STUDY PROTOCOL

Tranexamic acid by the intramuscular or intravenous route for the prevention of postpartum haemorrhage in women at increased risk: a randomised placebo-controlled trial (I'M WOMAN)

Sponsor: London School of Hygiene & Tropical Medicine (LSHTM)

Sponsor ID: 2021-KEP-588

Trial Coordinating Centre: LSHTM Clinical Trials Unit – Global Health Trials Group

Funding: Unitaid

Trial registration

Name of registry	ID number	Date registered
Clinicaltrials.gov	NCT05562609	3 October 2022
ISRCTN	ISRCTN12590098	20 January 2023

Protocol change	Version number	Version date	Details
Original	1.1	9th Jan 2023	First approved version
Amendment	1.2	1st Mar 2023	Corrected minor typographical errors.
Amendment	2.0	1st Jun 2023	Simplified consent procedure – removed the option to use a two-stage process where women can give verbal agreement then full informed consent after birth when they have capacity. Added statistical information on handling intercurrent events.

PROTOCOL SUMMARY

FULL TITLE OF STUDY	Tranexamic acid by the intramuscular or intravenous route for the prevention of postpartum haemorrhage in women at increased risk: a randomised, placebo-controlled trial				
SHORT TITLE	Intramuscular tranexamic acid to prevent heavy bleeding after childbirth in women at higher risk				
TRIAL ACRONYM	I'M WOMAN				
SPONSOR ID NUMBER	2021-KEP-588	**LSHTM ETHICS REF**	28252	**CLINICALTRIALS.GOV**	NCT05562609

BACKGROUND: Postpartum haemorrhage (PPH) causes about 70,000 maternal deaths every year. Tranexamic acid (TXA) is a lifesaving treatment for women with PPH. Intravenous (IV) TXA reduces deaths due to PPH by one third when given within 3 hours of childbirth. Because TXA is more effective when given early and PPH usually occurs soon after childbirth, giving TXA just before childbirth might prevent PPH. Although several clinical trials have examined TXA for the prevention of PPH, the results are inconclusive. Because PPH only affects a small proportion of births, we need good evidence on the balance of benefits and harms in this population before using TXA to prevent PPH. The I'M WOMAN trial will evaluate the effects of TXA for PPH prevention in women with one or more risk factors for PPH giving birth vaginally or by caesarean section. The trial will also evaluate the effect of the route of TXA administration. TXA is usually given by slow IV injection. However, recent research shows that TXA is well tolerated and rapidly absorbed after intramuscular (IM) injection, achieving therapeutic blood levels within minutes of injection. There may be fewer side effects with IM TXA because peak blood concentrations are lower than with the IV route. IM TXA also has practical advantages as it is quicker and simpler to administer.

AIM: To assess the effects of IM and IV TXA in women at increased risk of PPH

OBJECTIVES:

1. Assess the effect of TXA on the risk of PPH and other bleeding-related outcomes;
2. Compare the effects of IM and IV TXA on the risk of PPH;
3. Compare the effects of IM and IV TXA on the risk of adverse events.

PRIMARY OUTCOME: A clinical diagnosis of primary PPH.

SECONDARY OUTCOMES: Surgical and postpartum blood loss, interventions for bleeding (drugs for PPH treatment, blood transfusion, non-surgical and surgical interventions), prespecified maternal adverse events (nausea, retching, vomiting, dizziness, skin reaction or pain at injection sites, thromboembolic events, seizure, sepsis, organ dysfunction), days in ICU/HDU, length of hospital stay, death by cause, neonatal outcomes (breastfeeding, congenital abnormality, death by cause, thromboembolic event, seizure, intracranial or pulmonary bleeding, bruising), other adverse events.

TRIAL DESIGN: A randomised, placebo-controlled, three arm trial.

POPULATION: Women having a vaginal or caesarean birth, who are at increased risk of PPH

INCLUSION/EXCLUSION CRITERIA: Women thought to be aged 18 years or older at increased risk (one or more risk factors) of PPH who are admitted to hospital to give birth vaginally or by caesarean section are eligible. Women who have a clear indication or contraindication for the trial treatment should not be recruited.

TRIAL TREATMENT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION AND RESTRICTIONS:

a) 1 gram of tranexamic acid as two 5 ml IM injections (100 mg/ml) and IV placebo (10 ml 0.9% sodium chloride); b) 1 gram of tranexamic acid by IV injection and two 5 ml IM placebo injections; or c) matching placebo.

The trial treatment will be given just prior to skin incision (after draping) in caesarean births and at crowning in vaginal births. For IM administration, the 1 g dose (10 ml) is divided into two 5ml IM injections to reduce the injection volume, and given into the vastus lateralis (preferred), the ventro-gluteal region, or the deltoid. Women will receive all the usual care in labour and after birth. . The trial participation ensd will not result in any needed treatment being withheld. Women who develop PPH should be treated in the usual way.

SETTING: The trial will be conducted in hospitals in Africa and Asia where maternal mortality due to PPH is high.

DURATION OF PARTICIPATION: Trial participation ends at discharge, death or 42 days after randomisation, whichever occurs first.

CRITERIA FOR EVALUATION: Women who receive IM TXA will be compared with those who receive IV TXA in a per-protocol analysis. All those allocated to receive TXA will be compared to those allocated to receive placebo, whether they received the allocated treatment or not (intention-to-treat analysis).

CLINICAL PHASE	3	**PLANNED TRIAL START**	01/08/2023	**PLANNED TRIAL END**	14/09/2025

Contents

1. INTRODUCTION

1.1 BACKGROUND & RATIONALE

Postpartum haemorrhage (PPH) is a leading cause of maternal death, responsible for about 70,000 deaths each year, world-wide.[1,2] Tranexamic acid is a lifesaving treatment for women with PPH. The WOMAN trial recruited over 20,000 women with PPH and found that intravenous (IV) tranexamic acid given soon after PPH onset, reduces bleeding deaths by about one third.[3] The World Health Organization recommends that all women with PPH should receive tranexamic acid as a first line treatment.[4]

Tranexamic acid is more effective when given early, around the time bleeding starts. Every 15 minutes delay reduces the survival benefit by about 10%.[5] PPH usually occurs soon after childbirth. This suggests that giving tranexamic acid around the time of childbirth might prevent PPH. Although several clinical trials have examined the effectiveness of tranexamic acid for the prevention of PPH, the results are inconclusive. [6–8] Some bleeding-related outcomes were reduced by tranexamic acid but others were not, and in some trials, rates of nausea and vomiting were increased with intravenous tranexamic acid. Trials of tranexamic acid for PPH prevention give the trial treatment after cord clamping, which may be too late to prevent heavy bleeding in some women, as bleeding usually happens soon after childbirth.[6–9]

Before using tranexamic acid to prevent PPH, we need good evidence on the benefits and any potential harms. Only a small proportion of births are complicated by PPH, and even when PPH does occur, most women survive. Assuming the risk of PPH is 5% and that tranexamic acid cuts this risk by 20%, we would need to treat 100 women to prevent one PPH. If there are no important harms, this might be acceptable, but if there are harms, the balance of benefits and harms will need careful consideration.

The ongoing WOMAN-2 trial is evaluating the effects of tranexamic acid at cord clamping for the prevention of PPH in women with moderate and severe anaemia having a vaginal birth.[9] Anaemic women have a much higher risk of PPH and are more likely to die from bleeding if PPH occurs.[10–12] If tranexamic acid is found to be effective, the balance of benefits and harms should be favourable in anaemic women.

The I'M WOMAN trial will evaluate the effects of tranexamic acid just before birth for the prevention of PPH in women with one or more risk factors for PPH giving birth vaginally or by caesarean section (CS). The results will deepen our understanding of the benefits and harms of tranexamic acid for PPH prevention. The trial will also evaluate the effect of the route of tranexamic acid administration. Tranexamic acid is usually given by slow IV injection. However, recent research shows that tranexamic acid is well tolerated and rapidly absorbed after intramuscular (IM) injection, achieving therapeutic blood concentrations within minutes of injection.[13–17] The intramuscular route should be as effective as the IV route for preventing bleeding.

There may be fewer side effects with IM tranexamic acid. In general, the risk of side effects is increased at high blood concentrations. Although tranexamic acid is rapidly absorbed after IM injection, reaching therapeutic concentrations within minutes, because of the absorption phase, peak blood concentrations are lower than with the IV route. By avoiding high blood concentrations, the IM route might cause fewer side effects (e.g. nausea, vomiting, dizziness). A better safety profile would be particularly important when using tranexamic acid for PPH prevention. The IM route would also have practical advantages. By avoiding the need for IV-line insertion and a slow IV injection, it would free up overstretched midwives and doctors to focus on looking after the mother and baby.

Giving tranexamic acid before the bleeding becomes serious should maximise the benefits.[5] In vaginal births, bleeding can start after episiotomy or birth canal trauma as the baby is being born, so giving tranexamic acid at crowning should be more effective at preventing bleeding. In caesarean births, bleeding starts at skin incision. Women having a CS have an increased risk of PPH, surgical blood loss can be substantial and there is strong evidence that preoperative tranexamic acid safely reduces surgical bleeding.[18,19] Giving tranexamic acid just prior to skin incision should be most effective. A safety study of IV, IM and oral tranexamic acid in pregnant women having caesarean births found no evidence of maternal or neonatal adverse events. Tranexamic acid crosses the placenta but has a short half-life and is rapidly eliminated.[20]

1.2 Aim and Objectives

The I'M WOMAN trial is a randomised, placebo-controlled trial to assess the effects of IM and IV tranexamic acid on PPH, adverse events and other important maternal health outcomes in women at increased risk of PPH. It will:

1) Assess the effect of tranexamic acid on the risk of PPH and other bleeding-related outcomes;
2) Compare the effects of IM and IV tranexamic acid on the risk of PPH;
3) Compare the effects of IM and IV tranexamic acid on the risk of adverse events.

1.3 Trial design

The I'M WOMAN trial is a parallel, randomised, double-blind, three-arm trial comparing the effects of tranexamic acid by the intramuscular and intravenous route with placebo in women with one or more risk factors for PPH giving birth vaginally or by CS. About 30,000 women will be allocated to receive either: a) 1 gram of tranexamic acid as two 5 ml IM injections (100 mg/ml) and IV placebo (10 ml 0.9% sodium chloride); b) 1 gram of tranexamic acid by IV injection and two 5 ml IM placebo injections; or c) matching placebo. Treatment will be given at crowning in vaginal births and just prior to skin incision (after draping) in caesarean births.

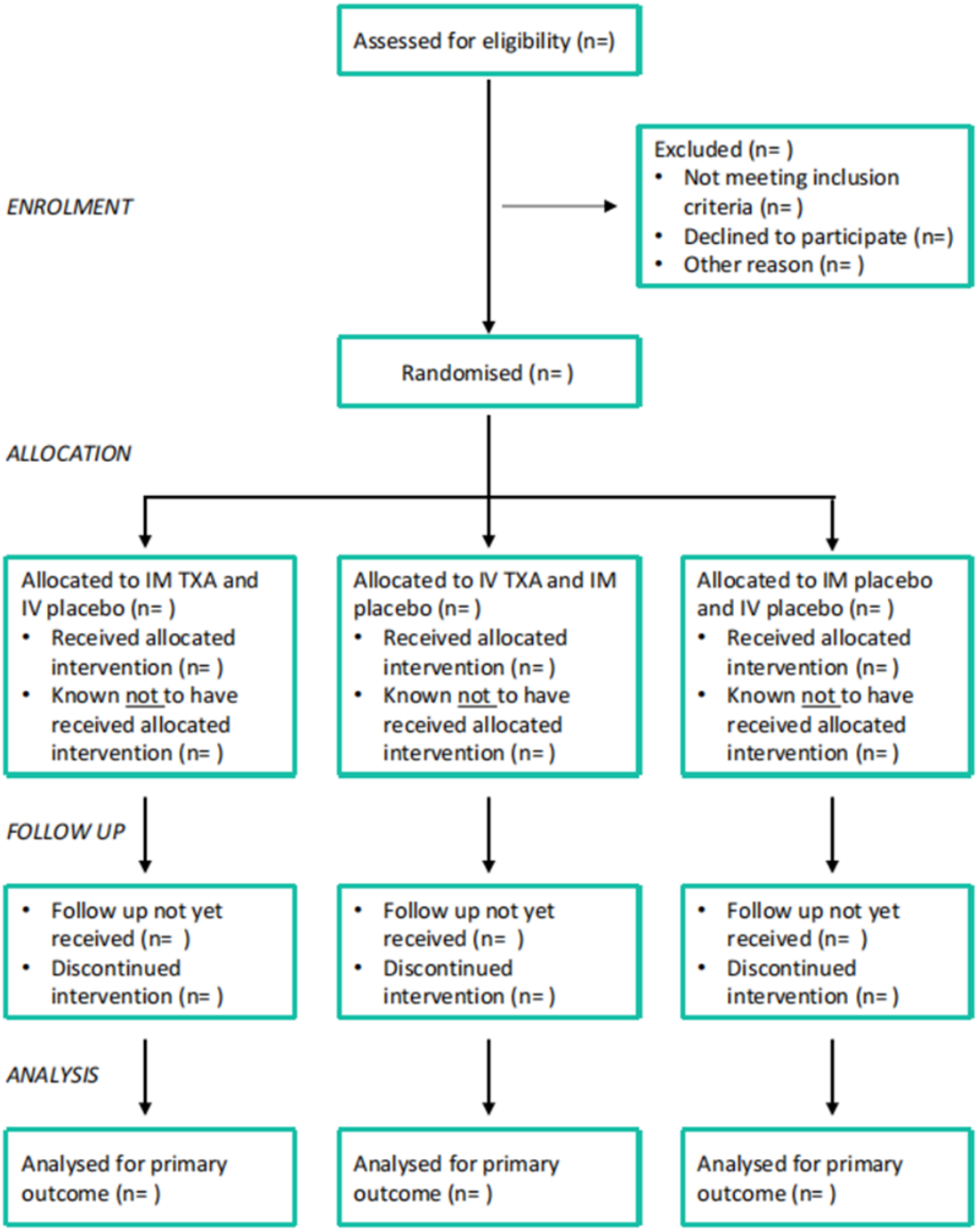


Figure 1. CONSORT flow diagram

2 METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

2.1 STUDY SETTING

We will conduct the trial in hospitals in Africa and South Asia where maternal mortality from PPH is high. Participating investigators and sites will be identified from the international network of health professionals that was established for the previous WOMAN trials. Before we start the trial, all relevant regulatory and ethics approvals will be in place. All principal investigators will be required to conduct the trial according to the Protocol, Good Clinical Practice guidelines and other relevant regulations. We will only progress countries and sites able to obtain the necessary regulatory and ethics approvals in acceptable timeframes.

2.2 Eligibility criteria

Inclusion criteria: Women thought to be aged 18 years or older admitted to hospital for a vaginal or caesarean birth, who are known to have one or more risk factors for PPH will be potentially eligible. A list of major risk factors is provided in Appendix 9. If accumulating trial data or newly published research suggest that a particular factor is not strongly associated with an increased risk of PPH, we will focus on recruiting women with other/additional risk factors.

Exclusion criteria: The fundamental eligibility criterion is the responsible doctor's 'uncertainty' whether to use tranexamic acid in a particular woman. Women should not be randomised if the responsible doctor believes that the trial treatment is clearly indicated (e.g., you have given tranexamic acid within 12 hours or plan to give tranexamic acid) or clearly contraindicated (e.g., known allergy to tranexamic acid).

2.3 TRIAL INTERVENTION

2.3.1 Name and description of investigational medicinal product

Tranexamic acid is a synthetic derivative of the amino acid lysine that has an antifibrinolytic effect by blocking lysine binding sites on plasminogen, inhibiting the binding of plasminogen to fibrin.[21] It is sold under various trade names for the treatment of bleeding due to general or local fibrinolysis in adults and children from one year of age. It is a well-known drug with an excellent safety profile.

2.3.2 Drug administration and dosage schedule

Women will be randomly allocated to receive:

i) 1g tranexamic acid as 2 x 5 ml IM injections (100mg/ml) and slow IV injection of placebo (1 x 10ml of 0.9% sodium chloride);
ii) 1g tranexamic acid by slow IV injection (1 x 10ml) and 2 x 5 ml IM injections of placebo;
iii) Placebo by 1 x slow 10ml IV injection and 2 x 5 ml IM injections.

In caesarean births, the trial treatment will be given prior to skin incision, immediately after draping. In vaginal births, the trial treatment will be given at crowning. There should be no delay in administering the trial treatment. Both IM injections should be given first, then the IV injection.

For IM administration, the 1 g dose (10 ml) is divided into two 5ml IM injections to reduce the injection volume (5 ml is considered the upper limit).[22] The IM injections should be given into the vastus lateralis, ventrogluteal region, or deltoid. The vastus lateralis is the preferred site because it is a large muscle with no major nerve structures.[23]

Each treatment pack contains clearly labelled IM and IV treatments. The IM treatment kit has two ampoules each containing 500 mg (5 ml) of TXA or placebo, two sterile 5 ml syringes and two needles.

The IV treatment kit has two ampoules each containing 500 mg (5 ml) of TXA or placebo, one sterile 10 ml syringe and one needle. Before administration of IM and IV treatments, the expiry dates should be checked and the randomisation number confirmed.

Appropriately qualified staff will prepare and administer IM treatment first, then the IV treatment:

IM treatment: Open the IM treatment kit and draw up the contents of each ampoule into each 5 mL syringe using the needles provided. Administer the two 5 ml IM injections first.

IV treatment: Open the IV treatment kit and draw up the contents of both ampoules into one 10 mL syringe using the needle provided. Administer one 10 ml injection as a slow intravenous injection at rate of about 1 mL/minute using the usual IV administration procedure, after administering the two IM injections.

2.3.3 Known drug reactions and interaction with other therapies

Tranexamic acid should not be mixed with other medicinal products (specifically, blood for transfusion or solutions containing penicillin should not be given in the same IV infusion as tranexamic acid).

2.3.4 Trial restrictions and the use of concomitant medication

All women should receive usual care in labour and after birth. There is no restriction on the use of concomitant medication. Participation will not result in any needed treatment being withheld. Women who develop PPH should be treated in the usual way, which may include tranexamic acid. If any contraindication to the trial treatment develops after randomisation, the trial treatment should be stopped.

2.3.5 Compliance

Site investigators should record the date and time of trial treatment administration. If the trial treatment is not given, or is given outside of the prescribed period, a reason should be given. Adherence to the Protocol will be monitored, and we will record whether the full dose was given.

2.3.6 Benefits and harms

Early tranexamic acid treatment cuts the risk of bleeding deaths in PPH and trauma by a third.[3,24,25] Giving tranexamic acid just before surgery cuts blood loss and the need for blood transfusion by about a third to one quater.[19,26] Although women in the postpartum period have an increased risk of venous thrombosis,[27] meta-analyses of randomised trials with tens of thousands of patients show no increase in thromboembolic events with tranexamic acid, even in women with PPH (Table 1).[3,18,24,28,29] Because severe bleeding is a strong risk factor for thromboembolic events, tranexamic acid might even reduce the risk of thrombosis.[30] The risk of seizures is increased at high doses but not with the dosage used in this trial.[29] Tranexamic acid is mostly excreted within 12 hours and there should be no risk of accumulation with a single dose. Unpublished data indicates that tranexamic acid passes into breast milk at about 1/100 of the concentration in the maternal blood, so this is very unlikely to produce an effect in the infant.[31] There was no increase in adverse events in the infants of mothers who received tranexamic acid in the WOMAN trial. A randomised trial of IV, IM and oral tranexamic acid in 120 pregnant women found no serious adverse events in infant(s) despite some placental transfer.[17]

Tranexamic acid is widely used and well tolerated. Potential adverse events reported by manufacturers to be associated with use of tranexamic acid according to frequency are:

- Common (≥1/100 to <1/10): diarrhoea, vomiting and nausea
- Uncommon (≥1/1000 to <1/100): dermatitis allergic

- Rare: hypersensitivity reactions including anaphylaxis; convulsions; visual disturbances including impaired colour vision; malaise with hypotension (generally following a too fast intravenous injection); arterial or venous thrombosis.

Table 1: Effect of tranexamic acid on thromboembolic events in the WOMAN trial

	TXA (n=10,033)	Placebo (n=9985)	RR (95% CI)	P value
Any thromboembolic event	30 (0.3%)	34 (0.3%)	0.88 (0.54 to 1.43)	0.603
Venous events	20 (0.2%)	25 (0.3%)	0.80 (0.44 to 1.43)	0.446
DVT	3 (0.03%)	7 (0.07%)	0.43 (0.11 to 1.65)	0.203
PE	17 (0.2%)	20 (0.2%)	0.85 (0.44 to 1.61)	0.611
Arterial events	10 (0.1%)	9 (0.09%)	1.11 (0.45 to 2.72)	0.827
Myocardial infarction	2 (0.02%)	3 (0.03%)	0.66 (0.11 to 3.97)	0.651
Stroke	8 (0.08%)	6 (0.06%)	1.33 (0.46 to 3.82)	0.599

2.3.7 Investigator's Brochure (IB)

Information about tranexamic acid will be detailed in an Investigator's Brochure (IB). The IB should be reviewed annually. Studies that provide reliable information on the safety and efficacy of TXA that would help investigators to assess the benefits and harms of TXA use will be included. Additionally, relevant information on updates from manufacturers of TXA will be included.

2.3.8 Preparation and labelling of medication to be used in the trial

TXA has Marketing Authorisation in the United Kingdom and will be purchased from the open market. Marketing Authorisation guarantees that drug manufacture and release comply with Good Manufacturing Practice (GMP). A GMP certified manufacturer will prepare the matching placebo (sodium chloride 0.9%). Tranexamic acid and placebo ampoules and packaging will be identical. A clinical trial supplies company will conduct the blinding process and first-stage Qualified Person release. The blinding process involves replacing the manufacturer's label with the clinical trial label. Other than the randomisation number (used for pack identification) and route of administration, the label text will be identical on all ampoules and comply with clinical trials requirements. To check the blinding, known tranexamic acid will be compared with blinded samples from a random set of treatment packs to determine which are tranexamic acid. The samples will then be un-blinded to confirm accuracy of the labelling.

2.3.9 Drug storage and supply

When a site is ready to start, a box of treatment packs will be sent by the LSHTM CTU Global Health Trials Group or the in-country Coordinating Centre. Site stock level depends on the site's average recruitment rate. Each time a participant is randomised and entered in the trial database, one pack from the site's stock will be automatically deducted. When stock reaches the site's minimum level, the LSHTM CTU Global Health Trials Group or in-country Coordinating Centre will send another box (or boxes). Sites should send screening and entry data to the LSHTM CTU Global Health Trials Group as soon as possible after randomisation (ideally within 24 hours). Sites must report all used, lost or damaged trial treatments packs to the LSHTM CTU Global Health Trials Group on a Drug Accountability Log.

At each site, the treatment packs will be stored securely in a place where they are always accessible to the trial team for randomisation. Although tranexamic acid is heat stable, it will be stored in a dry place where it is protected from excessive heat and freezing. The expiry date of the trial treatment

will be printed on the ampoule label, the treatment pack and drug box. When a batch of treatment packs is close to expiry, the Principal Investigator (PI)/trial pharmacist/delegate will be asked to arrange destruction of affected packs and record this on a Drug Destruction Form (DDF). When a site is to be closed, the PI/trial pharmacist/delegate will arrange destruction of all unused packs and return a completed DDF to the LSHTM CTU Global Health Trials Group to confirm disposal.

2.4 OUTCOMES

2.4.1 Primary outcome

The primary outcome is a clinical diagnosis of primary PPH. This may be an estimated blood loss of more than 500 mL in vaginal birth, or more than 1000 mL in caesarean birth, or any blood loss sufficient to compromise haemodynamic stability within 24 hours of birth. Haemodynamic instability is based on clinical judgement and assessed using clinical signs (low systolic blood pressure, tachycardia, reduced urine output). The total estimated blood loss at time of PPH diagnosis and presumed cause(s) of PPH will be recorded.

The true event rate of the primary outcome in the trial population is unknown. Interim analyses may indicate a lower-than-expected event rate, or new information may emerge that alters assumptions about the treatment effect, affecting the power of the study. To ensure the study has adequate power, prior to unblinding we will allow the primary outcome to be changed, with any changes set out in a statistical analysis plan.

2.4.2 Secondary outcomes

Secondary outcomes specific to caesarean births include:

- Intraoperative blood loss
- Surgery duration
- Intraoperative whole blood/red cell transfusion
- Postoperative Haemoglobin (Hb) or packed cell volume (PCV)

Secondary outcomes collected for all births include:

- Drape measured postpartum blood loss
- Blood pressure and heart rate
- Interventions for bleeding (uterotonics, non-trial TXA, blood transfusion, surgical and non-surgical interventions)
- Maternal mortality (all-cause, cause-specific, narrative)
- Prespecified maternal adverse events (nausea, vomiting, dizziness, thromboembolic events, seizure, sepsis, organ dysfunction, pain or adverse skin reactions at injection sites)
- Other maternal adverse events
- Length of hospital stay
- Days in ICU/HDU
- Transfer to another hospital
- Prespecified neonatal outcomes (breastfeeding, intracranial haemorrhage, pulmonary haemorrhage, bruising, thromboembolic event, seizure, stillbirth/intrapartum death, neonatal death, cause of death, congenital and genetic abnormalities, adverse events).

2.5 SAMPLE SIZE

Two main factors determine the number of patients needed in a trial - the estimated event rate and size of the treatment effect.

Estimated event rate: In trials of tranexamic acid for PPH prevention, the event rate (a clinical diagnosis of PPH) varies from 8-15% depending on the mode of delivery.[7,9,32] We assumed an event rate of 11.5% in the placebo group, based on a roughly 50:50 ratio of vaginal to caesarean births.

Size of the treatment effect: Based on existing evidence in PPH prevention and surgical trials, we assumed a 25% reduction in PPH with tranexamic acid (RR=0.75).

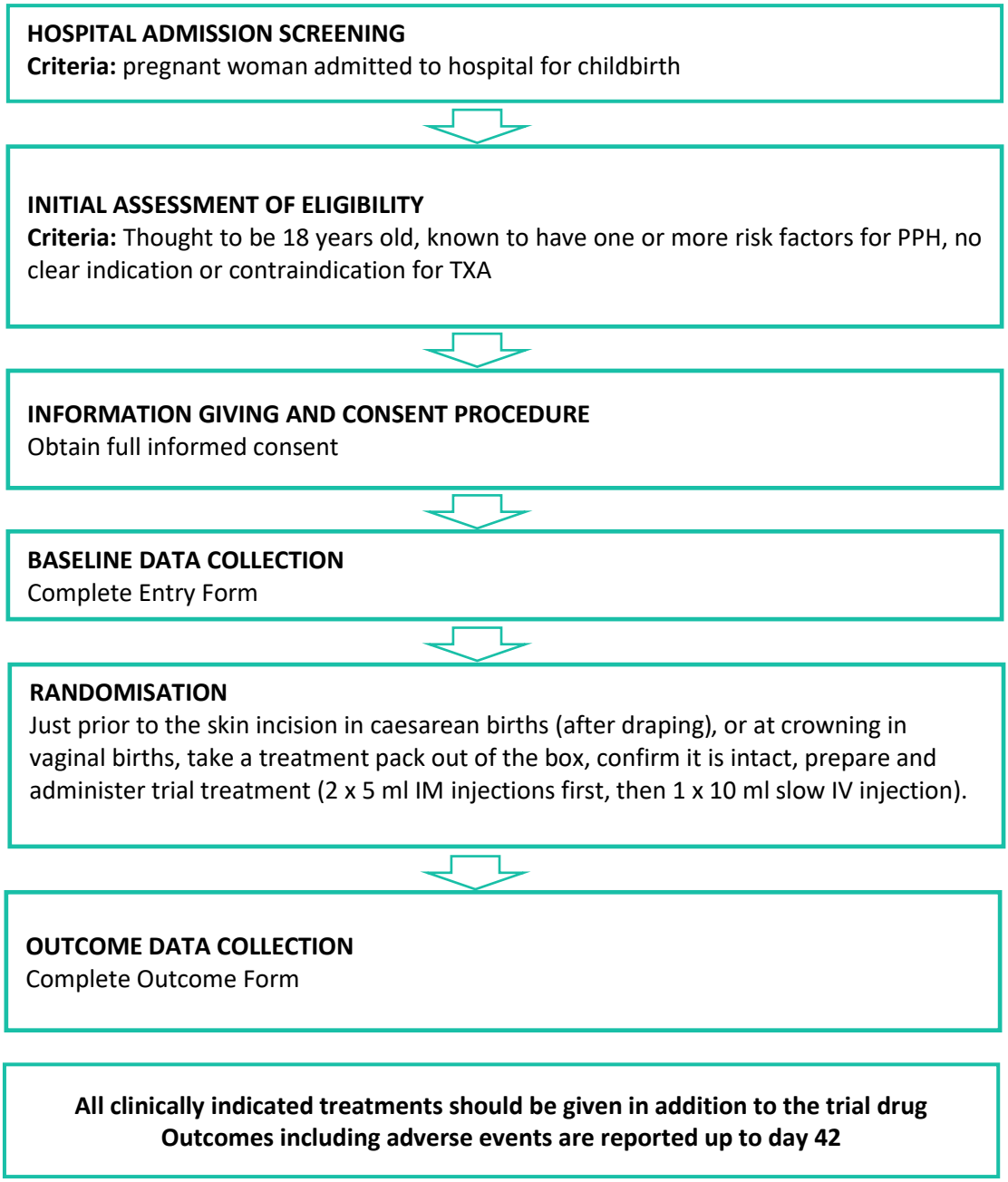
A trial of about 30,000 women has almost 90% power to detect that: 1) tranexamic acid is more effective than placebo, and 2) IM tranexamic acid is at least 60% as effective as IV tranexamic acid. We assumed a two-sided type 1 error rate of 5% for the superiority arm and a one-sided rate of 2.5% for the non-inferiority arm. Our sample size and power calculations were made using methods described by Stucke & Kieser (2012).[33] We confirmed our results using simulation. An optimal allocation ratio was used to maximize study power with patients allocated to receive IM tranexamic acid, IV tranexamic acid, and placebo.

Because the true event rate and treatment effect are unknown, we will re-estimate the sample size if unplanned interim analyses indicate a lower-than-expected event rate, or if new information emerges which changes beliefs about the expected treatment effect.

2.6 RECRUITMENT

We will use wall posters and brief information leaflets to inform pregnant women attending antenatal clinics and labour wards about the trial (Appendix 3). Information may also be provided in videos. To avoid unnecessarily approaching women who won't be suitable, the site investigator will screen the medical records of women attending hospital to give birth to see if they have a risk factor(s) for PPH and check how old they are or are thought to be. The site investigator will approach eligible women and invite them to take part in the trial and carry out formal screening. This will first involve giving information and seeking consent in line with Section 6.3.

2.7 PARTICIPANT TIMELINE



3 METHODS: ASSIGNMENT OF INTERVENTIONS

3.1 ALLOCATION SEQUENCE GENERATION, CONCEALMENT AND IMPLEMENTATION

An IT coding expert supported by a statistician will prepare a randomisation list detailing the allocation sequence (the order in which treatment groups are allocated) using a computerised random number generator. A unique randomisation number will be linked with each treatment allocation. We will use blocking to ensure the required allocation ratio is maintained throughout the trial. The IT expert will send the randomisation list to the clinical trial supplies company so that blinded treatment packs can be prepared. The company will produce, label and package tranexamic acid and placebo ampoules into patient treatment packs as per the randomisation list. Trial staff (coordinating centres and sites) and patients will not have access to the randomisation list until after final database lock.

Once a woman is confirmed to be eligible, just prior to incision in caesarean section births (after draping), or at crowning in vaginal births, a treatment pack will be taken from a box of packs. The woman is considered to have been randomised once administration of the first IM injection has started. Each site will keep a log of women they enrol into the trial.

3.2 BLINDING AND EMERGENCY UNBLINDING

Tranexamic acid and placebo ampoules will look identical. All women will receive two IM injections and one IV injection. The trial treatment packs will look identical except for the unique randomisation number. The IM and IV treatment kits within each treatment pack will be clearly labelled to show the intended route of administration.

There should be no need to unblind the allocated treatment. If a woman develops PPH, she should receive all clinically indicated treatments, which can include tranexamic acid. Because a second 1 g dose of tranexamic acid is well within the usual dosing range, it is not necessary to find out whether a particular woman received tranexamic acid or placebo as part of the I'M WOMAN trial. Even if a particular woman has received tranexamic acid within the trial, a second 1g dose of tranexamic acid can safely be given. Nevertheless, if the clinician believes that a woman's care depends importantly upon knowledge of whether the participant received tranexamic acid or placebo, it is possible to unblind. If urgent unblinding is necessary, the CTU will provide an emergency 24-hour telephone service. The caller will receive a voice message, text message or email informing them whether the woman received tranexamic acid or placebo. The investigator should complete an unblinding request/report form within five working days of unblinding. If a Suspected Unexpected Serious Adverse Reaction (SUSAR) is reported (see Section 5.6), unblinding may be needed for reporting to Regulatory Agencies and Ethics Committees.

4 METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

4.1 BASELINE

After completing the consent procedure, we will collect baseline data including the mother's age, gestational age, parity, recent Hb or PCV if known, multiple pregnancy, planned route of birth, previous PPH, hypertensive disease, placental abnormality, antepartum haemorrhage, and any other PPH risk factors. We will also collect the date and time of randomisation and IM injection sites.

4.2 FOLLOW-UP

We will follow up participants until discharge, death or until the end of the postnatal period (42 days), whichever occurs first.

4.2.1 Assessments

Caesarean births only: We will estimate intraoperative blood loss from skin incision to closure by measuring the amount of blood in sponges and drapes used in surgery and blood loss from suctioning (excluding amniotic fluid). We will record postoperative Hb/PCV up to the end of the second postoperative day, if known.

Clinical Diagnosis of PPH: We will record a clinical diagnosis of PPH up to 24 hours after birth.

Postpartum blood loss: Starting immediately after vaginal birth or once the women is shifted to a bed in the observation area after CS surgery, we will measure postpartum blood loss with a calibrated obstetric drape for 1 hour, or up to 2 hours if bleeding continues after 1 hour and the woman remains in bed. We will also record vital signs in the 24 h after birth or end of CS surgery. For women with a clinical diagnosis of PPH, the volume of blood loss at the time of diagnosis will be visually estimated.

Nausea, vomiting and dizziness: When the calibrated drape is removed, the woman will be asked about her nausea, vomiting and dizziness during and since the birth.

Reaction/pain at site of injections: When the calibrated drape is removed, each injection site will be inspected for local reactions and the woman will be asked about pain at her injection sites.

Adverse events: As described in Section 5, we will record adverse events up to 42 days.

4.2.2 Withdrawal

A woman can withdraw from the trial at any time. She may give her reason for withdrawal but she does not have to. We will ask her to return to hospital if she has medical concerns. If a woman withdraws from the trial, we will analyse data collected to the point of withdrawal, but no other data will be collected unless the woman gives permission. In all cases, we will respect the woman's wishes.

4.2.3 Definition of end of trial

Day 42 of follow-up of the last participant randomised is the end of the trial.

4.2.4 Trial closure

Trial closure will happen in the following circumstances:

- Scheduled closure at the end of the trial.
- Unscheduled closure which may be due to failure to obtain continuation funding or at the request of the Steering Committee (e.g. responding to information from the Data Monitoring Committee) or other unforeseen events (e.g. civil unrest, natural disaster, pandemic).

4.3 RETENTION

Follow up in hospital should be minimal and so there is no need for strategies to increase retention.

4.4 DATA MANAGEMENT

4.4.1 Source data

Source documents include, but are not limited to, hospital records (from which medical history, previous and concurrent medication, clinical outcomes, and adverse events may be summarised onto the CRFs), clinical and office logbooks, laboratory and pharmacy records, diaries and correspondence. We will keep trial data confidential and stored securely. On all trial-specific documents other than the consent form, we will refer to the participant by their screening ID number and randomisation number.

4.4.2 Access to source data

Study sites will provide access to authorised representatives of the Sponsor, the host institution and regulatory authorities to allow trial-related monitoring, audits and inspections.

4.4.3 Data recording and record keeping

Authorised site staff will enter all trial data onto paper CRFs then the trial database to allow easier data control. Participants will be identified by a unique randomisation number. We will not include name and other identifying details in the trial data electronic file used for analysis or publication. The LSHTM CTU Global Health Trials Group will provide an Investigator's Site File (ISF) containing the essential trial documents, which the site must keep updated throughout the trial.

4.5 STATISTICS

We will draft a Statistical Analysis Plan (SAP) for use by the DMC during their ongoing review. The SAP will be finalised before the trial database is locked for the final analysis.

4.5.1 Primary analysis

The primary analysis comparing IM and IV tranexamic acid will be a per protocol analysis. The analysis comparing tranexamic acid to placebo will be an intention-to-treat analysis. We will analyse the data and present statistics by randomised group. We will tabulate demographic and other baseline characteristics. Descriptive statistics for continuous variables will include the mean, standard deviation, median, range, and the number of observations. We will present categorical variables as numbers and percentages. Effect measures will be relative risk. Precision will be quantified using 95% confidence intervals. We will use the composite strategy to account for intercurrent events that may preclude the measurement of key efficacy and safety outcomes (e.g. early death, surgical interventions, discharge or transfer to another hospital).

In a large trial such as I'M WOMAN, baseline characteristics of participants that may influence the outcome should be evenly distributed between the treatment and placebo groups, so that any difference in outcome can be attributed to the intervention. However, it is still possible that a chance imbalance in important prognostic factors could influence the results. To investigate this possibility, an analysis adjusted for baseline risk will be conducted. A prognostic model will be built based on pre-specified baseline variables and used to estimate the predicted risk of the outcome at baseline.

4.5.2 Subgroup analyses

Planned subgroup analyses will be conducted on the primary outcome comparing tranexamic acid to placebo. Subgroup variables include severity of anaemia (no anaemia vs mild anaemia vs moderate/ severe anaemia) and route of birth (vaginal vs caesarean). We will explore potential confounding in

subgroup analyses. Randomisation creates treatment groups that are balanced; however, the strata of subgroups may not be balanced.[34] It is possible that some baseline variables will be associated with the subgroup variable and the treatment effect. We will investigate the association of anaemia and route of birth with other baseline variables and adjust for any potential confounders as necessary. We will report relative risks (RR) and confidence intervals alongside p-values from tests for interaction. Unless there is strong evidence of interaction ($p<0.001$), we will take the overall RR as the most reliable estimate of the RR in all subgroups.

4.5.3 Non-inferiority margin

To compare the IV and IM route of administration, we need to prespecify a non-inferiority margin – a predetermined margin of difference that is clinically acceptable. Women often experience treatment delays while waiting for a doctor or travelling to hospital. Because tranexamic acid's effectiveness falls by about 10% for every 15-minute delay, a one-hour treatment delay corresponds to a 40% reduction in effectiveness. If IM administration preserves 60% of the benefit achieved with IV administration, IM tranexamic acid would be equivalent to an IV injection with a one-hour delay. An effect of this size from a more accessible route of administration with potentially fewer side effects would be clinically relevant. A 60% preservation fraction corresponds to a relative risk between IM and IV tranexamic acid of 1.13. If the upper limit of the two-sided 95% confidence interval for IM versus IV tranexamic acid is less than 1.13 then evidence of non-inferiority will have been provided.

5 METHODS: MONITORING

5.1 DATA MONITORING COMMITTEE (DMC)

The Sponsor is primarily responsibility for monitoring the safety of participants in the trial, overseen by an independent DMC to support the safety monitoring. Membership includes expertise in maternal health, statistics, and study design (see Appendix 7). The DMC will review accumulating trial data and advise the Trial Steering Committee (TSC) on the continuing safety of trial participants and those yet to be recruited. The DMC Charter will list the composition, name, title and address of the chairperson and DMC members, in line with the DAMOCLES Study Group recommendations.[35] The DMC Charter will also include the schedule and format of the DMC meetings, format for data presentation, reporting method, timing of interim reports, and stopping rules. The DMC is independent of the Sponsor, ethics committees, regulatory agencies, investigators, steering committee membership, clinical care of the trial participants, and any other capacity related to trial operations.

The DMC is responsible for deciding whether to reveal the un-blinded results (overall or for a particular subgroup) to the TSC while the trial is underway. The DMC will do this only if two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is either definitely harmful/inferior, or definitely favourable for all or for a particular subgroup in terms of a major outcome; (2) the results are expected to substantially change the prescribing patterns of clinicians who are familiar with other existing trial results. Exact criteria for 'proof beyond reasonable doubt' are not and cannot be specified by a purely mathematical stopping rule but are strongly influenced by such rules. The DMC Charter will refer to the Peto-Haybittle stopping rule, whereby an interim analysis of a major outcome must involve a difference between the treatment and control of at least three standard errors to justify premature disclosure.[36,37] An interim subgroup analysis would have to be even more extreme to justify disclosure.

If there is a difference of at least three standard errors in favour of tranexamic acid compared to placebo, this will be taken as proof of a treatment benefit, and we will stop recruitment into the placebo group. The trial will continue to assess non-inferiority of IM tranexamic acid compared to IV tranexamic acid. While early stopping based on evidence of non-inferiority is not recommended, early stopping based on inferiority is recommended to minimise patient exposure to an inferior intervention. The Peto-Haybittle stopping rule is appropriate as both the treatment and active control are the same drug given via different routes, with no good biological reason to expect inferiority of the IM route. If there is a difference of at least three standard errors in favour of IV tranexamic acid compared to IM tranexamic acid, this will be taken as proof of inferiority, and we will stop recruitment into the IM tranexamic acid group. In summary, these stopping rules require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgment, with the advantage that the exact number and timing of interim analyses need not be pre-specified.

5.2 RISK ASSESSMENT

We collect data on adverse events that might be associated with postpartum bleeding or tranexamic acid use and will present these data to the DMC. The trial involves screening, seeking consent, giving the trial treatment and collecting baseline and outcome data (mostly from the hospital notes).

5.3 CENTRAL MONITORING

The trial will be conducted in accordance with the current approved Protocol, GCP, relevant regulations guidance provided in the Investigator's Site File (ISF) and the trial's standard operating

procedures. A detailed monitoring plan will be developed. In summary, the LSHTM CTU Global Health Trials Group will closely monitor the trial to ensure the rights, safety, and wellbeing of the trial participants, and the accuracy of the data. All coordinating centres and site teams will be trained in the trial procedures and provided with extensive guidance. We will use central monitoring methods. A sample of consent forms from all sites will be monitored to check they are properly completed. Data management and statistical checks (central statistical monitoring) will ensure inclusion criteria are met and the trial treatment is administered in line with the Protocol. Outcome event rates will be monitored. Quantitative variables will be monitored to check data validity using statistical methods such as the coefficient of variation and runs test. Sites with unusual event rates, or low variability or randomness in the data will be selected for further monitoring.

5.4 MONITORING AT LOCAL SITE

Sites flagged as high risk by central monitoring procedures may require onsite monitoring with source data verification. Site self-monitoring will also be carried out where needed. The site PI/delegate will monitor themselves against a standardised checklist. Site investigators and their institutions will provide access to source data and all trial-related documents for monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents including medical records, original consent forms and original CRFs must be kept safely. Investigators must plan in advance of the trial start where the trial-related documents will be stored and how they will be accessed. All documents must be made available for up for ten years after the end of the overall trial.

5.5 HARMS

5.5.1 Safety reporting

Maternal and neonatal events which occur as a consequence of the CS or vaginal birth, events which commonly occur in this population independent of the trial treatment, events which are present before randomisation, and events which are recorded as study outcomes, do not need to be reported as adverse events. Although congenital and genetic abnormalities cannot be attributed to the trial treatment because it is given minutes before birth, we will record these on the outcome form.

Events recorded on the outcome form up to discharge, death, or day 42 (whichever is sooner) will be presented to the DMC for regular review, and so will not be included in the definitions in Section 5.5.2 and will not be reported using the adverse events (AE) reporting procedure. For maternal outcomes this includes PPH, nausea, vomiting, dizziness, vascular occlusive events, seizure, infection, sepsis, organ dysfunction, and pain or adverse skin reaction at the injection site. For neonatal outcomes this includes stillbirth/intrapartum death, neonatal death, intracranial and pulmonary haemorrhage, bruising, seizure, and vascular occlusive events.

Other medical events that fulfil the AE definition below will be reported up to 42 days after administration of trial treatment (see Section 5.5.4 for reporting procedure). If a woman is discharged before 42 days, outcome events after discharge and up to 42 days that fulfil the AE definition will be reported, including those on the outcome form. At discharge, women will be given an ‘alert card’ identifying them as an I’M WOMAN trial participant and asked to present this card to anyone providing medical care after discharge, up to day 42. The card will have instructions to ensure the AE reporting procedures are followed. A safety reporting overview is provided in Appendix 5.

5.5.2 Definitions for safety reporting

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • In the case of any other investigational medicinal product, in the investigator brochure (IB) relating to the trial in question.

5.5.3 Causality

When completing the Adverse Event reporting form, the site PI or medical delegate will assign a causality using the definitions in the table below.

Relationship	Description
Suspected to be related	There is evidence to suggest a causal relationship with administration of the trial treatment and the influence of other factors is unlikely.
Not suspected to be related	There is little or no evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

If there is any doubt about the causality, the site PI or medical delegate will inform the LSHTM CTU Global Health Trials Group. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. If no agreement is made, both points of view will be recorded and reported onwards as required.

5.5.4 Reporting procedures

Adverse Reactions (ARs)/Adverse Events (AEs): Site investigators will report non serious ARs and AEs using the AE reporting forms provided to them.

Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs): The Site Principal Investigator (PI) or medical delegate must report AEs and ARs that fulfil the serious criteria to the LSHTM CTU Global Health Trials Group within 24 hours of the becoming aware of the event using the AE reporting form. The site PI or medical delegate will complete the form with as much detail as is available. A follow up report will be submitted promptly should any additional information arise (but no later than five working days of becoming aware of the event). The site PI or medical delegate will record an assessment of seriousness, causality and expectedness. Events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition will not be reported as SAEs.

Suspected Unexpected Serious Adverse Reactions (SUSARs): All SAEs assigned by the Site PI or medical delegate as suspected to be related to the trial treatment and which are unexpected, will be classified as suspected, unexpected, serious adverse reactions (SUSAR) and will be subject to expedited reporting to each participating Regulatory Authority, Ethics Committees and the Sponsor within seven working days of being reported to the LSHTM CTU Global Health Trials Group.

In the case of a SUSAR, the site staff will:

1. Contact the LSHTM CTU Global Health Trials Group immediately by phone or email to inform them of the event and obtain guidance on the reporting procedure if needed.
2. Submit an AE report, completed with all available information (signed and dated) within 24 hours, together with relevant treatment forms and anonymised copies of all relevant clinical investigations.
3. Submit any additional information promptly upon request.

Emergency contact details for advice on reporting SAEs and SUSARs can be found in the Investigator's Study File. AE reporting forms will be submitted either via the trial database (see Investigator's Study File for full details) or email to imwoman.data@lshtm.ac.uk. AEs that the site PI or the LSHTM CTU Global Health Trials Group consider related to the trial medication will be followed either until resolution or the event is considered stable.

5.5.5 Adverse Event Reporting to Relevant Authorities

The LSHTM CTU Global Health Trials Group or Sponsor Representative will report all SUSARs to the relevant regulatory authorities, Research Ethics Committees (REC) and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than seven calendar days after the LSHTM CTU Global Health Trials Group is first made aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. Treatment codes will be un-blinded for specific participants if required. Site PIs will be informed of all SUSARs for all studies sponsored by LSHTM that use tranexamic acid, whether the event occurred in the I'M WOMAN trial. All other AEs will be reported as requested by the relevant authorities.

5.6 PROTOCOL DEVIATIONS AND SERIOUS BREACHES

Deviations from clinical trial protocols and GCP occur commonly in clinical trials. A protocol deviation is a departure from the approved Protocol's procedures made with or without prior approval. Such departures may be major or minor/administrative. Most deviations do not result in harm to trial subjects or affect the scientific value of the trial. All deviations must be reported to the LSHTM CTU Global Health Trials Group within 24 hours of it becoming known to the trial team.

A serious breach is defined as "a breach of GCP or the trial protocol which is likely to affect to a significant degree (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial". If suspected, the site should inform the LSHTM CTU Global Health Trials Group within 24 hours. The LSHTM CTU Global Health Trials Group will report all serious breaches to the relevant regulatory authorities and REC within the timeline required by each participating country.

5.7 AUDIT

The study may be subject to audit by LSHTM under their legal obligation as sponsor. Additionally, inspections can be carried out by relevant REC and regulatory authorities to ensure adherence to the Protocol, Good Clinical Practice, relevant regulations, and funder requirements.

6 ETHICS, REGULATORY ISSUES AND DISSEMINATION

6.1 RESEARCH ETHICS APPROVAL

We will obtain approval from the LSHTM REC, and the relevant REC and regulatory authority of each participating country.

6.2 PROTOCOL AMENDMENTS

All changes to the Protocol will require the agreement of the Trial Steering Committee (TSC). We will notify the Sponsor of agreed amendments to decide if the amendment is substantial or not. The Chief Investigator or delegate will ensure all amendment notifications and associated documents are updated and submitted to the relevant parties (e.g., sites, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). All participating sites affected will be notified of the amendment in writing. All documentation relating to the amendment will be filed in the Trial Master File (TMF) and Investigator Site File (ISF).

6.3 CONSENT

If women can give fully informed consent, then information about the trial will be given and written consent will be obtained. An overview of the consent procedure is provided in Appendix 2.

First, a member of the site trial team will identify a potentially eligible woman and then approach the woman with the agreement of the primary carer. She will be given information about the trial (Appendix 4a) in a language she understands. The team member will explain the purpose of the trial, that it does not involve any change to her birth plan, and that she will receive all the usual interventions for preventing PPH and any other care she needs. The team member will explain that her participation is voluntary and that if she does not want to take part, we will respect her views and her decision will not affect her care. If she wants to take part, the team member will obtain written consent (Appendix 4). If she is unable to read or write, the participant information sheet will be read to her, and she will mark the consent form with a cross or thumbprint. In this case, an impartial witness must provide a signature confirming the mark. A copy of the information sheet and consent form will be given to the woman.

If the woman withdraws a previously given informed consent, data collected to the point of withdrawal of consent will be used as part of the analysis.

6.4 EQUIPOISE

For a woman to be eligible, the randomising clinician must be uncertain about whether to give tranexamic acid. If the clinician believes tranexamic acid is indicated based on existing evidence, they should not randomise the woman into the trial. During the trial, if accumulating evidence from other trials clearly demonstrates that tranexamic acid prevents PPH with a favourable balance of benefits and harms, it would be unethical to randomise women to receive a placebo. If this happens, the placebo arm will be dropped, and we will continue to recruit women into the IM and IV TXA arms.

6.5 CONFIDENTIALITY

Trial staff will ensure that participants' confidentiality is maintained. Participants will be identified only by a participant screening ID and randomisation number on all trial documents and any electronic database, except for the paper CRF which remains at participating sites, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with relevant Data Protection regulations including the UK General Data Protection Regulation.

Any identifiable data obtained by the LSHTM CTU Global Health Trials Group will be stored securely and confidentiality protected in accordance with the UK General Data Protection Regulation 2018. Local investigators will collect consent, baseline, outcome and adverse event data and send them to the LSHTM CTU Global Health Trials Group by entering them into the online trial database. Investigators will be given a unique username, password and PIN to access the database. The LSHTM CTU Global Health Trials Group will securely store copies of consent forms sent for monitoring and these will be destroyed at trial closure. Original copies of CRFs, consent forms and source data will be kept securely at each participating site. These must be archived securely for ten years after the overall end of the trial. Only people authorised by the Chief Investigator or Project Lead will have access to the I'M WOMAN trial database. The trial database will be accessed through a complex password system which includes password ageing mechanism (i.e. passwords will be changed every 90 days).

6.6 INDEMNITY

LSHTM accepts responsibility attached to its sponsorship of the trial and, as such, would be responsible for claims for any non-negligent harm suffered by anyone because of participation in this trial. The indemnity is renewed on an annual basis and LSHTM assures that it will continue renewal of the indemnity for the duration of this trial.

6.7 SPONSOR

The London School of Hygiene & Tropical Medicine (LSHTM) will act as the Sponsor for this trial.

6.8 FUNDING

Unitaid are funding this study. Women will not be paid for taking part as there is no special travelling or time off work needed. A supply of sanitary products will be given to women who participate as a thank you gesture. Where a woman returns to hospital for any adverse event associated with the trial, her travel costs will be reimbursed. Trial sites will be reimbursed for staff time and consumable costs associated with the conduct of the trial. An agreement with each site will be in place prior to the start of the trial. The design, management and finance of the study are entirely independent of the manufacturers of tranexamic acid, which is not a new product.

6.9 DECLARATION OF INTERESTS

We have no competing interests to declare.

6.10 DATA ACCESS

We are committed to sharing data for ethical research with justified scientific objectives. Until all planned analyses are completed by the LSHTM CTU Global Health Trials Group, data will be shared through a controlled access approach whereby researchers can make formal applications for data sharing. Afterwards, the anonymised dataset will be shared via the LSHTM CTU Global Health Trials Group data sharing platform at freebird.lshtm.ac.uk. All trial materials including training materials, CRFs and Protocol will be made available on the trial website and team YouTube channel.

6.11 DISSEMINATION POLICY

Publications will only contain anonymised data. We aim to publish the main results of the I'M WOMAN trial in a peer-reviewed journal under a CC-BY Licence. This license will ensure the publication is freely available and can be distributed by others if they give credit to the original creation. The main publication will follow the CONSORT statement. Links to publications will be made in any applicable

trial registers. The results will be disseminated via the media, trial website, and relevant maternal health organisations.

The success of the trial will be dependent entirely upon the collaboration of healthcare professionals in the participating sites. Hence, the chief credit for the study will be assigned to the collaborators from each participating centre and they will be named personally in the main publications. The results of the trial will be reported first to trial collaborators. The main publication of the trial results will be in the name of the Trial Collaborative Group (I'M WOMAN trial collaborators).

7 TRIAL MANAGEMENT & ORGANISATION

7.1 TRIAL MANAGEMENT GROUP

A Trial Management Group (TMG) will oversee trial progress, while the LSHTM CTU Global Health Trials Group will coordinate day-to-day trial management. The TMG will consist of the Protocol Committee members and data manager. The TMG and trial manager will act on behalf of the Sponsor and ensure that the Sponsor's responsibilities are carried out. These responsibilities include (but are not limited to): report to the Trial Steering Committee; maintain the Trial Master File; identify sites; assess site suitability confirm all approvals are in place before enrolment of participants and release of the trial treatment; provide training; provide study materials; data management; 24-hour unblinding service; monitoring; ensure data security and quality and observe data protection laws; safety reporting; ensure trial is conducted in accordance with the ICH GCP; progress updates; respond to questions about the trial; statistical analysis; publication of trial results.

7.2 PROTOCOL DEVELOPMENT

The Protocol Committee will be responsible for developing the Protocol. Subsequent changes to the final Protocol will require the agreement of the TSC. Members will be included as authors on the final published protocol.

7.3 TRIAL STEERING COMMITTEE (TSC)

The TSC will include (but is not limited to) an independent chair, experienced obstetrician, clinical trialist, clinical representative from a low- and middle-income country (LMIC), a statistician, lay representative, and some members of the TMG (Appendix 8). The TSC will supervise the trial and advise the Sponsor, with a focus on trial progress, protocol adherence, participant safety, and consideration of new information. The TSC must agree on the final Protocol and, throughout the trial, take responsibility for: major decisions such as protocol amendments; monitoring and supervising trial progress; reviewing relevant information from other sources; considering recommendations from the DMC; informing and advising the TMG. In general, we will aim to hold meetings about once per year unless there is a need to hold them more often. A TSC Charter agreed at the first meeting will detail the conduct of business.

7.4 NATIONAL COORDINATION FOR EACH PARTICIPATING COUNTRY

We will identify a National Coordinating Investigator for each participating country, who will be responsible for ensuring that all national approvals including those from regulatory agencies, ethics committees and relevant import licences are in place before the trial starts in their country. Additionally, they will support the LSHTM CTU Global Health Trials Group with ensuring recruitment is on target, safety reporting to all relevant agencies, and site training and monitoring as required.

7.5 SITE PRINCIPAL INVESTIGATOR'S RESPONSIBILITIES

A Site Principal Investigator will coordinate the trial at each participating hospital. Site-specific responsibilities detailed in an agreement in advance of starting the trial will include:

- Supervise the study at their site, comply with the final trial Protocol and amendments, obtain all appropriate approvals and account for trial treatments;
- ensure the trial is conducted in line with ICH GCP and fulfils all national and local regulatory requirements;
- keep trial staff aware of the current state of knowledge, the trial and its procedures (there are training materials to assist with this);

- delegate trial responsibilities to suitably trained, qualified personnel and document delegation;
- ensure that all potentially eligible women are considered promptly for the trial and consent is obtained in line with local approved procedures;
- ensure that the data are collected, completed and sent to the CTU Global Health Trials Group in a timely manner, including adverse events reporting;
- ensure the Investigator's Study File is up-to-date and complete;
- allow access to source data, including participants' medical records, for monitoring, audit and inspection;
- be responsible for archiving all original trial documents including medical records, investigator's study file, consent forms and data forms for at least 10 years after the end of the trial.

8 REFERENCES

1 Say L, Chou D, Gemmill A, *et al.* Global causes of maternal death: A WHO systematic analysis. *Lancet Glob Heal* 2014; **2**: 323–33.

2 GBD 2015 Maternal Mortality Collaborators NJ, Barber RM, Bhutta ZA, *et al.* Global, regional, and national levels of maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1775–812.

3 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389**: 2105–16.

4 World Health Organization. Updated WHO Recommendation on Tranexamic Acid for the Treatment of Postpartum Haemorrhage. 2017; : 1–5.

5 Gayet-Ageron A, Prieto-Merino D, Ker K, *et al.* Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet* 2017; **391**: 125–32.

6 Sentilhes L, Winer N, Azria E, *et al.* Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *N Engl J Med* 2018; **379**: 731–42.

7 Sentilhes L, Sénat M V., Le Lous M, *et al.* Tranexamic Acid for the Prevention of Blood Loss after Cesarean Delivery. *N Engl J Med* 2021; **384**: 1623–34.

8 Pacheco LD. LB 3: Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean Delivery: A Randomized Controlled Trial. *Am J Obstet Gynecol* 2022; **226**: S779–80.

9 Ker K, Roberts I, Chaudhri R, *et al.* Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: study protocol for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2018; **19**: 712.

10 Guignard J, Deneux-Tharaux C, Seco A, *et al.* Gestational anaemia and severe acute maternal morbidity: a population-based study. *Anaesthesia* 2021; **76**: 61–71.

11 Nair M, Choudhury MK, Choudhury SS, *et al.* Association between maternal anaemia and pregnancy outcomes: A cohort study in Assam, India. *BMJ Glob Heal* 2016; **1**: e000026.

12 Daru MBBS J, Zamora J, Thangaratinam S, *et al.* Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. *Lancet Glob Heal* 2018; **6**: e548–54.

13 Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. Blood Coagul. Fibrinolysis. 2019; **30**: 1–10.

14 Kane Z, Picetti R, Wilby A, *et al.* Physiologically based modelling of tranexamic acid pharmacokinetics following intravenous, intramuscular, sub-cutaneous and oral administration in healthy volunteers. *Eur J Pharm Sci* 2021; **164**. DOI:10.1016/J.EJPS.2021.105893.

15 Grassin-Delyle S, Semeraro M, Foissac F, *et al.* Tranexamic acid through intravenous, intramuscular and oral routes: an individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers. *Fundam Clin Pharmacol* 2019; **33**: 670–8.

16 Grassin-Delyle S, Shakur-Still H, Picetti R, *et al.* Pharmacokinetics of intramuscular tranexamic

acid in bleeding trauma patients: a clinical trial. *Br J Anaesth* 2020; published online Sept. DOI:10.1016/j.bja.2020.07.058.

17 Arribas M, Roberts I, Chaudhri R, *et al.* WOMAN-PharmacoTXA trial: Study protocol for a randomised controlled trial to assess the pharmacokinetics and pharmacodynamics of intramuscular, intravenous and oral administration of tranexamic acid in women giving birth by caesarean section. *Wellcome open Res* 2021; **6**. DOI:10.12688/WELLCOMEOPENRES.16884.1.

18 Devereaux PJ, Marcucci M, Painter TW, *et al.* Tranexamic Acid in Patients Undergoing Noncardiac Surgery. *N Engl J Med* 2022; published online April 2. DOI:10.1056/NEJMoa2201171.

19 Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. Br. J. Surg. 2013. DOI:10.1002/bjs.9193.

20 ClinicalTrials.gov. Pharmacokinetics and Pharmacodynamics of Tranexamic Acid in Women Having Caesarean Section Birth [WOMAN-PharmacoTXA] - NCT04274335. .

21 Okamoto S, Okamoto U. Amino-methyl-cyclohexane-carboxylic acid: AMCHA. A new potent inhibitor of the fibrinolysis. 1962 https://www.jstage.jst.go.jp/article/kjm1952/11/3/11_3_105/_pdf (accessed Feb 6, 2019).

22 Hopkins U, Arias C. Large-volume IM injections: a review of best practices. *Oncol Nurse Advis* 2013.

23 Nakajima Y, Fujii T, Mukai K, *et al.* Anatomically safe sites for intramuscular injections: a cross-sectional study on young adults and cadavers with a focus on the thigh. *Hum Vaccin Immunother* 2020; **16**: 189.

24 CRASH-2 trial collaborators, Shakur H, Roberts I, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet (London, England)* 2010; **376**: 23–32.

25 CRASH-2 collaborators, Roberts I, Shakur H, *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377**: 1096-1101.e2.

26 Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344**: e3054.

27 Galambosi PJ, Gissler M, Kaaja RJ, Ulander VM. Incidence and risk factors of venous thromboembolism during postpartum period: a population-based cohort-study. *Acta Obstet Gynecol Scand* 2017; **96**: 852–61.

28 Taeuber I, Weibel S, Herrmann E, *et al.* Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Surg* 2021; **156**: e210884–e210884.

29 Murao S, Nakata H, Roberts I, Yamakawa K. Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. *Crit Care* 2021; **25**: 1–11.

30 Pealing L, Perel P, Prieto-Merino D, Roberts I. Risk factors for vascular occlusive events and death due to bleeding in trauma patients; an analysis of the CRASH-2 cohort. *PLoS One* 2012; **7**. DOI:10.1371/JOURNAL.PONE.0050603.

31 Eriksson O, Kjellman H, Nilsson L. Tranexamic Acid in human milk after oral administration of Cyklokapron to lactating women. 1971.

32 Sentilhes L, Winer N, Azria E, *et al.* Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *N Engl J Med* 2018; **379**: 731–42.

33 Stucke K, Kieser M. A general approach for sample size calculation for the three-arm 'gold standard' non-inferiority design. *Stat Med* 2012; **31**: 3579–96.

34 VanderWeele TJ, Knol MJ. Interpretation of Subgroup Analyses in Randomized Trials: Heterogeneity Versus Secondary Interventions. *Ann Intern Med* 2011; **154**: 680–3.

35 DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005; **365**: 711.

36 Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer* 1977; **35**: 1.

37 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *http://dx.doi.org/101259/0007-1285-44-526-793* 2014; **44**: 793–7.

38 Maanongun MT, Daru PH, Pam VC, Swende TZ, Ojabo AO, Eka PO. Labour outcome in patients admitted in the second stage of labour at Jos University Teaching Hospital, Jos, Nigeria. *Trop J Obstet Gynaecol* 2022; **33**: 165.

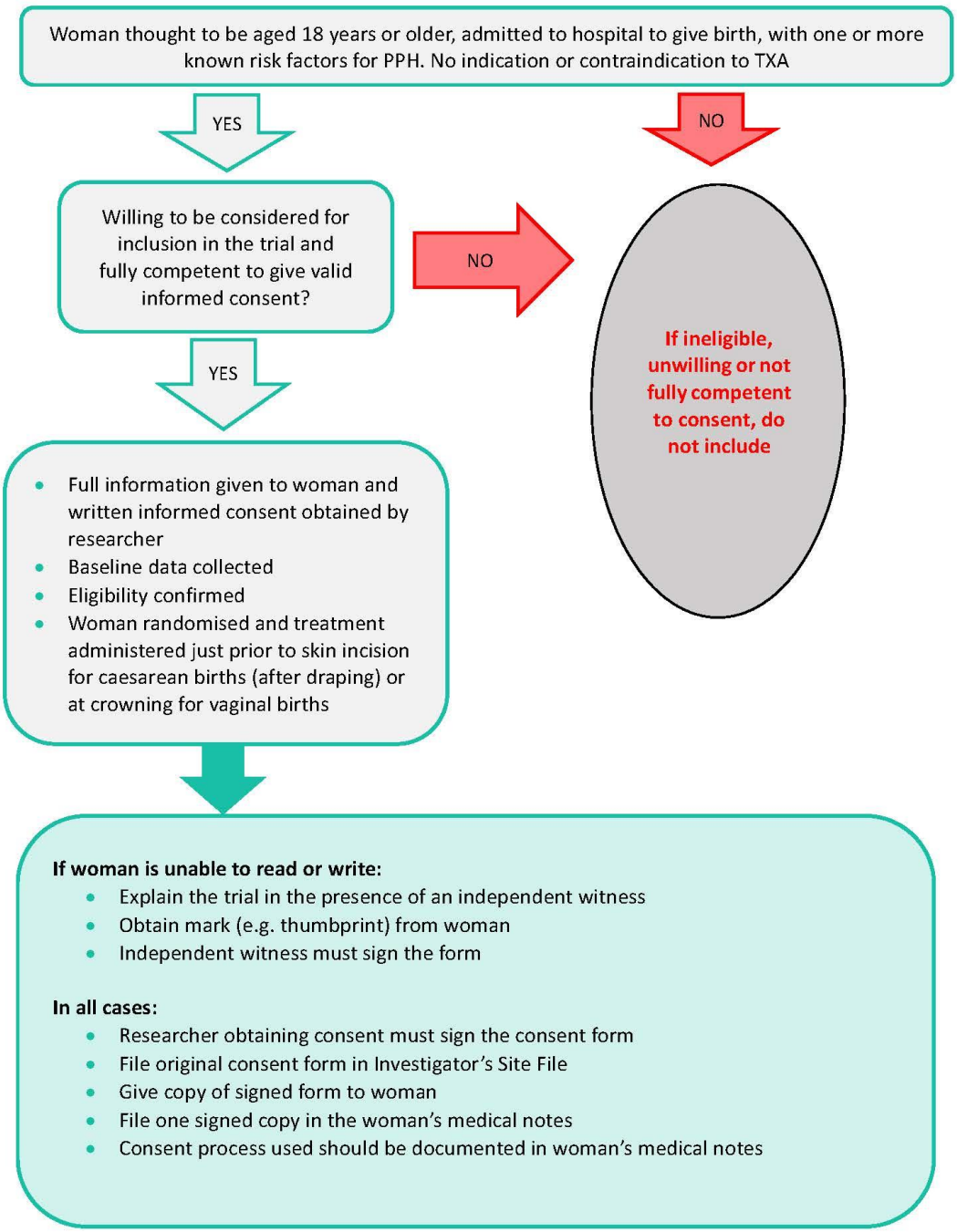
9 APPENDICES LIST

9.1 APPENDIX 1 – MAIN CONTACTS

LSHTM Clinical Trials Unit – Global Health Trials Group	I'M WOMAN Trial Clinical Trials Unit – Global Health Trials Group London School of Hygiene & Tropical Medicine, Keppel Street London, WC1E 7HT, UK Tel: +44(0)20 7299 4684 Email: IMWOMAN@lshtm.ac.uk Web: imwoman.lshtm.ac.uk
Pakistan Clinical Trials Unit	STMU-LSHTM Research Collaboration Centre Shifa Tameer-e-Millat University Secretariat Shifa International Hospital Pitras Bukhari Road, Sector H-8/4 Islamabad, Pakistan Tel: +44 (0) 2072994837 Email: pakistan.imwoman@lshtm-ctu.org
Nigeria Clinical Trials Unit	COMUI-LSHTM Research Collaboration Centre College of Medicine University of Ibadan Queen Elizabeth Road Ibadan, Nigeria Tel: +44(0)20 7958 2571 Email: nigeria.imwoman@lshtm-ctu.org
Tanzania Clinical Trials Unit	UDSM-LSHTM Research Collaboration Centre University of Dar es Salaam Mbeya College of Health and Allied Sciences P.O. Box 608 Mbeya, Tanzania Tel: +255252500082 Email: tanzania.imwoman@lshtm-ctu.org
Ethiopia National Principal Investigator	Dr Bethel Dereje Gulelat St. Paul's Hospital Millennium Medical College Switzerland Street, Postal code 1271 Addis Ababa, Ethiopia Mobile: +251-911386605 Office: +251-118582078 Email: bethel.dereje@sphmmc.edu.et
Sponsor	Research Governance & Integrity Office London School of Hygiene & Tropical Medicine, Keppel Street London, WC1E 7HT, UK Phone: +44 (0)20 7927 2626 Email: RGIO@lshtm.ac.uk
Emergency telephone	This emergency number is to be used only in the event urgent unblinding of the trial treatment: +44(0)7768 707500

9.2 APPENDIX 2 – CONSENT OVERVIEW

APPENDIX 2 - CONSENT PROCEDURE OVERVIEW



Clinicaltrials.gov ID: NCT05562609
Consent Procedure Overview Version 2.0; Date 01 June 2023 Page 1 of 1

9.3 Appendix 3 – Brief Information Sheet

BRIEF STUDY INFORMATION SHEET
THE I'M WOMAN TRIAL

This hospital is taking part in a research study to find ways to prevent heavy bleeding after childbirth. This leaflet explains why we are doing this study and what it involves.

What is the I'M WOMAN trial?
The I'M WOMAN trial is a study to see if a drug called tranexamic acid (TXA) can prevent heavy bleeding after childbirth when it is given into the muscle. About 30,000 women giving birth in hospitals around the world will be taking part. It has been approved by ethics and regulatory agencies in your country.

What is heavy bleeding after childbirth?
Vaginal bleeding after childbirth is normal. It usually stops on its own and is nothing to worry about. But some women have heavy bleeding – this is called a postpartum haemorrhage or PPH. A PPH can make women very unwell and is sometimes life-threatening.

What is tranexamic acid?
TXA is a drug that reduces bleeding. It is not a new drug. It is often used to reduce bleeding in operations and after serious injury. In an earlier study, we gave TXA to thousands of women who were having a PPH. It saved the lives of about 1 in 3 women who had a PPH, and it did not cause any serious side effects. The WHO recommends that all women who are having a PPH get TXA.

Why are we doing this study?

Our previous studies show that TXA is most effective when given early. This made us wonder if giving TXA before the birth of the baby might prevent PPH from happening in the first place. Preventing PPH might be better than treating a PPH after it happens. This study will find out if TXA can prevent PPH from happening.

TXA is usually given into a vein. But it can also be given into a muscle, like a vaccine. Giving TXA into a muscle is easier and quicker. We hope this study proves that both ways of giving TXA are equally good at preventing PPH. TXA sometimes causes mild side effects like feeling sick. This may be less likely if TXA is given into the muscle. We also hope the study proves this.

What does the study involve?
Taking part will not affect how you plan to have your baby. You will get all the usual care for women giving birth at your hospital. The study treatment is free. It will not cost you any money to take part.

We will review your medical records and may ask you some questions to see if you are at higher risk of PPH. If you are, you will be invited to take part. If you agree, just before your baby is born, you will receive two injections into different muscles and one into a vein. The injections will hold either TXA or placebo (a dummy

Clinicaltrials.gov ID: NCT05562609
Brief Study Information Sheet Version 1.1; Date 9 January 2023 Page 1 of 2

drug that is completely safe). What each injection holds is decided randomly. After you give birth, we will measure how much blood you lose and collect information on how you and your baby are getting on.

A small amount of the medicine might cross over to the baby through the placenta or breast milk. Earlier studies did not find any harmful effects in babies whose mothers who got TXA when they were pregnant, or who were breastfed by mothers who got TXA. TXA has been used in adults, children, and babies for many years without any harmful effects.

We will give you a card with contact details of the study doctor at this hospital, which you can show to doctors if you return to hospital, so that they know were in the study. If you return to hospital for any medical problem related to the study, we will pay your travel costs.

If you want more information about the study, the study coordinators at this hospital can be contacted on:
Name
Address
Phone
Email

The study is organised by the London School of Hygiene & Tropical Medicine (University of London) and is supervised in [Country] by xxxx. You can also contact them directly for information about the trial.
Name of NCC
Address
Phone
Email

9.4 Appendix 4 – Participant Information Sheet and Informed Consent Form

[Hospital Contact Details]
Name of PI
Name of Hospital
Hospital address
Contact phone number

The I'M WOMAN trial

Intramuscular tranexamic acid to prevent heavy bleeding after childbirth

in women at higher risk

(NOTE: final version will contain locally relevant, culturally sensitive images. These will be approved by the local REC before use).

STUDY INFORMATION FOR PARTICIPANTS

We invite you to take part in a research study called I'M WOMAN

- Before you decide, we want you to know why the study is being done and what it involves.
- Please read this information or ask the doctors or midwifes to explain it to you. Ask as many questions as you like before deciding whether to take part.
- Taking part is your decision. If you choose not to take part, the doctors and midwives will give you all the usual care given at this hospital.

Contents

1. What is the study for?

Vaginal bleeding after childbirth is normal. It usually stops on its own and is nothing to worry about. But some women have heavy bleeding - this is called a postpartum haemorrhage or PPH. A PPH can make women very unwell and is sometimes life-threatening. In this study, we are looking to see if a drug called tranexamic acid (TXA) can prevent PPH when it is given into the muscle.

TXA is a drug that reduces bleeding. It is not a new drug. It is often used to reduce bleeding in operations and after serious injury. In an earlier study, we gave TXA to thousands of women who were having a PPH. It saved the lives of about 1 in 3 women who had a PPH, and it did not cause any serious side effects. The WHO (World Health Organisation) recommends that all women who are having a PPH get TXA.

Our previous studies show that TXA is most effective when given early. This made us wonder if giving TXA before the birth of the baby might prevent PPH from happening in the first place. Preventing PPH might be better than treating a PPH after it happens. This study will find out if TXA can prevent PPH from happening.

TXA is usually given into a vein. But it can also be given into a muscle, like a vaccine. Giving TXA into a muscle is easier and quicker. We hope this study proves that both ways of giving TXA are equally good at preventing PPH. TXA sometimes causes mild side effects like feeling sick. This may be less likely if TXA is given into the muscle. We also hope the study proves this.

2. Why are you asking me to take part?

We are asking you to take part because your doctor thinks that you have a higher chance of PPH. You need to be 18 years or older to take part. About 30,000 women around the world will be taking part in this study. Whether you take part is your decision.

3. What will happen if I take part?

Taking part will not change how you plan to have your baby. You will get all the usual care for women giving birth at your hospital. The study treatment is free. It will not cost you any money to take part.

If you want to take part, we will ask you to fill in a consent form. Then we will collect information about you and your labour. Just before your baby is born, you will be given two injections into different muscles and one into a vein, which will contain either TXA or placebo (a dummy drug that is completely safe). What each injection holds is decided randomly. The study drug and the placebo look the same, so you and your doctors will not know which you got. After you give birth, we will measure how much blood you lose and collect information about your health and your baby while you are in hospital.

4. How long will I be in this study?

You will be in the study until you leave hospital, or for six weeks after you had your baby, whichever is sooner. If you or your baby become ill after leaving hospital and within six weeks of giving birth, please tell the doctor named on this form.

5. What are the benefits of taking part?

We do not know if taking part in this study will help you personally or not. We hope that TXA will reduce the amount of blood women lose in childbirth and prevent PPH. If you take part, you may get TXA but there

is a chance you won't (i.e. if you are in the placebo group). If you don't take part, you won't get TXA before childbirth as it is not currently recommended or given in hospital to prevent PPH. By taking part, we hope you will be better informed for the future and can share your knowledge with others.

In the future, what we learn from this study will help doctors care for women who are having a PPH or who are at higher risk of having a PPH. If TXA prevents PPH and causes less side effects when it is given into the muscle, this will help women who give birth in situations where having an injection into a vein is not possible – an injection of TXA into the muscle could save their lives.

6. Could I be harmed by taking part?

TXA is widely used. The WHO recommends TXA for women who are having a PPH. Lots of studies with thousands of people suggest that TXA has clear health benefits and no serious side effects. Sometimes TXA can cause minor side effects like feeling or being sick (nausea), diarrhoea, and dizziness. Studies suggest that giving TXA into a vein or a muscle has no serious side effects. There is a small risk of redness, pain, or bruising at the injection sites. Injections have a very rare risk of infection.

A small amount of TXA can cross over to the baby through the placenta or breast milk. Earlier studies did not find any harmful effects in babies whose mothers who got TXA when they were pregnant, or who were breastfed by mothers who got TXA. Your doctor will watch you and your baby and give you the best available care if there are any problems. They will also tell the people running the study if there are any problems.

If TXA reduces the amount of blood you lose after childbirth, this will not harm your health. Bleeding after childbirth has no benefits, losing too much blood can make you ill, and PPH can be dangerous.

7. Can I change my mind about taking part?

Yes. You can stop taking part in the study at any time. You just need to say something like, *"I've decided I don't want to be in this study"*. Your doctor and the hospital staff will still care for you in the usual way. If you have any medical problems after you stop taking part, we ask that you still tell us about them.

8. What happens afterwards?

We will give you a card with the contact details of the study doctor at this hospital. Please keep this card safe. If you become ill within six weeks of having your baby, please contact the study doctor on the card. Please show this card to anyone who treats you for any illness within six weeks of having your baby.

If you would like to know the results of this study, please let the study doctor know and they will make sure you get a copy of the results. You can also visit the study website to keep up to date with progress: [insert website]

9. What information do we keep private?

We will keep all information collected about you and your baby private and stored securely. The only people allowed to look at the information are the staff running the study at the London Coordinating Centre and the [Name] Coordinating Centre in your country, as well as regulatory authorities who check that the study is being carried out correctly. The London Coordinating Centre may want to collect or copy some information with your name on it such as the consent form. These will be destroyed, or your personal details removed immediately after use.

We will make the study results public so doctors, midwives and researchers can learn from the study. We will not include your personal information in any study reports, so you will not be identified. The study team may share study data with other researchers and the public but will remove all personal information first.

10. Who is doing this study?

An international group of doctors, nurses, midwives and researchers are working together to find ways to improve women's health worldwide. The study is coordinated by a team of researchers at the London School of Hygiene & Tropical Medicine (University of London) in the United Kingdom and is supervised in [Country] by [Professor/Doctor name].

Name:	
Address:	
Phone:	
Email:	

11. Who has reviewed the study?

The WHO and an independent group of people called a Research Ethics Committee [Name] have carefully checked this study and agreed that it is okay for us to do it.

Name:			
Address:			
Telephone:		Fax:	
Website:			

12. Who can I contact about any questions?

If you have any questions about the study, ask to speak with the study team who will do their best to help. The contact details for the doctor in charge of the study at this hospital are:

Name:	
Address:	
Telephone:	
Email:	

13. What if there is a problem?

If something goes wrong and you are harmed during the study, the London School of Hygiene & Tropical Medicine (the sponsor) would be responsible for claims for any non-negligent harm. If you wish to make a complaint, you can do this through the hospital's complaints procedure. Please ask the study doctors or midwives for details.

If you return to hospital for any medical problem related to the study, we will pay your travel costs. If your medical problem is directly caused by the study drug, the sponsor will pay for necessary treatment.

The sponsor is not responsible for medical expenses due to pre-existing medical conditions, underlying diseases, ongoing treatments, or negligence or wilful misconduct by you, the study doctor, study site or third parties.

14. What else do I need to know?

The study is sponsored by the London School of Hygiene and Tropical Medicine (University of London, UK) and funded by Unitaid. Neither of these institutions make TXA.

Signing the consent form does not affect your legal rights to seek compensation.

[Hospital Contact Details]
Name of PI
Name of Hospital
Hospital address
Contact phone number
Email

CONSENT FORM
THE I'M WOMAN TRIAL

Title of research: Intramuscular tranexamic acid to prevent heavy bleeding after childbirth in women at higher risk

Site ID Number		Name of Site Principal Investigator	
Participant Hospital ID number		Screening ID Number	
Name of Participant			

STATEMENT OF PERSON GIVING CONSENT:

1. I confirm that I have read/have had read to me the information sheet for the above study in a language I understand.
2. I have discussed with the doctor to my satisfaction, and I have had the opportunity to ask questions.
3. I understand that my participation is voluntary. I have been given enough information about the research study to judge that I want to take part in it.
4. I understand that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
5. I understand that I will be given a copy of this consent form and the information sheet to keep for myself.
6. I understand that the study staff may look at sections of my medical notes and those of my baby/ies. I give permission for these individuals to have access to these records.
7. I understand that my data (with all personal information removed) will be made freely available for the public.
8. I give permission for a copy of this consent form, which contains my personal information, to be made available to the Trial Coordinating Centre in London for monitoring purposes only.
9. I agree to take part in the above study, the I'M WOMAN trial.

_____	_____	_____
Name of woman	Date	Signature / Thumbprint or other mark (if unable to sign
_____	_____	_____
Name of witness	Date	Signature

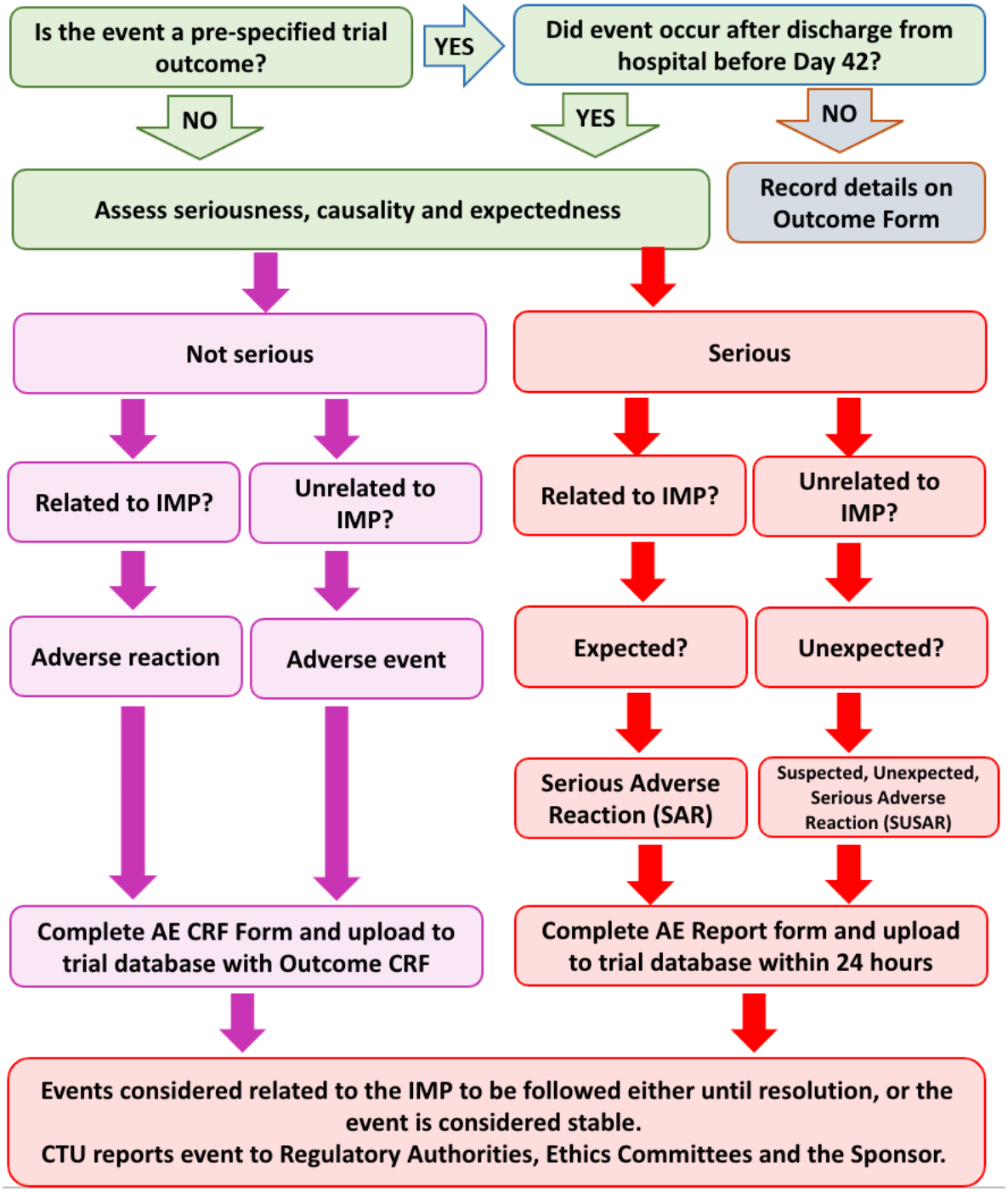
(A witness is needed if a patient cannot read or write)

STATEMENT OF PERSON OBTAINING INFORMED CONSENT:

I have fully explained this research to this participant and have given sufficient information, including about risks and benefits, to make an informed decision.

_____	_____	_____
Name	Date	Signature

9.5 Appendix 5 – Safety Reporting Overview



9.6 APPENDIX 6 – SCHEDULE OF EVENTS

Event	Routine visit to antenatal clinic	Admitted to hospital to give birth	Just prior to skin incision in CS	At crowning in vaginal birth	Immediately after vaginal birth or shifting woman to observation area after CS	1-2 hours after drape positioned	Up to 24 hours after birth	Discharge, death or 42 days after birth (whichever is earliest)
Trial information available	X							
Check medical records to assess potential eligibility before approaching participant		X						
Carry out consent process		X						
Begin baseline data collection		X						
Confirm eligibility		X						
If eligible, complete baseline data collection		X						
Randomise			X	X				
Administer trial treatment (2 x IM injections and 1 x IV injection)			X	X				
Position calibrated obstetric drape under woman					X			
Remove drape and collect outcome data						X		
Collect outcome data							X	
Collect outcome data								X
Provide alert card							◆	◆
Monitor and report adverse events			◆	◆	◆	◆	◆	◆

9.7 APPENDIX 7 – DATA MONITORING COMMITTEE MEMBERSHIP

NAME	AFFILIATION	EXPERTISE
Pollyanna Hardy (Chair)	National Perinatal Epidemiology Unit (NPEU) Nuffield Department of Population Health University of Oxford UK	Clinical trialist, Statistician and Director of the National Perinatal Epidemiology Unit (NPEU)
Olufunmilayo Fawole	Faculty of Public Heath University of Ibadan Nigeria	Professor of Epidemiology and Dean of the Faculty of Public Health
Andrew Weeks	Department of Women's and Children's Health University of Liverpool UK	Consultant obstetrician, Professor of International Maternal Health, and Director of the Sanyu Research Unit
Ester Ngadaya	National Institute for Medical Research (NIMR) Muhimbili Medical Research Centre Tanzania	Medical Doctor, Epidemiologist and Principal Research Scientist at the National Institute for Medical Research (NIMR).

9.8 APPENDIX 8 – TRIAL STEERING COMMITTEE MEMBERSHIP

NAME	AFFILIATION	EXPERTISE
Jolly Beyeza-Kashesya (Chair)	Department of Obstetrics and Gynaecology, Mulago Specialised Women and Neonatal Hospital, Makarere University, Uganda	Senior Consultant, Obstetrics and Gynaecology
Rema Ramakrishnan	National Perinatal Epidemiology Unit, University of Oxford, UK	Senior Statistician; experienced biostatistician/epidemiologist
Ave Maria Semakafu	Institute of Development Studies, Muhimbili University of Health and Allied Sciences, Tanzania	Lecturer, patient representative/advocate
Saturday Etuk	University of Calabar, Nigeria	Chief Consultant & Professor of Obstetrics and Gynaecology
Aziz un-Nisa Abbasi	Department of International Medical College Abbottabad, Pakistan; Society of Obstetricians and Gynaecologists of Pakistan	Professor & Head of Obstetrics and Gynaecology; President of SOGON
Syeda Batool Mazhar	Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan	Consultant & Professor of Obstetrics and Gynaecology
Nyanda Elias Ntinginya	NIMR Mbeya Medical Research Centre, Tanzania	Principal Research Scientist; Director; clinical trials expert
Ian Roberts	Clinical Trials Unit – Global Health Trials Group, London School of Hygiene & Tropical Medicine, UK	Chief Investigator; Professor of Epidemiology; clinical trials expert
Amy Brenner	Clinical Trials Unit – Global Health Trials Group, London School of Hygiene & Tropical Medicine, UK	Lead Investigator; clinical trials expert

9.9 APPENDIX 9 – LIST OF MAJOR RISK FACTORS FOR POSTPARTUM HAEMORRHAGE

- increased maternal age (≥ 35 years)
- parity ≥ 4
- multiple pregnancy (2 or more foetuses)
- caesarean birth planned
- preterm birth (gestational age <37 weeks)
- previous PPH
- gestational hypertensive disorder of pregnancy (pre-eclampsia, eclampsia or hypertension)
- abnormal placental implantation (eg. placenta praevia, placenta accreta)
- antepartum haemorrhage or placenta abruption present
- moderate or severe anaemia (≤ 10 g/dL)
- foetal macrosomia
- intra-amniotic infection, e.g., prolonged rupture of membranes
- prolonged labour (>12 hours)
- fibroids
- uterine anomalies
- polyhydramnios
- dead foetus in utero
- obesity (BMI (body mass index) >35)
- gestational diabetes

Clinical Trials Unit-Global Health Trials Group
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT, UK

Tel: +44(0)20 7299 4684
Email: imwoman@lshtm.ac.uk
Web: imwoman.lshtm.ac.uk