. Each Hub will be responsible for implementation of Clinical Trial Agreements with local participating health facilities (spokes) if required.

12.3 International Trial Management Groups (ITMG)

The ITMG includes those individuals responsible for the day-to-day management of the trial. This will include the trial Chief Investigator, lead methodologists, and the E-MOTIVE trial management staff from BCTU. The Group will meet at least quarterly, but this may be more frequent if deemed necessary by the members. The role of the Group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

As E-MOTIVE is an international trial involving multiple countries, each country may wish to convene a country-specific TMG. This group may consist of the National Principal Investigator (NPI), the National Coordinator (NC), the local champion from each local spoke facility, the lead research nurse and other senior clinicians as deemed appropriate by the NPI. The dates of country-specific TMGs should be notified to the BCTU as should events deemed as significant by the country-specific TMGs. Once Hubs are open, the Hub NPIs and NCs may be invited to attend ITMG meetings.

12.4 Site Organisation

Organisation of sites is adopting the Hub and Spoke model. The Hub will take responsibility for conduct and oversight of both its own site and its Spoke facilities.

12.5 Trial Steering Committee

The remit of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the protocol and relevant regulations.

The TSC will operate in accordance with a trial-specific TSC Charter. The TSC will meet approximately once a year (either face-to-face or via video/teleconferencing) or more often if required.

The specific tasks of the TSC may include:

● To approve and sign off the trial protocol and any protocol amendments.

● To resolve problems brought to it by the International Coordinating Centre at BCTU.

● To provide advice to the investigators on all aspects of the trial.

● To review recruitment, data completeness, and protocol deviations.

● To review recommendations from the DMC, and help with the decision-making that follows on from the recommendations of the DMC.

12.6. Data Monitoring Committee

Data will be supplied in strict confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants.

The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.[21]

The DMC is scheduled to meet prior to the trial commencing, half way and at the end of the control phase and then half way through the intervention phase after the point of randomisation (approximately 25%, 50% and 75% through recruitment to the whole study). Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of the trial. An emergency meeting may also be convened if required.

12.7. Finance

E-MOTIVE is a commissioned trial by the Bill & Melinda Gates Foundation. The Institute of Global Innovation and Alumni Fund of University of Birmingham are also financially supporting the study.

13. ETHICAL CONSIDERATIONS

The E-MOTIVE trial is designed and will be conducted in accordance with the principles set out by the World Medical Association (WMA) in the *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects* (2013). As the E-MOTIVE trial will be conducted in LMICs, the trial will also be performed in accordance with the Council for International Organisation of Medical Science (CIOMS) *International Ethical Guidelines for Health-related Research Involving Humans* (2016). Finally, as the E-MOTIVE trial is a cluster randomised trial, it will be performed in accordance with the *Ottawa Statement for the Ethical Design and Conduct of Cluster Randomised Trials* (2012).

The Ottawa Statement sets out seven ethical issues for cluster randomised trials. We use these to frame this section, with reference to the WMA *Declaration of Helsinki* and CIOMS *International Ethical Guidelines* as appropriate.

13.1. Justifying the cluster randomized design

The choice of a cluster randomised design must be justified (Ottawa Statement, recommendation 1; WMA, principle 22). The E-MOTIVE intervention aims to increase compliance with WHO recommendations for the treatment of PPH. The E-MOTIVE intervention targets healthcare providers to promote the uptake of evidence-based practice. Professional-level interventions like the E-MOTIVE intervention can only be rigorously evaluated with a cluster randomised design and, hence, the design is used by necessity.

13.2. Research ethics committee review

As the E-MOTIVE trial is research involving human participants, research ethics committee approval will be sought at all study sites (Ottawa Statement 2; WMA 23).

13.3. Identifying research participants

People who are targeted by the study intervention or control, with whom researchers interact, or whose identifiable private health information is collected ought to be considered research participants (Ottawa Statement 3; CIOMS, guideline 21). The E-MOTIVE evaluates a complex intervention to increase the early detection and evidence-based treatment of PPH by healthcare providers. As they are targeted by the E-MOTIVE intervention, healthcare providers attending childbirth are research participants.

Patients are not research participants in the E-MOTIVE trial. As the Ottawa Statement explains, "simply being a patient or a professional participating in a cluster randomised trial of an educational, knowledge translation, or quality improvement intervention does not make one a research participant" (Ottawa Statement 3). The CIOMS *International Ethical Guidelines* agree: "In cluster randomised trials in which health-care providers are the research subjects, the intervention may not be targeted at patients, but aggregate data from patients' records may be used to judge the effectiveness of the intervention… patients are not subjects in this type of study" (CIOMS 21). In the E-MOTIVE trial there will be no researcher interaction with patients, no additional data will be obtained specifically for the trial, and there is no non-clinically indicated follow-up. All patient data are routinely collected in clinical practice.

13.4. Obtaining informed consent

Informed consent will be sought from healthcare providers attending the E-MOTIVE training (Ottawa Statement 7; CIOMS 21; WMA 25, 26). Healthcare providers will receive the E-MOTIVE Information Sheet and Consent Form. The trial staff will be employed by the spoke facilities and will be carefully trained to discuss the proposed trial with participating healthcare providers and encourage them to ask as many questions as they need to understand the implications of enrolment. Healthcare providers will not be recruited in the presence of supervisors.

As patients are not research participants in the E-MOTIVE trial, their informed consent for research purposes is not required. This is consistent with the *Ottawa Statement* (4), the CIOMS *International Ethical Guidelines* (21) and other trials studying the implementation of WHO recommendations. For an example, see: Haynes AB, ... Gawande AA; Safe Surgery Saves Lives Study Group. A surgical safety

checklist to reduce morbidity and mortality in a global population. *N Engl J Med* 2009; 360(5): 491-499.

13.5. Gatekeepers

"Gatekeepers are individuals or bodies who may be called upon to protect the group-based interests that are affected by enrolment in a CRT" (Ottawa Statement 8-10). The E-MOTIVE trial will enrol 80 health facilities across 5 countries. In each case, permission will be obtained from the institutional leadership for the health facility to participate in the trial (Ottawa Statement 9; CIOMS 21).

Before any healthcare providers are enrolled into the trial, the Local Champion at each health facility is required to obtain local approvals. Spoke facilities will not be permitted to train healthcare providers or record anonymised routinely collected clinical data on women until written confirmation of approval is received by the Hub. It is the responsibility of the Local Champion to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect a woman's health.

13.6. Assessing benefits and harms

The benefits and harms of research participation must stand in reasonable relation (Ottawa Statement 11-13; WMA 16). First, the study intervention must be justified (Ottawa Statement 11). PPH is the leading cause of maternal death worldwide; accounting for 27% of maternal deaths.[1,2] The WHO published evidence-based "Recommendations for the Prevention and Treatment of Postpartum Hemorrhage" in 2012.[3] However, adherence to these recommendations is limited in each of the host countries. The E-MOTIVE trial evaluates a complex intervention to promote early detection and evidence-based treatment of PPH. While the components of the MOTIVE bundle are evidence based, it is not currently known whether the E-MOTIVE implementation intervention will be successful in changing provider behaviour. Thus, there is "uncertainty in the relevant community of experts as to the preferred practice," or equipoise, regarding the E-MOTIVE intervention (Ottawa Statement 11).

Second, the control condition must be justified (Ottawa Statement 12). According to the Ottawa Statement, "individuals in the control arm must not be deprived of effective care or programs to which they would have access if there were no study being conducted." Healthcare providers in health facilities randomised to the control condition will continue to provide care as they did before the trial, and they remain free to use uterine massage, oxytocin, tranexamic acid and intravenous fluids (the MOTIVE bundle) in the treatment of PPH. Additionally, WHO guidelines for the treatment of PPH will be distributed to healthcare providers in control facilities. Thus, the control condition is justified.

Third, the risks of data collection procedures must (1) be minimised and (2) reasonable in relation to the knowledge to be gained (Ottawa Statement 13). The E-MOTIVE trial only uses anonymised routinely collected clinical data. Health facility staff will extract anonymised data from registries for assessing health outcomes such as death or laparotomy. Patient information will be stored securely, and only people directly involved in the study will have access to anonymised data (WMA 24). Thus, risks of data collection are minimised, and reasonable in relation to the high social value of the study question.

13.7. Protecting vulnerable participants

Vulnerable participants are people who in the context of study participation "have an increased likelihood of being wronged" and they are entitled to additional protections (CIOMS 15). Healthcare providers work in hierarchical organisations and may be less able to express a free choice regarding study participation. In such circumstances: "When investigators are recruiting or obtaining consent from these individuals, they should conduct informed consent negotiations in such a way as to limit the potential for coercive influence from cluster or organizational leaders" (Ottawa Statement 15). Thus, in the E-MOTIVE trial healthcare providers will not be recruited in the presence of supervisors.

When research is conducted in low-resource settings, the sponsor and researchers must ensure the "research is responsive to the health needs or priorities of the communities or populations where the research will be conducted" (CIOMS 2). PPH is the leading cause of maternal mortality globally, and the toll is disproportionate in LMICs. When mothers die during childbirth in an LMIC, only 20% of children survive.[1] The E-MOTIVE trial seeks to enhance the early detection and evidence-based treatment of PPH and thereby prevent maternal morbidity and mortality in low-resource settings.

If the E-MOTIVE implementation intervention is effective in reducing severe PPH, surgery and death, the researchers will work with the Gates Foundation and host countries to ensure it is rolled-out to control health facilities and beyond.

14. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with all appropriate local and national guidelines.

When data are transferred between Hubs and local spoke facilities, data will be de-identified and will be identified using their unique E-MOTIVE trial number only. Any correspondence between BCTU and the Hubs will use the E-MOTIVE trial number.

The Investigator must maintain documents not for submission to BCTU (e.g., The E-MOTIVE Patient Identification Log) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete anonymised trial records.

BCTU will maintain the anonymity of all routinely collected data and will not disclose information by which women may be identified. Representatives of the E-MOTIVE trial team and sponsor will not access the medical records and routine clinical data collection, will rely solely on the health facility staff. The local champions of the spoke health facilities will be responsible for quality assurance purposes to audit information documents regularly to ensure the data are being reliably gathered.

15. FINANCIAL AND OTHER COMPETING INTERESTS

At the time of writing the protocol, not all sites and personnel had been identified. Information on financial and other competing interests (if any) will be collected and documented in the Trial Master File (TMF).

16. INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm, which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial.

The risk of the trial is no greater than the risk of the usual clinical care. Responsibility for the participants at health facilities remains with the organisation responsible for the clinical facility and it is therefore indemnified through their normal arrangements.

17. PUBLICATION POLICY

A meeting will be held after the end of the trial to allow discussion of the main results among the collaborators prior to publication. Results of the formative phase, pilot, trial, process evaluation and health economic evaluations will be submitted as publications in peer-reviewed journals.

The success of E-MOTIVE depends on the collaboration of a large number of healthcare providers across several countries. For this reason, all publications arising from this work will be attributed to the "E-MOTIVE Collaborative Group", with the writing committee and order approved by the ITMG.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the ITMG. Manuscripts must be submitted to the ITMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. The ITMG are also obliged, by the terms of our contract to notify the funder (Bill & Melinda Gates Foundation) before submitting any publications. Authors must acknowledge that the trial was performed with the support of The University of Birmingham and funding from the Bill & Melinda Gates Foundation (including relevant acknowledgment text that will be provided by the ITMG).

Site investigators may access the full dataset if a formal request describing the plans of the analysis is approved by the ITMG. Individual countries will be allowed to publish their efficacy results, however the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the ITMG decides otherwise.

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Appendix A

Modification of the Pakistan study design: Protocol for an E-MOTIVE before-and-after (implementation) study design

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Rationale for the modification of the Pakistan study design

Pakistan was added as a participating country (8 main trial and 2 adaptive cycle sites) in September 2022 to provide South Asian representation in the main E-MOTIVE trial. At this time, the other 78 hospitals in the four African countries (Tanzania, Kenya, South Africa, and Nigeria) had already completed the baseline phase of the trial and commenced the post-randomisation phase. The Data Monitoring Committee (DMC) met on 24-Jan-2023 and observed that the pre-specified total study sample size had been achieved from the four African countries, therefore the trial data should be published without waiting for Pakistan to contribute data. This recommendation was subsequently ratified by the Trial Steering Committee (TSC) on 22-Feb-2023. It was unanimously agreed that there was no good scientific reason for the final analysis to be delayed, and that there was an ethical obligation to make the results available at the earliest, especially given that some of the settings across the world continue to see a high rate of PPH and maternal deaths. The African sites completed data collection on 03-Mar-2023. The final results, with data analysed from the four African countries showed that early (E) detection of postpartum haemorrhage and use of bundled treatment (MOTIVE) led to a lower risk of the primary outcome, that is a **60% reduction** in the **composite outcome (severe PPH, laparotomy for bleeding, or maternal death from bleeding)** in the E-MOTIVE arm compared to the arm that received usual care (published in NEJM on 09-May-2023).

Publication link: https://www.nejm.org/doi/full/10.1056/NEJMoa2303966

Given the above result from the African setting, the study design in Pakistan will now be adapted to a 'before-and-after' study to test the implementation of E-MOTIVE in a South Asian setting.

Aim

To study the key implementation (process outcomes) of E-MOTIVE in Pakistan (as a representation of the South Asian setting)

Methods

Design: This is a before-and-after study design. The baseline data that was collected at the 8 sites (all sites followed usual care) as a part of the main E-MOTIVE trial will be used to represent the 'before' phase of the study.

Setting: Eight secondary-level health facilities across Pakistan

All the 8 health facilities that completed a 5 to 6-month baseline period (until 31-Mar-2023) in which they were following usual care with dissemination of the current guidelines, will enter a 2-month transition (allowing two months for full implementation and embedding of E-MOTIVE). Following this, all 8 sites will implement E-MOTIVE for 3-months. Mixed methods work along with baseline-and-implementation phase healthcare provider observations will be conducted (Figure A1).

Key implementation outcomes:

Co-primary:

1. PPH detection [women who objectively had PPH (source-verified blood loss ≥500 mL after weighing the drape) and were diagnosed with PPH by the birth attendants divided by the total number of women who objectively had PPH (source verified blood loss ≥ 500 mL after weighing the drape)] **AND**
2. Compliance with MOTIVE bundle (women who objectively had PPH and were treated with the PPH bundle following a diagnosis of PPH by the birth attendants divided by the total number of women who objectively had PPH (blood loss ≥ 500 mL after weighing of the drape)

Secondary:

1. PPH treatment (women diagnosed with PPH by the birth attendants divided by the total of women having a vaginal birth in the health facility)
2. Bundle usage (women treated with the PPH bundle following a diagnosis of PPH by the birth attendants divided by the total of women having a vaginal birth in the health facility)
3. Bundle usage for PPH (with the following numerator and denominator: women treated with the PPH bundle following a diagnosis of PPH by the birth attendant divided by the total of women diagnosed with PPH by the birth attendants)
4. Uterine massage
5. Oxytocin use
6. Misoprostol use
7. TXA use
8. Intravenous fluids use
9. Examination of the genital tract
10. Number of women receiving any treatment uterotonic
11. Number of women requiring additional treatment interventions (not responding to the MOTIVE bundle).

Sample size

The power for the sample size calculated below is based on the two primary implementation outcomes (these will be the co-primary outcomes for this study) from the baseline data (PPH detection and adherence to MOTIVE bundle). Assuming eight health facilities in Pakistan, an average of 1,100 women per cluster would give an expected number of 1,000 women in the baseline phase with PPH and 500 women in the post-randomisation phase with PPH. The study will have >90% power to detect a change from 50% to 90% in the co-primary outcomes, after accounting for clustering (ICC of 0.25), cluster size variation (cv = 0.5) and adjusting the alpha level for the co-primary outcomes (alpha = 0.025).

Analysis

This will remain the same as per the analysis of implementation outcomes in the main protocol (as described above).

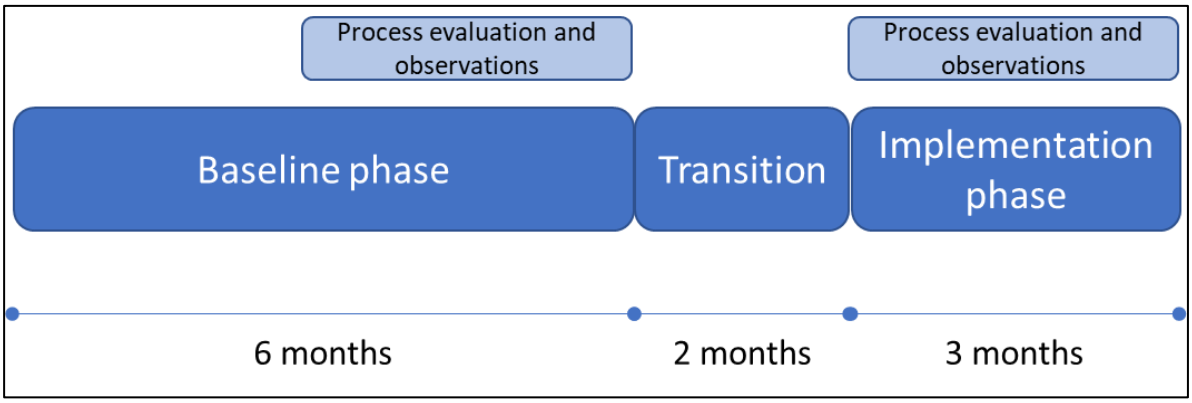

Figure A1. Timeline depicting the baseline, transition and implementation phase for E-MOTIVE 'before-and-after' design in Pakistan along with process evaluation and healthcare provider observations