Effects of intramuscular and intravenous tranexamic acid on severe postpartum bleeding: A statistical analysis plan for the I'M WOMAN trial

The I'M WOMAN Trial Collaborative Group

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Current trial protocol v4.0, 27 Jan 2026

SAP version number	Version date	Details
Original - 1.0	23-11-2026	First version

ABSTRACT

Background: Intravenous (IV) injection of tranexamic acid (TXA) for women with postpartum haemorrhage (PPH) reduces deaths from bleeding but the effects of giving TXA before the onset of severe bleeding and by intramuscular (IM) injection are uncertain. Trials have assessed the effects of IV TXA given after cord clamping, but this may be too late to prevent severe bleeding. The I'M WOMAN trial will assess the effects of IM and IV TXA given before birth on bleeding-related health outcomes.

Methods: This randomised, double blind, placebo-controlled, three-arm trial compares the effects of IM TXA, IV TXA and placebo on bleeding-related health outcomes in women giving birth. About 40,000 women will be randomly allocated to receive either (a) 1 g of TXA as two 5 mL IM injections (100 mg/mL) and IV placebo injection (10 mL 0.9% sodium chloride), (b) 1 g of TXA by IV injection and two 5 mL IM placebo injections, or (c) matching placebo in a 3:2:1 ratio, respectively. The primary outcome is a clinical diagnosis of PPH. Secondary outcomes are bleeding-related death or near miss, measured blood loss, haemoglobin concentration, interventions for bleeding, maternal and neonatal death and adverse events.

Discussion: The I'M WOMAN trial will provide evidence on the effects of early administration of TXA by the IM and IV routes on bleeding-related outcomes.

Registration: The I'M WOMAN trial was prospectively registered: ClinicalTrials.gov NCT05562609. Registered on 3 October 2022. ISRCTN Registry ISRCTN12590098. Registered on 20 January 2023. Pan African Clinical Trial Registry PACTR202305473136570. Registered on 18 May 2023.

Keywords: Antifibrinolytic, tranexamic acid, postpartum haemorrhage, clinical trial.

MAIN TEXT

Background

Severe bleeding after childbirth is an important cause of mortality and morbidity worldwide.[1] Intravenous (IV) tranexamic acid (TXA) given soon after the onset of severe bleeding reduces bleeding deaths by about one third.[2] The World Health Organization (WHO) recommends that all women with severe bleeding after birth should receive TXA.[3] Because TXA is most effective when given early,[4] and severe bleeding often occurs soon after birth, giving TXA before birth might prevent severe bleeding and improve maternal health outcomes. Some trials have examined the effect of TXA given after cord clamping, but this may be too late to avoid severe bleeding.[5–8]

TXA is usually given by slow IV injection. Although most women give birth in a health facility, many healthcare workers are not trained to give IV drugs, particularly in primary care settings. Even in tertiary hospitals, women may wait for hours to see a doctor. Alternative routes of administration that allow task shifting to community health workers and midwives would mean that more women can be treated, and treated sooner, in community and hospital settings. Recognizing this, the WHO considers finding alternative routes of TXA administration a research priority.[9] Studies in healthy volunteers, pregnant women, and trauma victims, show that TXA is well tolerated and rapidly absorbed after intramuscular (IM) injection, achieving therapeutic concentrations within minutes of injection.[10–12]

Aim and objectives

The I'M WOMAN trial aims to assess the efficacy and safety of TXA given before birth by the IM or IV route on a clinical diagnosis of PPH, and other bleeding-related and safety outcomes. The trial compares TXA (IM or IV) with placebo, and IM TXA with placebo or IV TXA.

Methods

Trial design: The I'M WOMAN trial is a randomised, double-blind, placebo-controlled, three-arm trial comparing TXA by the IM or IV route with placebo in women giving birth with one or more risk factors for severe bleeding. About 40,000 women will be randomly allocated to receive either:

- 1g of TXA as two 5 mL IM injections (100 mg/mL) and IV placebo (10 mL of 0.9% sodium chloride);
- 1g TXA by IV injection (10 mL) and two 5 ml IM injections of placebo;
- Placebo by IV injection (10 mL) and two 5 ml IM injections.

Setting: We conducted the trial in hospitals in Africa and South Asia, where the risk of death from bleeding is high. Sites were listed in country-specific protocols and on the trial website. Participating investigators and sites were identified from the international network of healthcare professionals established for the previous WOMAN trials. Before we started the trial, all relevant ethics and regulatory approvals were in place. All principal investigators were required to conduct the trial according to the protocol, Good Clinical Practice (GCP) guidelines, and other relevant regulations.

Eligibility and consent: Women aged 18 years or older admitted to hospital to give birth who had one or more risk factors for severe bleeding and no ongoing antepartum haemorrhage (APH) were potentially eligible. The risk factors are listed in the additional file. The fundamental eligibility criterion was the responsible doctor's 'uncertainty' about whether to use TXA in a particular woman. Women were not randomised if the responsible doctor believed that TXA was clearly indicated (e.g., had given

TXA within 12 hours or planned to give TXA) or clearly contraindicated (e.g., known allergy to TXA). If a woman was able to give fully informed consent, information about the trial was given and written consent was obtained. An overview of the consent procedure is provided in the additional file. Briefly, we identified potentially eligible women with the agreement of the responsible clinicians. We gave women information about the trial in their own language (see additional file). We explained the aims of the trial and made clear that women would receive all the usual interventions for bleeding. We explained that participation was voluntary, and that if women do not want to take part, we would respect this decision and it would not affect care. We obtained written consent from women who wanted to take part. For women unable to read or write, we read out the information sheet and asked women to mark the consent form with a cross or thumbprint in the presence of an impartial witness who provided a signature confirming the mark. We gave women a copy of the information sheet and consent form. If informed consent was withdrawn, we used data collected prior to withdrawal in the analysis.

Randomisation and masking: An independent statistician used a computerised random number generator to prepare the randomisation list. A unique randomisation number was linked to each treatment allocation. The statistician sent the randomisation list to the clinical trial supplies company so that blinded treatment packs could be prepared. The company produced, labelled and packaged TXA and placebo ampoules into patient treatment packs as per the randomisation list. TXA and placebo ampoules were identical. The trial staff (coordinating centres and sites) did not have access to the randomisation list until after database lock. Once a woman was confirmed to be eligible, after spinal anaesthesia and just prior to skin incision in caesarean birth, or in the hour before vaginal birth, a treatment pack was taken from a box of packs by a member of the research team. The woman was considered randomised after starting the first IM injection. Each site kept a log of women enrolled. Trial participants, trial staff, healthcare providers, outcome assessors and data analysts were blinded to the treatment allocation. The treatment packs were identical apart for the randomisation number.

All women received two IM injections and one IV injection to ensure blinding of the route of TXA administration. We clearly labelled the IM and IV treatments within each pack to show the intended route of administration. We used syringe labels to show the route of administration for each injection. Although it was possible to unblind the treatment allocation, there was usually no need. If a woman developed severe bleeding, she received all clinically indicated treatments (including TXA). Because a second 1 g dose of TXA is well within the dosing range, it was usually not necessary to unblind. Even if a woman had received TXA within the trial, a second TXA dose could be given. However, if the clinician felt that it was important for a woman's care to know the treatment allocation, they could unblind and we provided an emergency 24-hour telephone service for this.

Data collection: After completing the consent procedure, we collected baseline data including the woman's age, gestational age, parity, weight, multiple pregnancy, planned route of birth, and PPH risk factors (see additional file for list of risk factors). We measured haemoglobin (Hb), haematocrit (HCT) / packed cell volume (PCV), white cell and platelet count using a venous blood test. If the blood test results were unavailable, we recorded the most recent Hb, PCV, or HCT measurement in the participant's medical records taken within the last trimester. We recorded the date and time of randomisation, IM injection sites, and data on compliance (i.e., whether a full or partial dose was given). Participants were followed up until discharge, death or the end of the postnatal period (42 days), whichever occurred first. In caesarean births, intraoperative blood loss was measured by quantifying the amount of blood in sponges and drapes used in surgery and blood loss from suctioning, excluding amniotic fluid. Starting immediately after vaginal birth or after the end of caesarean surgery, we measured postpartum blood loss using a calibrated obstetric drape for 1 hour, or up to 2 hours if heavy bleeding continued and the woman remained in bed. Upon calibrated drape removal, we asked the woman about nausea, vomiting and dizziness during and after the birth, and about pain at the

injection sites. We inspected each injection site for local reactions. We recorded blood loss, interventions for bleeding, vital signs, maternal and neonatal death or complications, and a clinical diagnosis of PPH in the 24 h after birth. We took venous blood around 24 h after birth, or discharge if earlier, to measure Hb, HCT/PCV, white cell and platelet count. We recorded adverse events up to 42 days postpartum.

STATISTICAL ANALYSIS PLAN

Planned comparisons: In paper A (see below), we will compare TXA (IV or IM) versus placebo (superiority). In paper B (see below), we will compare IM TXA versus placebo (superiority) and IM TXA versus IV TXA (non-inferiority).

Trial profile: We will report the flow of study participants through the trial in a Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1). We will start with the total number of women randomised into the trial by treatment arm. Within each treatment arm we will detail the number of women who withdrew consent, the number for whom baseline data were collected, the number lost to follow up, and the number of women for whom outcome data were collected. We will report the number of women included in the primary and secondary analyses, and the reasons for any post-randomisation exclusions. We will count women that did not fulfil the eligibility criteria or did not receive their allocated treatment as having deviated from the protocol, but their data will be included in the intention to treat analysis.

Baseline characteristics: We will summarise baseline patient characteristics by randomised group (Table 1). We will summarise categorical variables using frequencies and percentages and continuous variables using the mean and standard deviation or the median and interquartile range. We will report the number of missing values.

Primary outcome: The primary outcome is a clinical diagnosis of primary PPH. This may be a blood loss of more than 500 mL in vaginal birth, more than 1000 mL in caesarean birth, or any blood loss sufficient to compromise haemodynamic stability within 24 h of birth. Haemodynamic instability is based on clinical judgement and assessed using clinical signs (low systolic blood pressure, tachycardia, reduced urine output).[12,13,14] Causes of PPH will be reported (not mutually exclusive).

Secondary outcomes

Bleeding-related death or near miss: The WHO recommends the use of the maternal near miss approach as a standard diagnostic criterion and a benchmark for maternal health care.[15] Bleeding-related death or near miss is biologically and clinically relevant, accurately measured, sufficiently common, and important to patients.[16] This key secondary outcome is defined as any of the following:

- Death due to bleeding within 24 h of birth
- Severe PPH (measured blood loss of ≥1500 mL, or peripartum Hb drop ≥25g/L) within 24 h of birth
- Surgical intervention for bleeding (hysterectomy, laparotomy, arterial embolization or ligation, uterine compression sutures) within 24 h of birth
- Blood transfusion of ≥5 units intraoperatively and up to 24 h after birth
- Cardiovascular dysfunction (shock, cardiac arrest, continuous vasoactive drugs, severe hypoperfusion, severe acidosis, cardiopulmonary resuscitation)
- Renal dysfunction (oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, severe acute azotaemia)

Severe PPH: We will assess the proportion of women with severe PPH (defined as a measured blood loss of ≥1500 mL or a peripartum Hb drop of ≥25g/L within 24 h of birth).

Measured blood loss: We will assess measured blood loss (defined as drape measured blood loss for vaginal births and intraoperative plus drape measured blood loss for caesarean births) up to 2 h after vaginal birth or the end of caesarean surgery, using continuous and categorical measures (0-299, 300-499, 500-999, 1000-1499 and ≥1500 mL). We will also assess intraoperative blood loss and drape-measured blood loss in caesarean birth up to 2 h after end of surgery as continuous measures.

Haemoglobin: We will assess transfusion-corrected postpartum Hb and peripartum Hb change around 24 h after birth. Postpartum Hb will be corrected for blood transfusion by subtracting 10g/L for every unit of blood transfused. Haematocrit or PCV values will be converted to haemoglobin values for patients with only pre-birth or postpartum HCT or PCV available. To obtain haemoglobin (g/L) from HCT (%), we will divide HCT by a factor of 0.3.[17] We will categorise corrected postpartum Hb into four anaemia categories (none=Hb≥110, mild=Hb 100-109, moderate=Hb 70-99, severe=Hb<70) according to WHO guidelines.

Interventions for bleeding: We will assess the number and percentage of women who received interventions for bleeding within 24 h of birth, including uterotonics, non-trial TXA, blood transfusion (intraoperatively and up to 24 h after birth), sutures, and surgical and non-surgical interventions.

Blood pressure and heart rate: We will assess the lowest recorded blood pressure and associated heart rate up to 24 h after birth.

Maternal deaths: We will assess deaths up to discharge or 42 days (all-cause and cause-specific).

Prespecified maternal adverse events: We will assess prespecified (vascular occlusive events, seizure, sepsis, organ dysfunction, coagulopathy) and other maternal adverse events up to 42 days postpartum. We will report the number and percentage of women with a vascular occlusive events and specific vascular occlusive events (DVT, PE, MI, Stroke) separately. We will report the number and percentage of women with a seizure. We will also report the number and percentage of women with seizures by dose of TXA (none, <2 g, ≥2 g), including both trial and non-trial TXA. Non-trial TXA is recorded up to 24 h after birth, but it is possible that additional doses of non-trial TXA may be given after 24 h.

Nausea, retching, vomiting and dizziness: We will assess the number of episodes or the score from 0 to 10 at the time of drape removal (1-2 hours after birth).

Pain or adverse skin reactions at injection sites: We will assess local reactions and injection site pain score at the time of drape removal (1-2 hours after birth).

Duration of surgery: We will assess the length of caesarean surgery.

Hospital stays: We will assess length of hospital stay, days in intensive care or high dependency unit after randomisation and transfer to another hospital, based on maternal condition only, not that of the neonate.

Neonatal outcomes: We will assess infant outcomes to maternal discharge, death or 42 days postpartum (breastfeeding within 24 h of birth, intracranial haemorrhage, pulmonary haemorrhage,

bruising, thromboembolic event, seizure, stillbirth/intrapartum death, neonatal death, cause of death, congenital and genetic abnormalities, adverse events up to 42 days postpartum).

Sample size and power

To calculate the planned sample size of 40,000, we assumed a 25% relative reduction in the primary outcome with TXA (RR=0.75) and estimated the event rate from the accumulating trial data.[18,19] Based on this effect size and an estimated primary outcome event rate of 7.5% in the placebo group, a trial of about 40,000 women would have greater than 99% power to detect that 1) TXA is more effective than placebo and 2) IM TXA is more effective than placebo. For the non-inferiority comparison of IM TXA versus IV TXA, we assumed the two routes were equally effective. For this comparison, the trial has about 86% power to detect the IM route is at least 60% as effective as the IV route, and about 99% power to detect that IM TXA is at least 30% as effective as IV TXA. We assumed a two-sided type 1 error rate of 5% for the superiority arms and a one-sided rate of 2.5% for the non-inferiority arm. An optimal allocation ratio (3:2:1) was used to maximize study power with patients allocated to receive IM TXA, IV TXA, and placebo, respectively.

We initially estimated a sample size of 30,000 based on a placebo group event rate of 11.5%, which would have almost 90% power to detect that IM TXA is at least 60% as effective as IV TXA.[17,18] Blinded interim analyses showed a lower than anticipated pooled event rate. Assuming the treatment effect was 0.75, this would reduce the statistical power available. Based on the above assumptions but the lower placebo group event rate of 7.5%, a trial of 30,000 women would have about 70% power to detect the IM route is at least 60% as effective as the IV route. This represents a 30% chance of failing to show non-inferiority if IM TXA is truly non-inferior to IV TXA. Given the public health importance of this research question, we must minimise any risk of declaring IM TXA inferior to IV TXA by chance alone. A study with 40,000 participants and the lower event rate would have close to the original planned power (86%), halving the risk of failing to show non-inferiority if IM TXA is truly non-inferior.

Monitoring, interim analysis and stopping rules

To ensure the safety of the trial participants, the accumulating data were reviewed by an independent Data Monitoring Committee (DMC). Unblinded interim analyses were conducted by an independent statistician. The DMC applied the Peto-Haybittle stopping rule, whereby an interim analysis of a major outcome requires differences of at least three standard errors to justify premature disclosure. The DMC used a combination of statistical and scientific judgment.

Adherence and protocol deviations

We will summarise protocol deviations and violations.

Paper A. Effects of TXA on bleeding-related outcomes and adverse events in mother and infant

Background: TXA reduces life-threatening postpartum bleeding and is more effective when given early,[4,19] but current guidelines recommend the use of TXA only for women with established PPH.[20] Several trials have evaluated the effects of TXA given after cord clamping and before PPH onset, but their results are uncertain.[6–8] Because severe bleeding often occurs soon after birth, giving TXA after cord clamping may be too late and randomised trials of earlier administration are needed.[21] Randomised trials in surgery show that TXA given prior to skin incision reduces surgical bleeding and the need for blood transfusion without any major side effects.[18]

Primary analysis: TXA versus placebo

The primary analysis will compare the proportion of women with the primary outcome (a clinical diagnosis of PPH) in those allocated tranexamic acid (IM or IV) versus those allocated placebo, on an intention to treat (ITT) basis (irrespective of whether they received the allocated treatment). The number and percentage of women with the primary outcome will be reported by treatment group. Percentages will be calculated from those with available data on the primary outcome. We will report the number of women with missing data. The results will be presented as a risk ratio with a 95% confidence interval (CI) calculated using a binomial regression model with a log link, including randomised treatment as the only covariate. We will set the results of the I'M WOMAN trial in the context of other large trials of TXA for bleeding after childbirth, using a forest plot to present individual and pooled effect estimates, confidence intervals and p-values from tests for interaction, with data stratified by anaemia severity, APH, and mode of birth (figure 4).[19,22]

Sensitivity analysis: The following sensitivity analyses will be carried out for the primary outcome.
(i) Women believed to be at high risk of severe bleeding sometimes receive non-trial TXA. We will conduct a sensitivity analysis excluding women who received non-trial TXA prophylactically (TXA given before or in the absence of a PPH diagnosis). In cases where the time of receipt of non-trial TXA is unknown and a PPH was diagnosed, it will be assumed that TXA was given after diagnosis of PPH (i.e., as treatment).

(ii) To increase precision, we will adjust for important baseline predictors (covariate adjustment) for severe bleeding. The following baseline variables will be included as covariates in the binomial regression model along with randomised treatment: country, age, pre-birth haemoglobin, abnormal placental implantation, APH, dead foetus in utero, hypertensive disorder of pregnancy, fibroids, multiple pregnancy, and mode of birth. In case of issues with convergence, we will conduct a logistic regression instead.

Protocol non-adherence and missing data: The primary analysis will be ITT. We will also conduct modified ITT and per protocol analyses. The modified ITT analysis will exclude women who did not receive the full dose of the allocated treatment and those randomised less than ten minutes prior to vaginal birth or skin incision (i.e. trial treatment potentially not completed before bleeding onset). Giving TXA just before birth may not allow enough time to reach therapeutic levels. After IM injection, it takes about 10 minutes to reach the blood concentrations needed to inhibit fibrinolysis.[10] The per protocol analysis will only exclude participants who did not receive the full dose of the allocated treatment. Because we expect little missing data (<0.5% for the primary outcome), we will report missing baseline and outcome variables, but we will not impute missing data. Women who were randomised but later found to be ineligible at baseline will be included in the ITT analysis and only excluded from the per protocol analysis if their eligibility violation is of clinical relevance to the treatment effect.

Subgroup analyses: We will conduct the following subgroup analyses on the primary outcome, comparing TXA to placebo, with results presented in a forest plot (Figure 2).

i) **Anaemia severity (no anaemia or mild anaemia vs moderate or severe anaemia)**
Women with moderate or severe anaemia can receive a clinical diagnosis of PPH despite only modest blood loss. There is some suggestion that RBCs and TXA work synergistically to inhibit fibrinolysis.[23] In either case, TXA may be less effective in women with moderate or severe anaemia. Because women with moderate or severe anaemia are more likely to have APH, intrauterine foetal death or give birth vaginally, we will control for these variables in a multivariable model. We will also assess effect modification by pre-birth haemoglobin level as a continuous variable. We will fit an interaction term with randomised group and use a likelihood ratio test to compare the models with and without the interaction. If there is evidence of effect modification by haemoglobin, we will present a plot showing the spline of the marginal treatment effect against haemoglobin level.

ii) **Placental abruption and/or antepartum haemorrhage and/or intrauterine foetal death vs none**
Placental abruption, often accompanied by foetal death, is an important cause of disseminated intravascular coagulation. However, the precise timing of coagulation activation in abruption is hard to determine and may have occurred hours before birth. Because TXA is most effective given soon after coagulation activation, TXA may be less effective in women with abruption/APH/intrauterine foetal death.[4,5] Because these women are more likely to have severe anaemia, give birth vaginally or be randomised just before birth (less than ten minutes), we will control for these variables in a multivariable model.

iii) **Mode of birth (caesarean vs vaginal)**
We do not expect the effect of TXA to differ by mode of birth. TXA works by inhibiting blood clot breakdown and reduces death from PPH regardless of the cause of bleeding.[2] Because women giving birth vaginally may be more likely to have severe anaemia, APH, or be randomised just before birth (less than ten minutes), we will control for these variables in a multivariable model.

We will fit interaction terms with randomised group in a model. We will first attempt to use binomial regression and if it fails, use Poisson regression with robust error variance. We will use interaction tests to explore whether the effect of treatment differs by subgroup. Results will be presented using forest plots, with unadjusted and adjusted relative risks and a measure of precision (95% confidence intervals) within each subgroup, and a p-value for the interaction test. Unless there is strong evidence of interaction ($p < 0.001$), we will take the overall RR as the best estimate of the RR in all subgroups.

Secondary outcomes: The following statistical approaches will be used to analyse secondary outcomes. Binary outcomes will be analysed using the same approach used for the primary outcome. The frequency and percentage of women with the outcome will be reported along with risk ratios and 95% CIs from a binomial regression model with randomised treatment as the only covariate. For continuous outcomes we will report the number of observations, mean and standard deviation by treatment group. Linear regression models (ANCOVA) with the baseline values included as a covariate (where appropriate) along with randomised treatment will be used to estimate treatment effects, which will be reported as difference in means with 95% CIs. If a baseline value is unavailable, we will estimate difference in the mean and 95% CI using a two-sample t-test. If a continuous outcome is found to violate the assumption of normality, an appropriate transformation may be applied or a non-parametric method of analysis may be used. We will use histograms to compare measured blood loss

and postpartum Hb distribution by randomised group (figure 3). For ordered categorical outcomes, we will report the number and percentage of women in each category. We will estimate an odds ratio and 95% CI using an ordinal logistic regression model with randomised treatment as the main covariate, and for some outcomes we will adjust for the baseline value e.g. Hb. The number of AEs, SAEs, and SUSARs grouped by MedDRA® codes and the number of patients with at least one event will be compared between arms using a Chi-squared test (or Fisher's exact test), with RRs and 95 % CIs.

Exploratory analyses: For completeness, we may undertake exploratory analyses comparing IV TXA versus placebo on an ITT basis.

PAPER B. The effects of IM TXA on severe bleeding and adverse events

Background: Many women give birth in places where IV drugs cannot be given, such as at home or in primary care facilities, and so cannot access lifesaving TXA treatment for PPH. IM TXA administration could expand access to TXA and reduce maternal deaths. IM TXA would also have practical advantages in healthcare facilities. Although many healthcare workers can give IV injections, by avoiding the need to slowly inject TXA over ten minutes, the IM route could reduce time to treatment and free up healthcare workers for other important activities. TXA is rapidly absorbed after IM injection but due to the absorption phase, peak blood concentrations are lower than with the IV route.[10] By avoiding high peak concentrations, there may be fewer adverse effects (e.g., nausea, vomiting) with IM TXA, which would be important for prophylactic TXA use in lower-risk women. The slow, continuous absorption of IM TXA keeps therapeutic drug levels active in the body for longer than IV TXA. If IM TXA was similarly effective, it could be given shortly before taking women to the operating theatre for caesarean birth, which could reduce the risk of inadvertent intrathecal TXA injection at the time of spinal anaesthesia.[24]

To inform whether IM TXA could be used to reduce severe bleeding in women for whom IV treatment is not an option, we will assess the effects of IM TXA on a clinical diagnosis of PPH and other bleeding-related outcomes compared to placebo, in superiority analyses on an ITT basis. To inform whether IM TXA could substitute for IV TXA administration in places where IV treatment is available, we will conduct non-inferiority analyses on a per protocol basis. To examine the impact of route of administration on safety and tolerability, we will compare minor side effects in the IM TXA and IV TXA groups in superiority analyses on a per protocol basis.

Primary analysis - IM TXA vs placebo – effectiveness and safety (superiority)

We will compare the proportion of women with the primary outcome in those allocated IM TXA versus those allocated placebo, on an ITT basis (irrespective of whether they received the allocated treatment). The number and percentage of women with the primary outcome will be reported by treatment group. Percentages will be calculated from those with available data on the primary outcome. We will report the number of women with missing data. The primary analysis results will be presented as a relative risk with a 95% confidence interval (CI) calculated using a binomial regression model with a log link, including randomised treatment as the only covariate.

Sensitivity and subgroup analyses: We will conduct the same sensitivity analyses as for paper A. We will not conduct subgroup analyses as there is no reason to expect subgroup effects to differ from paper A and we will have less statistical power.

Protocol non-adherence and missing data: The primary analysis is ITT. We will also conduct modified ITT and per protocol analyses. The modified ITT analysis will exclude women who did not receive the full dose of the allocated treatment and those randomised less than ten minutes prior to vaginal birth or skin incision (i.e. trial treatment potentially not completed before bleeding onset). The per protocol analysis will only exclude women who did not receive the complete dose of IM TXA. We will report missing baseline and outcome variables, but we will not use methods to impute missing data.

Secondary outcomes: We will analyse the secondary outcomes with the approach used in paper A, though these analyses will have less statistical power.

Secondary analysis - IM TXA vs IV TXA – effectiveness (non-inferiority)

Non-inferiority trials are used to assess whether a new treatment, or route of administration, is not worse than an existing treatment or route by more than a stated amount. The new treatment may have advantage over the existing treatment, for example it may be safer or easier to use. To compare the effects of IM TXA and IV TXA, we need to prespecify a non-inferiority margin. Specifically, we must decide what fraction of the treatment benefit from IV TXA must be preserved with the IM route (the preserved fraction). The choice of preservation fraction is a judgement that depends on the clinical scenario and the balance of risks and benefits, and it would be inappropriate to specify a single measure.

Severe bleeding is a life-threatening emergency and TXA is a lifesaving drug with no serious adverse effects. When considering whether IM TXA should replace IV TXA for PPH treatment in a setting where IV treatment is feasible, we would want a high preservation fraction. Women in healthcare settings often experience TXA treatment delays while waiting for a doctor to insert an IV line. Because the effectiveness of TXA in severe bleeding falls by about 10% with every 15-minute delay, a one-hour delay corresponds to a 40% reduction in effectiveness. If IM TXA preserves 60% of the benefit of IV TXA administration, IM TXA 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.

The non-inferiority analysis is conditional on demonstrating assay sensitivity in paper A i.e. evidence that TXA improves bleeding-related health outcomes. We will compare the proportion of women with the primary outcome (a clinical diagnosis of PPH) in those who received the full dose of IM TXA versus those who received the full dose of IV TXA. 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. If deciding whether IM TXA should be used for women with severe bleeding in community settings where IV treatment is not possible, a lower preservation fraction of 30% would be appropriate, corresponding to relative risk of 1.23. We will present all non-inferiority analyses for completeness, regardless of the paper A results.

Protocol non-adherence and missing data: The primary analysis is per protocol. We will also conduct ITT and modified ITT analyses. The modified ITT analysis will exclude women who did not receive the full dose of the allocated treatment and those randomised less than ten minutes prior to vaginal birth or skin incision (i.e. trial treatment potentially not completed before bleeding onset).

Secondary outcomes: We will compare the frequency of the key secondary outcome (bleeding-related death or near miss) and other bleeding-related outcomes between the IM TXA and IV TXA arms, reporting the numbers, proportions and effect estimates with a 95% confidence interval (CI). These analyses are supportive rather than confirmatory.

Secondary analysis - IM TXA vs IV TXA – safety and tolerability (superiority)

The effect of TXA on local and systemic adverse events may vary by route of administration. An important objective of the I'M WOMAN trial is to provide information on the incidence and severity of local adverse reactions to IM TXA, pain at the injection site, and the incidence of minor, common adverse events in a large sample of women. We will report the IM and IV injection site pain scores and significant skin reactions at the injection sites in women who receive IM TXA versus IV TXA, on a per protocol basis. We will also compare retching and vomiting episodes, nausea and dizziness scores in women who receive IM TXA versus IV TXA.

ANALYSES TO BE REPORTED IN SEPARATE PUBLICATIONS

Cost effectiveness analysis: We will develop a decision model to assess the cost-effectiveness of IM and IV tranexamic acid for the prevention of postpartum bleeding. We will use data from the WOMAN trial, WOMAN-2 trial and I'M WOMAN trial to inform model parameters, supplemented by estimates from the literature. We will estimate costs (calculated in US$), life-years, and quality-adjusted life-years (QALYs) with and without tranexamic acid, calculate incremental cost-effectiveness ratios (ICERs), and compared these to threshold values in the participating countries. Costs will be assessed from a health-care provider perspective and discounted at 3% per year in the base case analysis. We will conduct a series of one-way sensitivity analyses and probabilistic sensitivity analysis to assess the robustness of the results to parameter uncertainty.

Individual patient data meta-analysis: Although the I'M WOMAN trial will be one of the largest randomised trials of TXA for the prevention of postpartum bleeding conducted to date, even large trials will have limited power to detect the effects of the trial treatment on certain important outcomes, or in patient subgroups. For this reason, it is important to set the results of the I'M WOMAN trial in the context of other large randomised trials of TXA for bleeding after childbirth. We must also examine how the balance of benefits (e.g., bleeding risk) and potential harms (e.g., thrombotic risk) might vary according to the baseline risks of these outcomes and by patient subgroups. We will explore these issues by conducting a systematic review and IPD meta-analysis that will assess the effects of TXA on the risk of life-threatening postpartum bleeding, thromboembolic events, and on other outcomes that matter to women. We will examine how the effects of TXA on life-threatening bleeding and thromboembolic events vary by the baseline risks of these outcomes, by baseline level of haemoglobin, type of birth (vaginal versus caesarean birth), and timing of treatment. A protocol and statistical analysis plan for this analysis has been presented elsewhere.[25]

Hierarchical endpoint analysis using win ratio: Although maternal death is undoubtedly one of the most important consequences of severe post-partum bleeding, even very large trials have limited power to detect the impact of the trial treatment on this critical patient outcome. Including death as a component of a composite outcome is an alternative approach but the effect of the intervention on the individual outcomes is lost and not all of the components of the composite outcome may have the same importance for the patient. Pocock and colleagues have described an analytical approach (hierarchical composite endpoint analysis using the win ratio) that considers endpoints in a hierarchical way thus gaining statistical power while respecting the relative priorities of the component outcomes.[26] In a separate paper, we will report an analysis of the I'M WOMAN trial using the win ratio approach with death (1), near miss death related to bleeding (2), hysterectomy for bleeding (3), and a clinical diagnosis of postpartum haemorrhage (4), as the ranked outcomes.

Anaemia and the risk bleeding, shock, and death in caesarean birth: Maternal mortality after caesarean section is high in sub-Saharan Africa and South Asia. Although half of pregnant women in these settings are anaemic, the impact of anaemia on outcomes after caesarean section remains unexplored. We will conduct a cohort analysis of women giving birth by caesarean in Nigeria, Tanzania and Pakistan, using data from the I'M WOMAN trial. The exposure will be pre-operative haemoglobin. The maternal outcomes will be measured blood loss, shock, and death or near miss. The neonatal outcome will be stillbirth or intrapartum death. Measured blood loss will be calculated from intraoperative blood loss and postoperative drape-measured blood loss. Shock will be defined as a postpartum shock index ≥1.1. We will use multivariable logistic regression to examine the association between pre-birth haemoglobin and maternal and infant outcomes after adjusting for potential confounding factors.

TRIAL STATUS

The study has been actively recruiting since April 2024. End of recruitment is planned for March 2027, with end of follow-up in May 2027. Further information is available at https://imwoman.lshtm.ac.uk/.

DISCUSSION

This statistical analysis plan is an update to our previously published protocol. Because of the lower-than-expected event rate, we have included bleeding-related death or near miss as a key secondary outcome. This composite outcome, derived from the WHO definition of maternal death or near miss, is sufficiently common, accurately measured, and biologically and clinically relevant. We present our plan for the statistical analyses in advance of the database lock and unblinding to guard against post hoc data dependent analyses. The I'M WOMAN trial will provide reliable evidence on the benefits and harms of TXA for the prevention of postpartum bleeding and the effects of the IM route of administration.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the LSHTM ethics committee (ref. 28252), WHO ERC (ref. 2021-KEP-588), and all required national and local ethics committees in collaborating countries and participating sites. Informed consent was sought from eligible patients prior to enrolment.

Consent for publication

Not applicable.

Availability of data and materials

Following publication of the primary and secondary analyses detailed in this statistical analysis plan, the trial data will be made available via our data sharing portal: The Free Bank of Injury and emergency Research Data (freeBIRD) website (http://freebird.Lshtm.ac.uk). This will allow for maximum use of the data to improve patient care and advance medical knowledge.

Competing interests

The authors declare that they have no competing interests.

Funding

This study is funded by Unitaid. The funder had no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

AB - Conceptualization, funding acquisition, project administration, supervision, data curation, analysis, investigation, methodology, writing – original draft preparation, review & editing
JL - Project administration, supervision, data curation, analysis, investigation, methodology, writing – original draft preparation, review & editing
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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data monitoring committee
DVT	Deep vein thrombosis
Hb	Haemoglobin
HCT	Haematocrit
MI	Myocardial infarction
PCV	Packed cell volume
PE	Pulmonary embolism
PPH	Postpartum haemorrhage
RBC	Red blood cells
SAP	Statistical analysis plan
TSC	Trial steering committee
TXA	Tranexamic acid
WHO	World Health Organization

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