woman3

THE EFFECTS OF TRANEXAMIC ACID ON ANAEMIA, MENSTRUAL HEALTH AND THE WELLBEING OF WOMEN: AN INTERNATIONAL RANDOMISED, PLACEBO-CONTROLLED TRIAL AMONG MENSTRUATING WOMEN WITH ANAEMIA

CLINICAL TRIAL PROTOCOL

Sponsor's ID Number:	2024-KEP-1055
Clinicaltrials.gov registration:	NCT06519422

	NUMBER	DATE	DETAILS
VERSION	1.0	30/08/2024	Submitted to LSHTM REC
VERSION	1.1	12/12/2024	Re-submitted to LSHTM REC
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TRIAL COORDINATION CENTRE: LSHTM Clinical Trials Unit
SPONSOR ID: 2024-KEP-1055

This protocol describes the procedures for enrolling participants into the WOMAN-3 trial. It does not provide guidance on patient management. Although it was drafted with care, corrections or amendments may be necessary. These will be circulated to investigators in the trial as applicable. Questions about the WOMAN-3 trial should be referred to the Clinical Trials Unit (CTU) at the London School of Hygiene and Tropical Medicine (LSHTM). The trial will follow the principles outlined in the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, the trial protocol, and applicable local regulations.

PROTOCOL SUMMARY

FULL TITLE OF TRIAL	The effects of tranexamic acid on anaemia, menstrual health and the wellbeing of women: an international randomised, placebo-controlled trial among menstruating women with anaemia				
SHORT TITLE	Tranexamic acid for anaemia trial				
TRIAL ACRONYM	WOMAN-3				
SPONSOR ID NUMBER	2024-KEP-1055	**LSHTM ETHICS REF**	31315	**CLINICALTRIALS.GOV**	NCT06519422

BACKGROUND: World-wide, half a billion women of reproductive age are anaemic. Anaemia has major health consequences for pregnant women and their babies. Anaemia increases the risk of ante-partum haemorrhage, prematurity, stillbirth, neonatal death, post-partum haemorrhage and maternal death. Unfortunately, global efforts to reduce anaemia prevalence are far off track. Anaemia worsens bleeding through multiple biological mechanisms. Anaemia increases blood flow from bleeding vessels due to reduced blood viscosity and anaemic blood clots are more susceptible to fibrinolysis. Although iron and multivitamin replacement is the mainstay of anaemia treatment, iron stores in young women depend more on menstrual iron loss than on dietary iron intake. Because anaemia worsens bleeding, women with anaemia have heavier periods than if they were not anaemic. For this reason, offering iron replacement without reducing menstrual iron loss may be inefficient. The antifibrinolytic drug tranexamic acid (TXA) reduces menstrual bleeding by preventing blood clot breakdown. We propose that giving TXA with iron and vitamin replacement will be more effective in treating anaemia than iron and vitamin replacement alone.

AIM: To determine the effect of giving TXA during menstruation for anaemia treatment.

PRIMARY OUTCOME: The proportion of women with anaemia (Hb<120 g/L, venous blood tests) at the end of the intervention period (6 completed menstrual cycles, i.e., about 6 months).

SECONDARY OUTCOMES: Haemoglobin concentration, serum ferritin (marker of iron storage, venous blood tests); time to anaemia resolution; participant reported menstrual blood loss, health and wellbeing; and adverse effects.

TRIAL DESIGN: An international, multicentre, randomised controlled trial of TXA versus placebo in 4,000 women.

POPULATION: Adult women with anaemia (Hb<120 g/L) who menstruate.

INCLUSION CRITERIA: Adult women with anaemia (Hb<120 g/L) who menstruate.

EXCLUSION CRITERIA: Women taking TXA, women with known contra-indications to TXA treatment (including allergy to TXA, renal impairment, active thromboembolic disease, history of venous or arterial thrombosis, history of convulsion) and women who plan to become pregnant during the trial period.

TRIAL TREATMENT AND REFERENCE THERAPY:

Tranexamic acid 1 gram orally taken three times a day from the first to the last day of the menstrual period for up to 5 days, for 6 successive menstrual periods. The comparator is matching placebo.

In addition, women will receive standard of care iron and folic acid supplementation orally for three months from randomisation.

SETTING: Educational and healthcare facilities and community settings where anaemia is prevalent in South Asia and Sub-Saharan Africa including but not limited to Nigeria, Tanzania, and Pakistan.

DURATION OF TREATMENT AND PARTICIPATION: We will ask participants to take the trial treatment for 6 menstrual periods. Participants will also take standard of care supplements of iron and folic acid 3 months from randomisation. Trial participation ends after primary outcome assessment after the 6th menstrual period (or 9 months (+/- 1 week) after randomisation, whichever occurs first).

CRITERIA FOR EVALUATION: 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**	01/08/2024 (start of set-up phase)	**PLANNED TRIAL END**	30/09/2028

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1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Anaemia is common and dangerous for pregnant women, their babies, and menstruating women.

World-wide, half a billion women of reproductive age (30%) are anaemic, with a particularly high prevalence in sub-Saharan Africa and South Asia.[1] Iron deficiency is believed to be the most common cause. Anaemia symptoms include fatigue, breathlessness, palpitations, headaches and cognitive impairment, which can lead to reduced educational achievements, loss of labour productivity and increased healthcare costs.[2, 3] In non-pregnant women, anaemia may disrupt menstrual cycles and affect fertility.[4-6] In pregnancy, anaemia is a serious risk to the baby and the mother. Anaemia increases the chance that a baby will be born early or small and will die soon after birth.[7] Babies born iron deficient due to insufficient iron loading from their mothers have worse neurocognition and bonding.[8, 9] Anaemia is also dangerous for mothers. Post-partum haemorrhage (PPH) is believed to be responsible for over 50,000 deaths each year and anaemia is a strong risk factor.[10] Women with severe anaemia have a sevenfold increased odds of death or near miss compared with moderate anaemia.[11] Most maternal deaths attributed to PPH are in countries where anaemia is common.[1, 12]

New strategies are needed to reduce anaemia in women at the pre-conception stage.

The global target, set in 2000, to halve the prevalence of anaemia in women of reproductive age by 2025 was not met.[13-15] The prevalence of anaemia in pregnant women was 41% in 2000 and 36% in 2019. In non-pregnant women, the prevalence of anaemia was 31% in 2000 and 30% in 2019.[16] Preventing anaemia prior to conception is critical. Anaemia and iron deficiency in early pregnancy can have irreversible adverse effects on foetal neurodevelopment.[17-19] To date, efforts to reduce anaemia in young women have focused on supplementing iron, folic acid and vitamin B12 intake. However, the side-effects of iron supplementation can reduce compliance.[19, 20] Furthermore, iron stores depend more on menstrual iron loss than on dietary intake.[21] However, menstruation is often overlooked in efforts to reduce anaemia in young women.[15, 18, 22, 23]

Anaemia increases the risk of bleeding and reduces the ability to tolerate bleeding

It is known that bleeding causes anaemia but less well known that anaemia worsens bleeding.[11, 24-29] For example, removing two units of red blood cells (RBCs) from healthy volunteers increased their bleeding time by 60%. The bleeding time returned to normal after reinfusion of the RBCs.[29] In pregnant women, every 10 g/L decrease in pre-birth haemoglobin increases the odds of a PPH diagnosis by about 30%.[11] Anaemia worsens bleeding through multiple mechanisms.[30, 31] The increased heartbeat and reduced blood viscosity in anaemia leads to increased blood flow from bleeding vessels.[32, 33] Anaemia also influences platelet function, thrombin generation and fibrinolysis.[31, 34-36] In addition, it has been suggested that iron deficiency, which often underlies anaemia, increases the risk of heavy menstrual bleeding.[37]

Tranexamic acid could reduce anaemia by reducing menstrual bleeding.

Adding tranexamic acid (TXA) during menstruation to iron and folic acid supplementation has the potential to improve the effectiveness of anaemia treatment. Because anaemia increases bleeding, anaemic women are likely to have heavier periods than if they were not anaemic. TXA reduces menstrual bleeding by reducing endometrial fibrinolysis.[38-40] Menstruation is triggered through progesterone withdrawal, which results in an endometrial environment that is pro-haemorrhagic and favours fibrinolysis.[41-43] Endometrial fibrinolysis is more pronounced in women with heavier bleeding.[39, 44-46] A major advantage of reducing excessive menstrual bleeding is that it should improve the treatment of anaemia regardless of its cause. If TXA improves anaemia, this treatment could have major policy implications. A high-quality trial could impact anaemia control policy globally, improve the wellbeing of millions of women, and help achieve global targets for anaemia reduction. Early intervention to reduce the risk of anaemia before pregnancy offers the potential to reduce adverse maternal and neonatal outcomes and improve well-being across the reproductive life course.

1.2 EXISTING EVIDENCE ON POTENTIAL BENEFITS AND RISKS

TXA reduces surgical, traumatic and postpartum bleeding by about a third.[47-50] We have systematically reviewed the evidence from randomised trials of TXA in menstruating women. We searched several bibliographic databases for trials assessing the effects of TXA (compared to placebo or standard care) on menstrual bleeding. We found seven trials [51-57] that compared oral TXA with placebo in women with suspected or diagnosed heavy menstrual bleeding or low haemoglobin levels due to menstrual blood loss. The trials were small, and all were conducted in high-income countries. All trials were described as double-blind; however, other aspects of methodological quality were poorly reported, and we are uncertain about their validity. Blood loss was the most common outcome with six trials contributing data. The pooled estimates indicate that TXA reduces blood loss per menstrual cycle by an average of 50 mL (MD= -49.06, 95% CI -56.45 to -42.68). There is weak evidence that TXA improves quality of life, although this outcome was not widely reported in the available trials. Unwanted side-effects were infrequently reported. The number of women with thromboembolic events were reported in two trials; Only one event occurred in the placebo group of one trial and there were no events in the other trial. There was no evidence for an increased risk of side-effects (e.g., nausea and vomiting) with TXA use. In summary, the available trials are of uncertain methodological quality and there is little evidence about the effects of TXA on haemoglobin in women with anaemia. There is also insufficient information about the effect of TXA on other important outcomes such as quality of life and side effects and no trials have been conducted in low- and middle- income countries.

2 TRIAL OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine the effect of giving oral TXA during menstruation in adult women for the treatment of anaemia.

2.2 SECONDARY OBJECTIVES

We will also assess the effects of TXA on serum ferritin (a key secondary outcome); participant reported menstrual health and blood loss, wellbeing; adverse effects and treatment adherence.

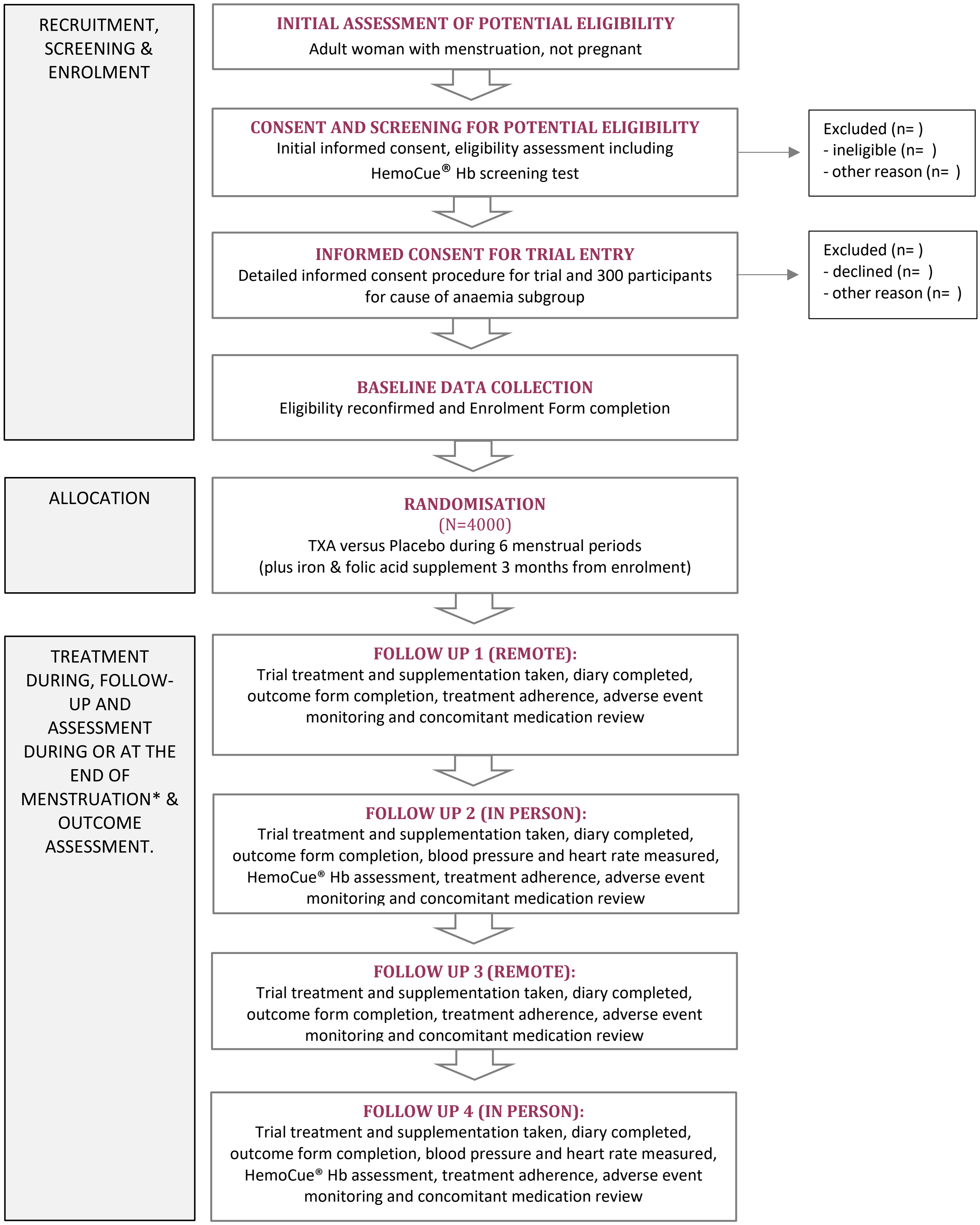
3 TRIAL DESIGN

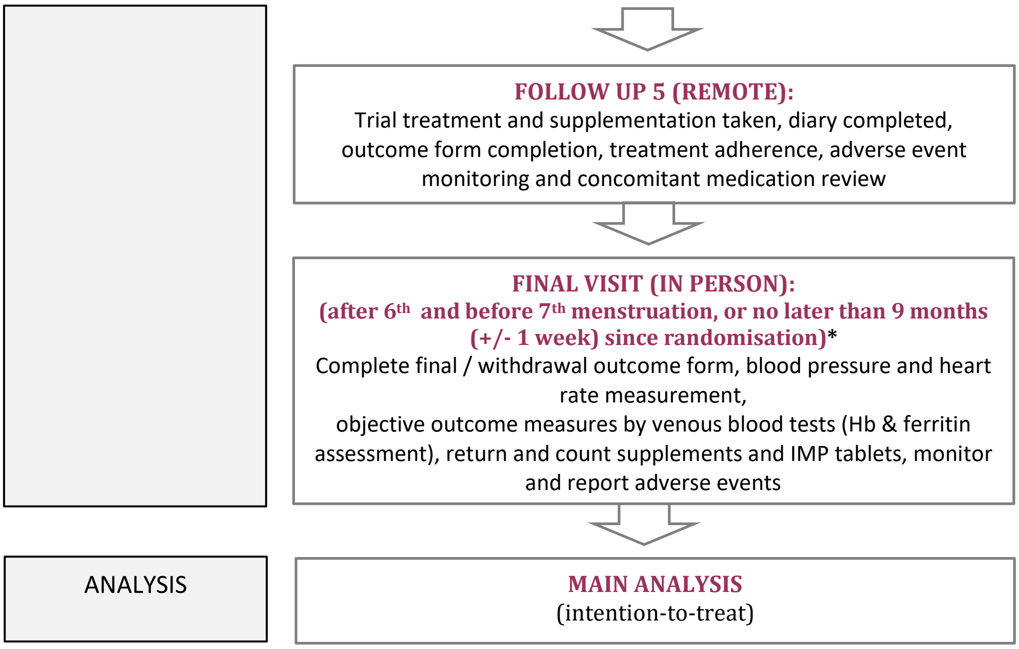
3.1 OVERVIEW

We will conduct an international, multicentre, placebo-controlled randomised trial. We will randomly allocate trial participants to receive TXA, or matched placebo taken over six menstrual periods. In addition, we will provide participants with standard of care iron and folic acid supplementation for 3 months from randomisation.

3.2 TRIAL FLOW CHART

Figure 1 – Flow chart of the WOMAN-3 trial





* We will ask participants to take the trial treatment during six consecutive menstrual periods starting from their 1st menstrual period after randomisation. The standard of care iron and folic acid supplements will be given for 3 months from randomisation. The final assessment will be performed as soon as possible after the sixth and before the seventh menstrual cycle or at early withdrawal. To account for variations in individual menstrual cycle lengths, the final visit should be completed within a window of nine months (+/- 1 week) post-randomisation.

A detailed schedule of events chart is included in Appendix II.

4 PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

4.1 SETTINGS, PARTICIPANTS, AND RECRUITMENT METHODS

We will conduct a multi-centre trial in South Asia and Sub-Saharan Africa including but not limited to Nigeria, Pakistan and Tanzania, where the prevalence of anaemia among women of reproductive age is ≥40% according to recent national surveys.[58-62] Recruiting in more than one country with a flexible recruitment approach will reduce the risk of under-recruitment due to natural disasters or political instability.

We aim to recruit a total of 4,000 participants (see sample size calculation in section 6.4 below). This includes 2,000 participants in the TXA arm and 2,000 participants in the placebo arm.

We will recruit participants from diverse settings where anaemia in women is more prevalent. This will include but will not be limited to higher education institutions, vocational training centres, institutions with professional and apprenticeship training schemes and at healthcare facilities with community outreach. Median age at first birth is less than 25 years old[63] in participating countries so recruiting in the proposed settings should facilitate enrolment of women prior to first conception and help reduce loss to follow-up. We will disseminate information about the trial via channels such as websites, newsletters, WhatsApp groups, wall posters and brief information leaflets (see appendix III for an example trial advertisement). Videos to explain anaemia and the trial (in local language) may be used if required and approved by local ethics committees.

We will use a two-stage participant consent procedure. The first stage will be an initial brief informed consent to allow for eligibility screening. The second stage will be detailed informed consent prior to enrolment. (Please see consent section 8.4, and participant information sheets and consent forms in Appendices IV-V).

4.1.1 Recruitment and enrolment strategies

To maximise recruitment and enrolment, we will employ a multi-faceted approach. The specific recruitment and enrolment approach used will be tailored to the local context, regulatory requirements, and infrastructure of each participating site and country. PPI groups have contributed to the overall strategies below. Specifically, PPI groups have requested that information on anaemia and its impact be made available for the education of young women who are the target population. This will be location specific and based on by local PPI and clinician advice.

- **Recruitment**
    - We will recruit from diverse settings such as educational institutions (e.g. colleges, universities and vocational training centres), healthcare facilities (including community outreach areas), and community organisations (e.g., women's groups).
    - Information about anaemia and its impact and the trial will be available in various formats, including group presentation by medical and nursing personnel, printed materials such as flyers, visual presentations, and short film clips.
    - Anaemia and trial information will be shared either in face-to-face meetings, via official channels (e.g. newsletters, noticeboards, campus radio stations, students WhatsApp groups), digital platforms (e.g. relevant social media channels, community websites, online forums) and at relevant community events.
    - Women who will act as champions within the community will be identified to disseminate trial information.
    - Word of mouth dissemination via local champions, community partners and trial participants will be used.

- **Enrolment**
    - Community and group meetings will be held where potentially eligible women will be invited. Information on anaemia, its impact and current treatments will be presented by appropriate healthcare professionals. Brief information about the trial will also be presented.
    - Potential participants who express initial interest will be given brief information about the trial so they can decide whether they want to take part.
    - Study visits will offer flexible timings, and travel or other incurred costs will be reimbursed.
    - Adequate time will be given for consent review and trial staff will be trained to clearly explain the study commitments and answer questions.
    - During consent, trial staff will use open dialogue to gauge participant understanding of demands and identify barriers to adherence to the trial treatment and visit schedule.
    - Participants will receive a thank you gift, newsletters and a contact card to support engagement.

4.2 ELIGIBILITY CRITERIA

4.2.1 Inclusion Criteria

- Adult women (aged 18 years and older)
- Having menstrual periods at least every 38 days that last at least 2 days
- Having anaemia (Hb < 120 g/L) according to point-of-care finger prick screening test
- Willing to provide informed consent
- Able to attend the in-person follow-up visits during the trial period

Individuals with known thalassaemia and sickle cell disease are eligible to participate and take the trial treatment but will not be given standard of care iron supplementation unless it is prescribed by their own treating clinician. They will continue to receive their usual standard care.

4.2.2 Exclusion Criteria

- Planning to get pregnant during the trial period
- Already taking TXA
- Known to have possible contraindications to TXA treatment (including allergy to TXA or its excipients, renal impairment, active thromboembolic disease, history of venous or arterial thrombosis, history of convulsion.)

4.3 TRIAL INTERVENTION

4.3.1 Name and description of investigational medicinal product (IMP)

Tranexamic acid is a synthetic derivative of the amino acid lysine that has an antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules, inhibiting the binding of plasminogen to fibrin. This results in stabilization of the preformed fibrin meshwork produced by secondary haemostasis.[64]

4.3.2 Legal status of drug

TXA is a generic drug sold under various trade names. It is licensed by the UK Medicines and Healthcare Products Regulatory Agency, the European Medicines Agency, the US Food and Drug Administration, Nigeria National Agency for Food and Drug Administration and Control, Tanzania Medicines and Medical Devices Authority and Drug Regulatory Agency of Pakistan for the treatment of various bleeding conditions.[65-67]

4.3.3 Investigator’s Brochure

The Investigator’s Brochure (IB) will include the latest version of the Summary of Product Characteristics of the TXA product to be used in the trial and detailed information about the safety and efficacy of TXA. We will review the IB annually and update it if necessary. We will include studies that provide reliable information on the safety and efficacy of TXA. Additionally, we will include relevant updates from TXA manufacturers.

4.3.4 Preparation and labelling of IMP

We will prepare an Investigational Medicinal Product Dossier (IMPD) which will contain data on the quality, production, labelling, release, storage, and control of the medicinal product being researched. The Quality section will provide information on the active medicinal product (TXA) and placebo. The Safety and Efficacy section will include a summary of data from all clinical and non-clinical studies, with an overall assessment of the risks and benefits. In brief, TXA which has Marketing Authorisation in the United Kingdom, or the European Union 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. The placebo will contain only inactive ingredients. TXA and placebo tablets and packaging will look 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), the label text will be identical on all packaging and comply with EU GMP guidance[68].

4.3.5 Drug storage and supply

The LSHTM CTU Global Health Trials Group will send a stock of IMP to the National Coordinating Centres (NCC) once all regulatory approvals have been obtained. National Coordinators will be overall responsible for their IMP stock and ensure compliance with sponsor requirements and national regulatory requirements. At sites, the Principal Investigator is overall responsible for the IMP. The IMP packs will be stored securely (in a dry place under ambient temperatures), where they are always accessible to the trial team for randomisation. Site stock levels will depend on their average recruitment rate. Each time a participant is randomised and entered in the trial database, one pack from the stock will be automatically deducted. When stock reaches a minimum level, the LSHTM CTU Global Health Trials Group will send additional stock of IMP. All used, lost, or damaged IMP must be reported to the LSHTM CTU Global Health Trials Group on a Drug Accountability Log.

4.3.6 Drug administration and dosage schedules

Participants will be randomly allocated to receive one gram of TXA or matching placebo to be taken three times daily for six menstrual cycles. Treatment will be for a maximum of five days per cycle. The maximum dose of TXA to be taken by each participant for the duration of the trial is ninety grams. The first dose of trial treatment for each cycle will be taken immediately when menstruation starts. Participants will be asked to take two 500mg tablets three times a day for up to five days (depending on the duration of their menstrual bleeding) from the first day of menstruation.

The selected TXA dosage of 1 gram three times daily aligns with standard recommendations for heavy menstrual bleeding (HMB) treatment.[65] The relatively frequent administration is necessary due to the short half-life of TXA.[65, 69] Most HMB treatment trials in a recent Cochrane review have used this regimen.[40] Similarly, the selected treatment duration aligns with current guidance and use in previous HMB trials. TXA can be given during menstruation as long as needed for up to four days [65] or up to five days in case of prolonged bleeding.[70] A regimen of up to five days has significantly reduced menstrual blood loss in various previous trials.[52-54, 71-74] No increased risk of side effects compared to placebo has been observed under this regimen (also see section 1.2 above).

We will ask participants to take the trial treatment for six menstrual periods post-randomisation and the standard of care iron and folic acid supplements from randomisation for three months. A mathematical model, designed to simulate the expected changes in haemoglobin levels and iron stores in response to TXA treatment and standard of treatment across multiple cycles, was used to determine the number of menstrual cycles for treatment. Our modelling estimates that with three months iron and folic acid supplementation and six months TXA treatment we expect that the mean haemoglobin value will have increased above the 120 g/L threshold (unpublished data on file, LSHTM CTU Global Health Trials group). Previous studies have shown that six months TXA treatment during menstruation is safe and acceptable.[40, 75, 76]

4.3.7 Known drug reactions

Although the patient information leaflet for TXA reports the following events as rare (<1 in 1,000) (itchy or swollen skin, colour vision disturbance, blood clot in the eye) and as very rare (<1 in 10,000) (allergic reaction, thrombosis, nausea, vomiting and diarrhoea), we do not anticipate an increase of these events in the WOMAN-3 trial. This is because the treatment period is short (total of thirty days over six to nine months and a maximum total dose of ninety grams of TXA). TXA is widely used for the treatment of heavy menstrual bleeding and is well tolerated. In many countries, TXA is available for purchase for HMB without the need for a prescription. A Cochrane systematic review on TXA for heavy menstrual bleeding concluded that "oral administration of antifibrinolytic therapy does not seem to be associated with any increase in major adverse events.[40]" Our more recent systematic review of randomised trials, mentioned in section 1.2 above, also found no evidence of increase in any adverse effects. TXA is widely used in elective surgery and data from randomised trials with tens of thousands of patients show no increase in thromboembolic events with TXA.[49, 50, 77-80] High intravenous doses of TXA (10g to 20 g) can cause seizures but there is no evidence that TXA causes seizures at the doses used in this trial. We will collect data on thrombosis, nausea, vomiting, diarrhoea and seizure routinely as adverse outcomes for all participants.

4.3.8 Interactions with other therapies

Because TXA is an antifibrinolytic, it might potentially counteract the thrombolytic effect of fibrinolytic preparations (such as Alteplase for heart attack treatment).

4.3.9 Trial restrictions and use of concomitant medication

Trial participants should receive all clinically indicated treatments required for their care. There is no restriction on the use of concomitant medication. Participation will not result in any needed treatment being withheld. If any contraindication to the trial treatment or iron and folic supplementation develops after randomisation (e.g. allergic reaction, thromboembolic event or the need for fibrinolytic treatment) the trial treatment or supplement should be stopped.

4.3.10 Assessment of adherence

We will measure adherence to the trial IMP by means of self-report, participant diary records and tablet count. Additionally, up to six hundred participants who are menstruating at the time of their study visit, will have a finger-prick blood sample taken using Mitra® cartridges (based on Volumetric Absorptive Micro-sampling (VAMS™) technology). We aim to include participants from each country. The trial staff will label the cartridges with the date and time of last IMP dose, date and time the sample was taken and with the participant Study Identification number. They will then send them to Dr Stanislas Grassin-Delyle's laboratory at the University Versailles Saint Quentin in France for analysis and determination of TXA levels. No participant identifiable data will be transferred to the laboratory. Storage and destruction of the blood samples will be handled in accordance with the requirements of each participating country. (Please see Appendix IX – 'Biological sample management' for details.)

4.3.11 Name and description of non-investigation medicinal product (NIMP)

To ensure all enrolled participants have access to standard of care (SOC) anaemia treatments, we will provide oral iron and folic acid supplementation free of charge.[81] Given that there are no local country guidelines in Nigeria and Pakistan, and for consistency across the trial, we will define SOC in line with the WHO (World Health Organisation) treatment guidelines.[82] In all participating countries, participants will be given approximately 120mg elemental iron and 400µg Folic acid daily for three months from randomisation. The NCCs, following their own country's procedure, will procure iron and folic acid supplements locally from reputable sources using recommended and licenced formulations.

In case of side effects, including nausea, vomiting, constipation, and gastrointestinal discomfort, the dose of iron can be reduced. If a participant cannot tolerate iron supplements, the supplements can be stopped.

4.4 OUTCOME MEASURES

All trial outcomes, including domain, measurement, specific metric, aggregation method and time point, as recommended by the SPIRIT-Outcomes 2022 Extension[83], are detailed in Appendix VI. We present a summary of all outcome measures below.

4.4.1 Primary outcome

Anaemia

The primary outcome is the proportion of participants with anaemia (Hb < 120 g/L, [84]) at the end of the intervention period. Haemoglobin will be measured using a venous blood sample at baseline and end of treatment/early withdrawal.

4.4.2 Key secondary outcomes

Anaemia severity, serum ferritin and haemoglobin levels

Secondary outcomes will include time to anaemia resolution and the Hb and serum ferritin concentration. We will also use WHO definitions for the grading of the severity of anaemia in non-pregnant women to determine mild, moderate, and severe anaemia levels.[84]

Iron status and iron deficiency anaemia

We will measure serum ferritin at enrolment and at the end of the intervention period to assess iron status. As ferritin alone can be misleading during inflammation, we will also measure C-reactive protein (CRP, a marker of acute inflammation) to statistically adjust ferritin values in the final analysis.[85, 86]

We will report change in iron status from baseline and iron deficiency using two thresholds: the traditional WHO cut-off of ferritin < 15 ug/L[86], and the newer clinical consensus definition of < 30 ug/L.[87] By combining ferritin and Hb levels, we will also determine the proportion of participants with iron deficiency anaemia.

Menstrual health, anaemia symptoms and wellbeing

We will assess participant reported secondary outcomes related to menstrual health and wellbeing [88] including menstrual bleeding (MB). We have aligned our outcomes with the 'core outcome set' (COS) for standardised outcome reporting in heavy menstrual bleeding intervention trials where possible (see Appendix VI).[89]

We will use a visual analogue scale to assess intensity and impact of menstrual bleeding - HMB-VAS; the SAMANTA scale, to assess the impact of menstruation on daily life and quality of life, addressing factors such as inconvenience and limitations posed by menstrual bleeding; the FACIT questionnaire to assess overall wellbeing with a focus on fatigue using the FACIT-fatigue subscale. These three instruments are established and validated to measure outcomes in clinical trials, with the SAMANTA scale being a validated menstruation specific tool.[90-92] We will also assess symptoms commonly reported in people with anaemia (dizziness, breathlessness, restless legs and pica (the urge to eat non-food items). The FACIT-fatigue subscale is already translated into local languages, and we will complete linguistic validation of the SAMANTA scale, HMB-VAS and anaemia symptoms before use. Participants will also be asked to record menstrual product usage throughout the study period as an objective measure of the impact of menstrual bleeding.[93]

We will compare the relevant mean end scores between treatment groups. We will also report participants' subjective assessment of change in menstrual bleeding from baseline, as detailed in Appendix VI.

4.4.3 Other secondary outcomes

Further menstrual health-related outcomes

We will assess menstrual cycle metrics, including frequency, duration, regularity and flow volume, and the occurrence, frequency, and severity of period pain [89]).

Hb concentration, serum ferritin and vital signs during follow-up visits

We will measure blood pressure, heart rate and HemoCue® finger prick tests to monitor Hb levels at each in person follow-up visit except the final/early withdrawal visit when a laboratory measurement of serum ferritin and Hb concentrations will be done as part of full blood count from venous blood samples.

Economic outcome measures

We plan to do a cost-effectiveness analysis which will be detailed in the SAP.

Satisfaction with trial treatment

At the final visit, we will assess participant satisfaction with the trial treatment.[89]

Treatment side effects and adherence

We will collect data on side effects of the trial treatments, as detailed in the outcome table in Appendix VI and in 'safety reporting' section 7.11. In addition, we will assess treatment adherence as outline in the 'assessment of adherence' section 4.3.10.

Participant's feedback about the trial

Throughout the trial, we will ask participants to provide open feedback on their trial experiences. We will also seek their agreement for future contact regarding result dissemination or further research.

4.5 PARTICIPANT AND PUBLIC INVOLVEMENT

This trial protocol was written after seeking the views of potential trial participants. We have involved a lay representative with lived experience of anaemia in the protocol development group. Women who would be invited to participate in the trial were involved in testing of the data forms and specifically the Participant Reported Outcomes (measuring menstrual health, anaemia symptoms and wellbeing) and the Diary. The Participants Information Sheets, Consent Forms and Posters have also been reviewed. We have also assessed willingness to take the trial treatment. We are involving women groups and organisations focussed on women's health from each country to advise on recruitment and retention, and for the dissemination of findings.

5 ASSIGNMENT OF TRIAL INTERVENTIONS

5.1 RANDOM SEQUENCE GENERATION, ALLOCATION CONCEALMENT AND BLINDING

We will randomly allocate women who fulfil the eligibility criteria to receive one gram TXA or matching placebo orally three times daily from the first day to the last day of their menstrual period for up to five days, over six menstrual cycles.

We will use block randomisation to increase the probability that each arm will contain a similar number of individuals. The block size will only be detailed in the IMP manufacturing process to safeguard against prediction of allocation sequence. An IT coding expert supported by an independent statistician (not involved in the conduct of the trial) will prepare the randomisation codes using a computer random number generator. They will then pass the list on to the IMP manufacturer, who will print randomisation codes on all participant treatment packs. Apart from the randomisation code, all participant treatment packs, and their content (three tablet bottles each containing 60 tablets of TXA or matched placebo) will look identical. The participant treatment packs will be placed in site boxes that will be shipped to the trial sites. At the trial sites, the research staff will confirm eligibility of participants and randomise participants to the next available lowest numbered treatment pack.

5.2 UNBLINDING

All participants, CTU and NCC staff working on the trial and all local site staff will remain blinded to the trial treatment allocation. In the event an adverse event develops believed to be related to the IMP, the drug can simply be stopped. However, if a clinician believes that a participant's care depends importantly upon knowledge of whether the participant received TXA or placebo, it is possible to unblind. The LSHTM CTU will provide an emergency 24-hour unblinding service that will reveal whether the woman received TXA or placebo. The investigator should complete an unblinding request/report form within five working days of unblinding. If a Suspected Unexpected Serious Adverse Reaction is reported, unblinding may be needed for reporting to Regulatory Agencies and Ethics Committees (see 'Safety reporting' section 7.11).

6 DATA COLLECTION, MANAGEMENT AND ANALYSIS

We have provided an overview of the trial procedures and patient timeline in Section 3.2 (trial flowchart) and Appendix II (schedule of procedures/events). Below, we provide details on assessments to be completed at each stage of the trial, and information regarding data management and analysis.

6.1 BASELINE

6.1.1 Screening

Trial staff in each country will invite potentially eligible women for screening. As many women screened will not be eligible for the trial, we will give information about the purpose of the screening and what it involves and obtain written consent for screening (stage 1 consent).

The screening will include:
- Questions to assess the inclusion and exclusion criteria listed in the eligibility criteria section above
- HemoCue® point-of-care test to screen for anaemia
- Collecting personal information to allow sites follow-up participants

Research staff will record the data in the Screening Form (see case report form (CRF) in Appendix VII). The trial team may not be able to provide care for anaemia, apart from the iron and folic acid supplements given in addition to the trial treatment. We will therefore advise all women with anaemia to seek care from their own health care professional.

We will invite fully eligible women to take part in the trial, provide them with detailed information, and obtain their consent (stage 2 consent, see consent section below for details.) Additionally, we will complete a separate Personal Information Form to allow for identification of participants (as there is no other means of confirming a participant exists) and to allow sites to follow-up participants. The form will be securely held separately from the trial data.

6.1.2 Assessments at enrolment (pre-randomisation)

After completing the Stage 2 consent procedure, research staff will complete the Enrolment Form that reconfirms eligibility, and collects medical history, vital signs, socio-demographic, anaemia- and menstruation-related data. We will also obtain venous blood sample for CRP, serum ferritin and full blood count. (see CRF in Appendix VII). If the enrolment visit occurs more than two weeks after the HemoCue® screening test, or if participants report that they have received a blood transfusion or intravenous iron infusion since then, eligibility must be reconfirmed by repeating the HemoCue® test.

6.1.3 Additional assessments for subgroup of participants to investigate main causes of anaemia

We will invite a subgroup of 300 participants to undergo further assessments aimed at estimating the prevalence of the main causes of anaemia among the trial population. A specific date will be set for each participating country (Nigeria, Tanzania, and Pakistan) from which participants will be recruited into the sub-group. We plan to recruit about 100 sub-group participants per country, this may vary depending on recruitment rate in each country. We will obtain consent for the following additional tests. All samples will be analysed in local accredited laboratories:

- Venous blood samples for red blood cell folate and vitamin B12, Hb electrophoresis (for thalassemia and sickle cell anaemia), microscopic malaria tests, creatinine, PT (Prothrombin Time), APTT (Activated Partial Thromboplastin Time),
- Urinary schistosomiasis (one complete urine sample),
- Stool samples for intestinal schistosomiasis and soil-transmitted helminths, including hook worm, round worm, and whip worm. (We will ask participants to collect three stool samples, ideally on consecutive days. Samples will be returned daily.)

Participants for this subgroup will receive an additional thank you present for the additional time needed for providing the samples. We will also reimburse transport costs if needed for all visits to the study site. (See CRF - Cause of Anaemia Data Form in Appendix VII)

6.1.4 Provision of allocated trial drugs, supplements, participant diary and menstrual products

After randomisation, participants will be provided with their allocated IMP, iron and folic acid supplements, and a supply of menstrual products (appropriate products may be pads/towels/tampons/menstrual cups). The menstrual products are needed for the standardized self-assessment of menstrual blood loss. We will also give participants a diary to complete for the duration of the treatment period. Study staff will provide both verbal and written instructions on how to take the IMP and supplements and how to complete the diary (see Appendix VIII). Participants will also receive a pocket-sized trial contact card (alert card) with their ID/randomisation number and trial contact information.

6.2 FOLLOW-UP

6.2.1 Assessments during follow-up

All participants will complete a diary for the treatment period which will be paper-based or electronic (depending on personal preference). Data recorded will include treatment adherence, menstrual bleeding, period pain, adverse effects, concomitant medication, and use of iron and folic acid supplements (see diary in Appendix VIII). Study staff will review the diaries at each follow-up and complete the relevant visit Outcome forms (see CRF in Appendix VII).

We will follow up participants during/after each of their next six menstrual periods. Participants will be followed up in person at follow-up visits 2, 4 and final visit/early withdrawal visit. Participants will be followed up remotely by phone or other preferred method at follow-up visits 1, 3 and 5. For up to 600 participants who are menstruating at the time of their in-person study visit, we will collect finger prick blood samples to assess TXA levels as described in section 4.3.10. In the event of adverse events, participants will be asked to attend the trial site for review.

If a participant does not have their sixth menstrual period approximately nine months from baseline, the final visit will be conducted at nine months (+/- 1 week).

In the event of early withdrawal, the Final/Withdrawal CRF will be completed.

During the final/early withdrawal visit, study staff will collect venous blood samples for laboratory testing of Hb, ferritin and CRP. A total of about 8 millilitres of blood will be needed.

These samples will be analysed in accredited local laboratories. Participants can receive their results via an agreed-upon communication method. Those with persistent anaemia at the end of study, or who refuse venous blood sampling, or do not wish to know their results, will be encouraged to seek external health care for further follow-up.

We will reimburse transport costs for all trial associated visits to the trial site (including visits for adverse event reporting and return of biological samples) if needed; Participants will also receive thank you presents. (The value will depend on local purchasing power and will be specified in the local ethics application form).

Participants will receive reminders (via their preferred means of communication) at an agreed frequency to take their IMP, complete their diary and attend study visits. This method of reminders was seen as suitable by the PPI groups.

6.2.2 Withdrawal

Participants can withdraw from the trial at any time. They may give their reason for withdrawal but do not have to. We will encourage completion of the withdrawal visit to ensure the participant is leaving the trial safely, but they can refuse this. We will encourage participants to let us know if they have medical or other concerns. If an adverse event is ongoing at withdrawal, we will ask the participant to continue follow-up of the event, but they are free to refuse.

If a participant withdraws from the trial, we will analyse data collected to the point of withdrawal; no data will be collected after withdrawal unless the participant gives permission. In all cases, we will respect the participant's wishes.

6.2.3 Retention

To minimise loss to follow-up, we will employ the following strategies:
- Recruit from settings where participants are more likely to be stable for the trial period e.g. engaged within education institutions, healthcare facilities and community settings with strong social support networks.
- Provide clear and detailed information in the Participant Information Leaflet on the requirements of the trial and assess a potential participant's ability to adhere with the trial protocol by asking questions around their schedule, availability, and whether they can attend necessary visits.
- Ensure that enrolment and follow-up sites are easily accessible and located in convenient locations
- Plan to carry out recruitment and follow-up as near as possible to where participants are recruited
- Ask participants for their preferred method of communication and frequency of reminders.
- Provide updates on the trial electronically if participants agree.
- Request participants to provide alternative contact information, if agreeable, for instances when they are unreachable (e.g. loss of mobile phone).
- Reimburse transport and other incurred costs where needed and provide thank you gifts for their time and commitment.
- Obtain local advice from PPI group(s) in each country
- Monitor retention figures closely and develop additional retention strategies if needed, based on literature evidence and team discussions.

6.2.4 Definition of end of trial

The end of the trial will be at completion of follow-up of the last participant. This would be no later than 10 months after randomisation of the last participant. This will allow for all participants to complete treatment, follow-up, and the post-treatment adverse event reporting period.

6.2.5 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.

- at the request of the Steering Committee following discussion with the Sponsor, e.g. responding to information from the Data Monitoring Committee
- other unforeseen events, e.g. civil unrest, war, natural disasters, or a pandemic.

We will develop trial specific standard operating procedures (SOP) and/or working practice documents (WPD) to ensure that trial closure and site close outs are in line with LSHTM policies and other relevant rules and regulations.

6.3 DATA MANAGEMENT

We will develop a detailed data management plan (DMP) explaining how we will ensure that data management complies with LSHTM policies, GCP, and the UK General Data Protection Regulation.[94] We will also comply with the data protection requirements of each participating country.

6.3.1 Source data

Source documents include but are not limited to participant personal information forms, paper CRFs, participant diaries, office logbooks, participant attendance diaries, correspondence, electronic memory of sphygmomanometers, laboratory equipment, and HemoCue® machines.

We will keep trial data confidential and stored securely. On all trial-specific documents other than the consent form and personal information form, and log of participants who wish to receive the trial results, we will refer to the participant by their participant ID number. Also, participants name will be linked to their participant ID on the screening and randomisation logs.

6.3.2 Access to source data

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

6.3.3 Data recording and record keeping

Authorised research staff will enter trial data onto paper CRFs, then a central trial database. Participants will be identified by a unique ID number. The LSHTM CTU Global Health Trials Group will provide an Investigator Site File (ISF) containing the essential trial documents, which the site must keep updated throughout the trial and stored after the end of the overall trial for 10 years or longer if required by relevant national regulatory authorities.

The Personal Information Form will be destroyed once the participant has completed the trial, no later than at the time of the final database lock. If the participant has agreed to be contacted again regarding the dissemination of results or related future research, we may keep their contact details for longer in a secure location in line with relevant data protection laws and for no longer than required.

6.3.4 Data storage

Trial data, source data and all documentation including consent forms which constitute the Trial Master File, will be stored for 10 years after the overall completion of the trial or longer if required by relevant national regulatory authorities.

6.4 STATISTICS AND DATA ANALYSIS

6.4.1 Sample size calculations

The sample size for a clinical trial depends on the baseline event rate and the size of the treatment effect. All women enrolled in the trial will be anaemic and will receive the standard care (micronutrient supplementation with iron and folic acid). To determine the baseline event rate (the prevalence of anaemia in the control group following treatment with daily iron/folic acid supplementation), we identified a systematic review of the effect of daily iron supplementation for anaemia in menstruating women. There was a 61% reduction in anaemia with daily iron supplementation (RR 0.39, 95% CI 0.25 to 0.60).[95] Assuming around a 60% reduction in anaemia with daily iron, the event rate in the control group will be around 40% (reduced from 100%). A study of 4,000 women would have over 90% power at the 0.01 level of significance to detect a 15% relative reduction in the prevalence of anaemia from 40% to 34% (RR=0.85) with oral TXA treatment. Because TXA is inexpensive and widely practicable even a modest reduction would be clinically worthwhile and probably cost-effective. The trial will therefore include about 4,000 women.

We have based our sample size calculation on the estimated anaemia prevalence in the control group following daily iron supplementation. However, the true rate of anaemia in the trial population after iron supplementation is unknown. Interim analyses may indicate a higher- or lower-than-expected overall event rate, or new information may emerge that alters assumptions about the TXA treatment effect over the course of six menstrual cycles, 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.

6.4.2 Statistical analysis

We will draft a Statistical Analysis Plan (SAP) for use by the Data Monitoring Committee during their ongoing review. We will finalise and publish the SAP on our trial website before the trial database is locked for the final analysis.

The primary analysis comparing TXA to placebo will be an intention-to-treat analysis. We will analyse the data and present statistics by randomised group. We will tabulate socio-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.

In a large trial such as WOMAN-3, 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. We will therefore adjust analyses for relevant variables pre-specified in the SAP based on the literature and biological plausibility.

Variables for planned subgroup analyses include severity of anaemia (mild, moderate, and severe). We will explore potential confounding in subgroup analyses. Randomisation creates treatment groups that are balanced; the strata of subgroups, however, may not be balanced.[96] 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 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 we will take the overall RR as the most reliable estimate of the RR in all subgroups.

We will describe other analyses regarding primary and secondary outcomes, including further subgroup analyses and sensitivity analyses in the SAP.

7 TRIAL MANAGEMENT AND MONITORING

7.1 TRIAL STEERING COMMITTEE

The Trial Steering Committee (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 accept the final protocol for first use in the trial and, throughout the trial, take responsibility for:

a) major decisions such as protocol amendments
b) monitoring and supervising trial progress
c) reviewing relevant information from other sources
d) considering recommendations from the Data Monitoring Committee
e) informing and advising the trial management group

The TSC will include (but will not be limited to) an independent chair, clinical trialist, representative from a participating country, statistician/epidemiologist, clinical expert in reproductive/menstrual health/anaemia, lay representative, Chief Investigators. At least 50% of the TSC members will be independent of the investigators. Appendix XI lists the names and roles of TSC members. We will aim to convene meetings annually unless there is need for more frequent meetings. A TSC Charter agreed at the first meeting will detail the conduct of business.

7.2 DATA MONITORING COMMITTEE

The Sponsor is primarily responsible for monitoring the safety of participants in the trial, overseen by an independent Data Monitoring Committee (DMC) to support the safety monitoring. The DMC will review accumulating trial data and advise TSC on the continuing safety of trial participants and those yet to be recruited. The DMC will include members with expertise in public health/reproductive health/anaemia, statistics, and randomised controlled trials.

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[97]. Appendix XII lists the DMC membership. 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, research ethics committees, regulatory agencies, investigators, steering committee, 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 or 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[98, 99]. An interim subgroup analysis would have to be even more extreme to justify disclosure.

7.3 TRIAL MANAGEMENT GROUP

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated through the LSHTM Clinical Trials Unit (CTU). The TMG will include the Chief Investigators, Principal Investigator, a trial manager, data manager and trial administrator. Additional members can be co-opted depending on the needs of the trial. The CTU and TMG 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):

- Maintaining the Trial Master File
- Identifying sites
- Assessing site suitability
- Confirming all approvals are in place before enrolment of participants and release of the trial treatment
- Providing training
- Providing study materials
- Data management
- 24-hour unblinding service
- Monitoring
- Ensuring data security and quality and observe data protection laws
- Safety reporting
- Ensuring the trial is conducted in accordance with the ICH GCP
- Progress updates
- Responding to questions about the trial
- Statistical analysis
- Publication of trial results
- Reporting to the DMC and TSC

7.4 NATIONAL COORDINATION FOR EACH PARTICIPATING COUNTRY

The National Coordinating Investigator for each participating country will be responsible for:

- Appointing and supervising national coordinating centre staff
- Identifying and supervising site principal investigators
- Ensuring that all national and local approvals (including ethics, regulatory agencies and import licences) are in place before the trial starts in their country
- Maintaining and updating NCC SOPs, and ensuring trial sites comply with ICH-GCP, the trial protocol, and any amendments.
- Creating and managing a compliant NCC Trial Master File, including secure archiving and handling of essential documents.
- Training and supporting trial staff and keeping them updated on trial procedures and current knowledge (there are training materials to assist with this).
- Monitoring recruitment progress and ensuring that targets are met across participating sites.
- Overseeing safety reporting to all relevant agencies and ensuring regulatory compliance.

- Managing IMP import, storage, distribution, and accountability, as well as consumables and equipment.
- Supporting trial sites with approvals, materials, and monitoring activities.
- Managing the country-level budget, site payments and financial reporting

7.5 SITE PRINCIPAL INVESTIGATOR

The Principal Investigator for each participating site will be responsible for:

- The overall conduct of the study at their site and ensuring compliance with the trial protocol and any relevant amendments, trial procedures and ICH GCP
- Obtaining all appropriate approvals/favourable opinions before trial start and during the trial as necessary
- Delegating trial responsibilities only to trained and qualified staff and documenting delegation appropriately.
- Training relevant staff and ensuring they remain informed about the trial protocol, procedures, and current knowledge (training materials will be provided in the Investigator's Site File and on the trial website to aid this).
- Ensuring that all potentially eligible women are considered promptly for the trial and that consent is obtained in line with approved local procedures.
- Ensuring participant confidentiality is maintained and compliance with all applicable data protection laws.
- Ensuring timely, complete, and accurate data collection and submission to the CTU Global Health Trials Group, including for safety reporting.
- Ensuring the Investigator's Study File is up-to-date and complete throughout the trial.
- Ensuring trial treatments at the site are appropriately managed and documented, including drug accountability and storage.
- Allowing access to source data for monitoring, audit, and inspection
- Archiving all essential trial documents (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.

7.6 RISK ASSESSMENT

We are conducting this trial in countries with high rates of women living with anaemia. The procedures to be carried out are routine and are low risk.

Biological sampling

We will complete routine finger-prick tests to check for anaemia. We will complete additional finger prick tests in up to 600 participants to check blood levels of the trial treatment. We will also collect small amounts of venous blood from all participants. The finger prick tests, and venous sampling could cause pain and discomfort. We will also collect additional blood, urine and stool samples from a subgroup of 300 participants. Participants are allowed to collect the urine and stool samples at home to minimise embarrassment. We have detailed in Appendix IX how we will safeguard all biological samples taken.

Adverse events

We will collect symptoms and adverse events associated with tranexamic acid, iron and folic acid supplementation, anaemia, and menstruation as outcomes on all women in the trial and these will be routinely reviewed by the independent DMC. Tranexamic acid has a well-known safety profile with risks of adverse events extremely low.

Questions about menstruation, health and wellbeing may cause embarrassment

The risk is low as we will engage with potential participants in advance to advise on how best to approach women and ask questions relating to these topics. Also, questions will be asked in private where conversations cannot be overheard.

Personal information

Sites will collect participants' personal information on a Personal Information Form including name, address, phone number and email address to allow for follow-up. This information will be separated from trial data and will only be used for follow-up of the participant.

7.7 CENTRAL MONITORING

We will conduct the trial in accordance with the current approved Protocol, ICH-GCP, Sponsor SOPs and trial procedure documents. We will develop a detailed monitoring plan. In brief, 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 NCC staff and site teams will be trained in GCP, the trial procedures and provided with extensive guidance. We will use central monitoring methods. We will monitor a sample of consent forms from all sites 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.

7.8 MONITORING AT LOCAL SITES

Sites flagged as high risk by central monitoring procedures may require additional onsite monitoring with source data verification. National Coordinating Investigators/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 participant 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. Laboratories carrying out blood and other biological sample analysis are also subject to monitoring. All source documents must be made available for ten years after the end of the overall trial or longer in line with relevant national regulatory requirements.

7.9 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. 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 them becoming known.

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 a serious protocol breach occurs or is suspected, the LSHTM CTU Global Health Trials Group must be informed within 24 hours of it becoming known. The LSHTM CTU Global Health Trials Group will report serious breaches to the sponsor, relevant regulatory authorities and research ethics committees within the timeline required by each participating country.

7.10 AUDITS AND INSPECTIONS

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

7.11 SAFETY REPORTING

The safety reporting guidance below applies to relevant events or reactions that happen after participants have been randomised to their trial treatment until 28 days after the last dose of the trial treatment.

The safety reporting procedure below will NOT apply to the following:

- Events that are present before randomisation unless they worsen during the trial.
- Events that are recorded as study outcomes on the outcome form up to the final study visit. These outcome events include anaemia and related symptoms (headache, dizziness, palpitations, breathlessness, fatigue), iron deficiency, heavy menstrual bleeding, irregular menstrual bleeding, menstrual pain/cramps, gastro-intestinal symptoms (including diarrhoea, constipation, nausea, vomiting, stomach pain/cramps, heartburn, darkened/black stools during iron supplementation), metallic taste in mouth during iron supplementation, colour vision disturbances, seizures, thrombosis and allergic reactions. These outcomes will be presented to the DMC for review and will therefore not be included in the definitions in section 7.11.1.

Any relevant events that are not study outcomes or that are study outcomes, but occur after the final visit, will be recorded up to 28 days after the last dose of the trial treatment. If the latter is unknown, events will be reported up to 28 days after the final visit.

At baseline, we will give participants a ‘contact card’ identifying them as a WOMAN-3 trial participants. We will ask them to present this card to anyone providing medical care to them, up to day 28 after their last trial IMP consumption. The card will have instructions to ensure the safety reporting procedures are followed. A safety reporting overview is provided in Appendix X.

7.11.1 Definitions

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 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 the trial treatment, 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 SmPC/IB.

7.11.2 Causality

When completing the Adverse Event reporting form, the National Coordinating Investigator/ 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 medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

If there is doubt about the causality, the National Coordinating Investigator/ Site Principal Investigator (PI) should 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.

7.11.3 Reporting Procedures

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the LSHTM CTU Global Health Trials Group. The flow chart in Appendix X provides an overview of the reporting procedures.

Non-serious Adverse Reactions (ARs)/Adverse Events (AEs)

Site investigators will report all non-serious ARs and AEs to the LSHTM CTU Global Health Trials Group using the AE reporting forms provided to them.

Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs)

The National Coordinating Investigator/Site PI or medical delegate must report SAEs and SARs to the LSHTM CTU Global Health Trials Group within 24 hours of becoming aware of the event using the AE reporting form. The National Coordinating Investigator/ Site PI or medical delegate will complete the form with as much detail as available at that time. A follow up report should be submitted promptly should any additional information arise. The National Coordinating Investigator/ Site PI or medical delegate will record the event with an assessment of seriousness, causality, and attribution. The CIs will assess expectedness using Version 1.1 dated 04/07/2025 of the Investigator's Brochure.

Events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

Suspected Unexpected Serious Adverse Reaction (SUSARs)

All SAEs assigned by the National Coordinating Investigator/ Site PI or medical delegate as suspected to be related to IMP-treatment and which are unexpected will be classified as SUSAR. SUSARs will be subject to expedited reporting to each participating Regulatory Authority, Ethics Committee, and the Sponsor within seven 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 a completed AE form (signed and dated) within 24 hours; add as much detail and (anonymised) information as is available at that time.
3. Submit any additional information promptly upon request.

Emergency contact details for advice on reporting SAEs and SUSARs can be found in the ISF. AE reporting forms will be submitted either via the trial database (see ISF for full details) or email to woman3data@lshtm.ac.uk. AEs that the National Coordinating Investigator/ Site PI or the LSHTM CTU Global Health Trials Group consider related to the trial medication will be followed either until resolution or until the event is considered stable.

Adverse event reporting to relevant authorities

The LSHTM CTU Global Health Trials Group, Sponsor Representative or National Coordinating Investigators will report all SUSARs to the relevant regulatory authorities, research ethics committees, 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. National Coordinating Investigators will be informed of all SUSARs for all studies sponsored by LSHTM that use oral TXA. All other adverse events will be reported as requested by the relevant authorities.

8 REGULATORY ISSUES

8.1 CLINICAL TRIALS AUTHORISATION

We will obtain clinical trials authorisation from the relevant competent authorities prior to participant recruitment in each country recruiting participants to the trial.

8.2 ETHICS APPROVAL

Prior to participant recruitment, we will obtain approval from the LSHTM Research Ethics Committee (REC), as well as from all relevant national/local RECs in the participating countries. Correspondence with ethics committee will be filed in the ISF and Trial Master File. We will comply with all reporting requirements stipulated by the RECs.

8.3 PROTOCOL AMENDMENTS

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

8.4 CONSENT

We will employ a two-stage informed consent process, including:

- Stage 1: Brief written informed consent prior to screening which covers only the screening procedures (Appendix IV)
- Stage 2: Detailed written informed consent prior to trial enrolment. We will have two versions of Participant Information Sheets and Consent Forms:
    - (1) for the 300 subgroup participants to assess the prevalence of main causes of anaemia in each country and (Appendix V(1))
    - (2) for all other participants (Appendix V(2))

Leaflets and forms will be personalised to each country and translated into local languages as required. Participants can choose to record their consent either electronically or by using a paper-based form. A copy of their signed consent will be given to the participant.

Authorised research staff will seek consent from each participant only after giving a full explanation, offering the information leaflet, and allowing time for consideration. They will respect the right of the participant to refuse to participate without giving reasons. All participants are free to withdraw at any time from the trial without giving reasons. The National Coordinating Investigators/ site Principal Investigators are responsible for ensuring that all participants are protected and participate voluntarily in an environment free from coercion or undue influence.

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

8.5 CONFIDENTIALITY

Trial staff will ensure that participants' confidentiality is maintained. Participants will be identified only by a participant ID and randomisation number on trial documents and the trial data. Where participants have chosen to complete their diaries electronically or have agreed to receive electronic reminders, their personal information needed to contact them will be securely stored electronically separated from the trial data. All documents will be stored securely and will only be accessible by trial staff and authorised personnel. The trial will comply with each participating country's Data Protection regulations including the UK General Data Protection Regulation.[94]

8.6 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.

8.7 SPONSOR

LSHTM will act as the main sponsor for this study. The sponsor may delegate responsibilities to others and in each case, this will be detailed in writing.

8.8 FUNDING

The trial set up and the recruitment of the first 200 patients is funded by The Jon Moulton Charity Trust. We have obtained a grant from Open Philanthropy for full funding. Trial sites will be reimbursed for staff time, consumables and participant recruitment costs associated with the conduct of the trial. An agreement with each country and site will be in place prior to the start of the trial.

The design, management and financing of the study are entirely independent of the manufacturers of TXA, which is not a new product.

8.9 DECLARATION OF INTEREST

We have no competing interests to declare.

8.10 PROTOCOL DEVELOPMENT COMMITTEE

This protocol has been developed by the Protocol Committee, including the following investigators who are responsible for developing, and agreeing to, the final protocol approved before recruitment of first patient. After start of recruitment, changes to the protocol will require the agreement of the TSC.

- Professor Ian Roberts, CTU, LSHTM, London, UK (Co-Chief Investigator)
- Professor Haleema Shakur-Still (Emeritus), CTU, LSHTM, London, UK (Co-Chief Investigator)
- Dr Sima Berendes, CTU, LSHTM, London, UK (Scientific Advisor)
- Ms Sana Shahid, Rawalpindi, Pakistan (Lay member)
- Professor Hilary Critchley, Centre for Reproductive Health, University of Edinburgh, UK (Clinical Advisor)
- Professor Rizwana Chaudhri, Translational Research Department, Shifa Tameer-e-Millat University, Islamabad, Pakistan (National Coordinating Investigator, Pakistan)
- Dr Aasia Kayani, Translational Research Department, Shifa Tameer-e-Millat University (Research Coordinator, Pakistan National Coordinating Centre, Pakistan).
- Dr Kiran Javaid, Translational Research Department, Shifa Tameer-e-Millat University (Assistant Research Coordinator, Pakistan National Coordinating Centre).
- Professor Folasade Adenike Bello, University College Hospital, Ibadan, Nigeria (National Coordinating Investigator, Nigeria)
- Professor Oladapo Olayemi, University College Hospital Ibadan, Nigeria (National Coordinating Investigator, Nigeria)
- Professor Projestine Selestine Muganyizi, Mbeya College of Health and Allied Sciences, University of Dar es Salaam, Dar es Salaam, Tanzania (National Coordinating Investigator, Tanzania)
- Ms Eni Balogun, CTU, LSHTM, London, UK (Senior Trial Manager)

- Ms Danielle Prowse, CTU, LSHTM, London, UK (Senior Data Manager)
- Dr Amy Brenner, CTU, LSHTM, London, UK (Assistant Professor)

9 DISSEMINATION POLICY

9.1 PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the TMG or Chief investigators. Publications will only contain anonymised data. The results of the trial will be reported first to trial collaborators. The first publication of the trial results will be either in the name of the Trial Collaborative Group (WOMAN-3 trial collaborators) or by named authors (depending on the journal's policy); these will include at least the trial's chief investigators, national coordinating investigators, site principal investigators, statistician, data manager and senior trial manager. Members of the TMG and the DMC will be listed and all collaborators at all sites will be cited by name. Authorship of parallel studies initiated outside of the TMG will be according to the individuals involved in the trial but must acknowledge the contribution of the WOMAN-3 collaborative group.

We aim to publish the main results of the WOMAN-3 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 all applicable trial registers. The results will be disseminated via the media, trial website, and relevant women's health organisations.

9.2 DATA SHARING

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; thereby researchers can make formal applications for data sharing. Afterwards, we will share the anonymised dataset via the LSHTM CTU Global Health Trials Group data sharing platform at freebird.lshtm.ac.uk or a similar platform. We will make all relevant trial materials available on the trial website.

10 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
APTT	Activated Partial Thromboplastin Time
BNF	British National Formulary
CI	Chief Investigator
95% CI	95% Confidence Interval
COS	Core Outcome Set (For Standardised Outcome Reporting In Heavy Menstrual Bleeding Intervention Trials)
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FBC	Full Blood Count
g	Gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HMB	Heavy Menstrual Bleeding
IB	Investigator’s Brochure
ICH-GCP	International Conference On Harmonisation-Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
L	Litre
LSHTM	London School Of Hygiene & Tropical Medicine
MB	Menstrual Bleeding
MBL	Menstrual Blood Loss
mg	Milligram
mL	Millilitre
NCC	National Coordinating Centre
NIMP	Non-Investigation Medicinal Product
uL	Microlitre
PBAC	Pictorial Blood Assessment Chart
PI	Principal Investigator
PPH	Post-Partum Haemorrhage
PPI	Participant And Public Involvement
PT	Prothrombin Time
REC	Research Ethics Committee
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOC	Standard Of Care
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group

TSC	Trial Steering Committee
TXA	Tranexamic Acid
US	United States
VAMS™	Volumetric Absorptive Micro-sampling
VAS	Visual Analogue Scale
WHO	World Health Organisation
WPD	Working Practice Documents

11 APPENDICES

The following are constituent parts of the Protocol. Some documents will be held separately due to size or need to personalise for each country.

APPENDIX I - MAIN CONTACTS

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APPENDIX IV - SAMPLE STAGE 1 PARTICIPANT INFORMATION SHEET & CONSENT FORM

APPENDIX V(1) - SAMPLE STAGE 2 PARTICIPANT INFORMATION SHEET & CONSENT FORM (FOR CAUSE OF ANAEMIA SUBGROUP

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APPENDIX X - SAFETY REPORTING OVERVIEW

APPENDIX XI - TRIAL STEERING COMMITTEE

APPENDIX XII - DATA MONITORING COMMITTEE

APPENDIX XIII - COUNTRY SPECIFIC PROTOCOL REQUIREMENTS

11.1 APPENDIX I - MAIN CONTACTS

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Sponsor	The London School of Hygiene & Tropical Medicine is the main sponsor for this trial. For further information regarding the sponsorship conditions, please contact: Research Governance and Integrity Office London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT, UK Email: RGIO@lshtm.ac.uk
Scientific Advisor	Sima Berendes, Assistant Professor Clinical Trials Unit London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT, UK Email: woman3@lshtm.ac.uk Phone: +44 (0)20 7958 8161
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Pakistan National Coordinating Centre	WOMAN-3 Trial Coordinating Centre STMU-LSHTM Research Collaboration Centre Department of Translational Research Shifa Tameer e Millat University (STMU) Park Road Campus, P/O Tarlai Kalan, Tehsil & District Islamabad, Pakistan Tel: +92 320 551 4960 Email: pakistan.woman3@lshtm-ctu.org
Tanzania National Coordinating Investigator	Projestine Selestine Muganyizi Professor of Obstetrics and Gynaecology Principal, Mbeya College of Health and Allied Sciences, University of Dar es Salaam, Dar es Salaam, Tanzania Email: promuga@gmail.com

Tanzania National Coordinating Centre	WOMAN-3 Trial Coordinating Centre UDSM-LSHTM Research Collaboration Centre University of Dar es Salaam, Mbeya College of Health and allied Sciences P.O. Box 35091 Dar es Salaam, Tanzania Phone: +255252500082 Email: tanzania.woman3@lshtm-ctu.org
TXA Laboratory/ Analysis	Professor Stanislas Grassin-Delyle Laboratory at UFR Simone Veil - Santé University Versailles Saint Quentin 2 Avenue de la source de la Bièvre 78180 Montigny le Bretonneux, France Email: s.grassindelyle@hopital-foch.org
Emergency 24-hour unblinding service	This emergency number will be used only in the event of urgent unblinding of the trial treatment: +44(0)7768 707500

11.2 APPENDIX II - SCHEDULE OF PROCEDURES/EVENTS

	Screening	**Enrolment**	**Follow up***					**Final visit*§**	**Post-study AE reporting^**
Timepoint	$-t_1$	t_0	t_{m1}	t_{m2}	t_{m3}	t_{m4}	t_{m5}	$t_{m6//}$ ≤9 mo.)*/Withdrawal visit	t_{ae}
	In person visit	In person visit	Remote follow-up	In person visit	Remote follow-up	In person visit	Remote follow-up	In person	Remote/or in person visit
Protocol activity	(day -14 to 0)	(Enrolment)	(1st menstr.)	(2nd menstr.)	(3rd menstr.)	(4th menstr.)	(5th menstr.)	(6th menstr.). After 6th menstruation and before 7th, or 9 months (+/- 2 weeks) or at early withdrawal	(28 days after last IMP dose/ t_f)
Screening									
Stage 1 informed consent	x								
Complete eligibility screening form	x								
Complete personal information form	x								
HemoCue® Hb screening test	x								
Provide detailed information (written and verbal) to eligible participants and book enrolment visit	x								
Enrolment									
Stage 2 informed consent		x							
Confirm eligibility		x							
Complete enrolment form		x							
Update personal information form		x	x	x	x	x	x		
Blood pressure & heart rate measurement		x							
Venous blood tests (Full blood count, serum ferritin, CRP)		x							
Additional venous blood (red blood cell folate and vitamin B12, Hb electrophoresis (for thalassemia and sickle cell anaemia), microscopic malaria tests, creatinine, PT		(x)							

(Prothrombin Time), APTT (Activated Partial Thromboplastin Time), urine, and stool tests (for 300 cause of anaemia subgroup participants only)									
Treatment allocation/ Randomisation		x							
Give allocated IMP		x							
Give supply of iron/folic acid supplements (start treatment)		x							
Give diary, period products and contact card		x							
Treatment/ Follow up									
Use treatment (TXA/Placebo)			x	x	x	x	x		
Give allocated IMP		x		x		x			
Iron/folic acid supplement taken for three months starting at randomisation			x	x	x				
Complete outcome form			x	x	x	x	x		
Blood Pressure and Heart rate				x		x			
HemoCue® Hb test				x		x			
Monitor & report adverse events			x	x	x	x	x		
Concomitant medication review			x	x	x	x	x		
Participant Diary completion (treatment adherence, pad count, pain, adverse event, and concomitant medication)			x	x	x	x	x		
Diary information review and upload to database if paper diary used			x	x	x	x	x		
Mitra® TXA testing (up to 600 samples only, from participants who took IMP < 12 hrs ago)			(x)	(x)	(x)	(x)	(x)		
Return and count iron/folic acid supplements				(x)		(x)			
Return and count IMP tablets				x		x			
Final visit									

Complete Final / Withdrawal outcome form			(x)	(x)	(x)	(x)		x	
Blood pressure & heart rate measurement								x	
Venous blood tests (Hb/FBC, serum ferritin, CRP)								x	
Satisfaction with trial								x	
Agreement for future contact								x	
Return and count iron/folic acid supplements								x	
Return and count IMP tablets								x	
Collect paper diary and upload data								x	
Monitor & report adverse events								x	
Other									
After final visit: Record lab results in outcome form and report results to participant if requested									x
Reimburse travel costs if needed	x	x	(x)	(x)	(x)	(x)	(x)	x	
Provide thank you present		(x)	(x)	(x)	(x)	(x)	(x)	x	
Advise participant to seek (external) clinical care if needed	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Post treatment period adverse event reporting									x

AE= adverse event, CRP= C-reactive protein, Hb= haemoglobin, FBC=full blood count, f= final, menstr./m= menstruation, mo.= months, t= timepoint

* Follow-up will be approximately 3 days after start of menstruation to maximum 14 days after end.

§ Final visit will be at early withdrawal or after 6th menstruation and before 7th or 9 months +/- 2 weeks

^ If time of last IMP dose unknown, AEs will be reported up to 28 days after the final visit

11.3 APPENDIX III - SAMPLE TRIAL ADVERTISEMENT

11.4 APPENDIX IV - SAMPLE STAGE 1 PARTICIPANT INFORMATION SHEET & CONSENT FORM

11.5 APPENDIX V(1) - SAMPLE STAGE 2 PARTICIPANT INFORMATION SHEET & CONSENT FORM (FOR CAUSE OF ANAEMIA COHORT)

11.6 APPENDIX V(2) – SAMPLE STAGE 2 PARTICIPANT INFORMATION SHEET & CONSENT FORM (FOR ALL OTHER PARTICIPANTS)

11.7 APPENDIX VI - LIST OF OUTCOMES

(Detailed list, in line with SPIRIT-Outcomes 2022 Extension reporting guidance[83]; the final version with revision as necessary will be included in the statistical analysis plan)

Outcome type/ Domain	Outcome	HMB-COS?* (y/n)[89]	Method of measurement	Metric & Method of aggregation	Timepoint^	Comment, reference
Primary						
Anaemia	Anaemia (Hb<120 g/L) *[objective]*	n	Haemoglobin (Hb) measured on venous blood (collected in EDTA tube, analysed as part of Full Blood Count, FBC)	Binary variable; Proportion at final timepoint	Final visit	WHO definition of anaemia for non-pregnant women aged 15–49 years[84]
Key Secondary						
Anaemia	Haemoglobin *[objective]*	n	Hb measured on venous blood (collected in EDTA tube, analysed as part of FBC)	Continuous variable (g/dL or g/L); Mean value at final timepoint; change from baseline	Baseline and Final visit	
Anaemia	Haemoglobin Time from randomisation to resolution of anaemia	n	Hb measured on venous blood (collected in EDTA tube, analysed as part of FBC) at baseline and HemoCue measurement at each in person visit	Tome from baseline to reach Hb of >12g/dl (or 120 g/L)	Baseline and Hb at each in person visit	
Anaemia	Mild Anaemia (Hb=110-119 g/L) *[objective]*	n	Haemoglobin (Hb) measured on venous blood (collected in EDTA tube, analysed as part of FBC)	Binary variable; Proportion at final timepoint	Final visit	WHO definition of mild anaemia in non-pregnant women (age>15 years)[84]
Anaemia	Moderate Anaemia (Hb=80-109 g/L) *[objective]*	n	Haemoglobin (Hb) measured on venous blood (collected in EDTA tube, analysed as part of FBC)	Binary variable; Proportion at final timepoint	Final visit	WHO definition of moderate anaemia in non-pregnant women (age>15 years)[84]
Anaemia	Severe Anaemia (Hb < 80 g/L) *[objective]*	n	Haemoglobin (Hb) measured on venous blood (collected in EDTA tube, analysed as part of FBC)	Binary variable; Proportion at final timepoint	Final visit	WHO definition of severe anaemia in non-pregnant women (age>15 years)[84]
Iron status	Ferritin *[objective]*	n	Serum ferritin (from venous blood sample)	Continuous variable (ug/L);	Final visit	Participants must not take iron supplements during the two days before the final

				Mean value at final timepoint		visit, because serum ferritin is acutely elevated, independent of body stores, for two days after a high dose of supplemental iron.[100]
Iron status	Ferritin	n	Serum ferritin from venous blood	Percent change from baseline	Baseline and Final visit	See below
Iron status	Iron Deficiency (Ferritin <15 ug/L, WHO definition[86] AND Ferritin <30 ug/L, new clinical consensus, as advocated in MacLean et al, 2023[87]) *[objective]*	n	Serum Ferritin (from venous blood sample)	Binary variable, Proportion at final timepoint [To compute CRP-adjusted ferritin levels– see comments]	Final visit	The SAP will include details on how ferritin values will be corrected by taking into account CRP levels (inflammation marker), because normal ferritin concentrations may mask an iron deficient state if inflammation is present.[8] [85] [86]
Inflammation	*C-reactive Protein (CRP)* *[objective]*	n	CRP by serum assay (from venous blood sample), Elevated CRP [>5 mg/L[86]] AND CRP concentration	Binary variable, proportion with elevated CRP value at final timepoint AND Continuous variable, mean value at final timepoint (for regression-correction approach in iron deficiency status analysis)	Final visit	Needed for CRP-adjustment of iron deficiency measure (serum ferritin), to avoid false-negative iron deficiency assessments, due to relatively high levels of inflammation/ infection in low- and middle-income settings (Georgieff 2020[8] , Suchdev 2017 [85], WHO 2020[86]) [Details will be provided in the SAP.]

Anaemia & Iron status	Iron-deficiency anaemia (Anaemia & Iron deficiency) *[objective]*	n	Presence of both anaemia (Hb<120 g/L) plus iron deficiency (ferritin <15 ug/L AND/OR <30 ug/L), measured as detailed above (using CRP-adjusted ferritin levels, as explained above)	Binary variable; Proportion at final timepoint	Final visit	
Menstrual health and wellbeing (MB-related)	Menstrual blood loss (MBL) *[subjective, PRO*]	y	Self-reported number of menstrual products used	Mean/median values or proportions	Self-assessed during menstrual periods and recorded in participant diary	[93]
Menstrual health and wellbeing (MB-related)	Change in MBL *[subjective, PRO*]	y	Participant's subjective assessment of intensity and impact of menstrual bleeding, using visual analogue scales (HMB-VAS)	Mean and/or median end score, mean change or proportion of participants reporting improvement	Baseline and Final visit	[90]
Menstrual health and wellbeing *&* *condition-specific Quality of Life (QoL)*	Degree of effect of menstrual disturbance on health-related QoL	y	Questionnaire, using the SAMANTA scale: sum of values	Mean end score or binary variable (using cutoffs pre-specified in the SAP) Change from baseline	Baseline, FU and Final visit	References for SAMANTA scale: [91, 101]
Other secondary						
						[89]
Menstrual health and wellbeing (MB-related)	Menstrual cycle metrics	y	Self-reported frequency, duration, regularity, and flow volume, included in participant diary	Mean/median values and proportions	Self-assessed during each menstrual period and	

					recorded in participant diary and/or at FU	
Menstrual health and wellbeing (MB-related)	Severity of menstrual pain (dysmenorrhoea)	y	Self-assessed, using pain scale 0-10 scale	Average score for all assessed cycles Difference in mean pain scores	Self-assessed during each menstrual period and recorded in participant diary	
Anaemia	Symptoms of anaemia	n	Symptoms of anaemia commonly reported (headache, dizziness, palpitations, breathlessness, fatigue)	Proportion of participants with symptoms; Mean score	Recorded at FU and Final visit	
Anaemia	Symptoms of anaemia	n	Other symptoms of anaemia commonly reported (restless legs syndrome and Pica (craving for non-food items). Use of FACIT scale for fatigue assessment.	Proportion of participants with symptoms; Mean score	In person FU and Final visit	Reference for validation of FACIT fatigue scale in iron-deficiency anaemia: [92]
Anaemia	Haemoglobin *[objective]*	y	HemoCue® finger prick test	Continuous variable (g/dL or g/L); Mean values	Screening and In person FU and Final visit if venous blood cannot be done)	
Anaemia/ general health	Symptoms of anaemia/ general health *[objective]*	n	Blood pressure and heart rate (measured with digital blood pressure device)	Continuous variables [mmHG and beats per minute (bpm)]; mean/median	Baseline, and at in person FU and Final visit	

				values and/or proportions		
Anaemia/ general health	Full blood count *[objective]*	(y)	In addition to Haemoglobin (Hb), as part of Full Blood Count measured on venous blood (collected in EDTA tube): Red Blood Cell count/ Erythrocyte count, Haematocrit (HCT)/Packed Cell Volume (PVC), Mean Corpuscular Volume - Red cell (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), White Blood Cell count (WBC)/ Total Leucocyte Count (TLC), Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils, Platelet Count	Mean values and/or proportions	Final visit	
Satisfaction	Degree of satisfaction with trial treatment (TXA/placebo)	y	Questionnaire question to assess degree of satisfaction with primary IMP on a Likert scale	Categorical/ binary variable; Median score and/or proportions	Final visit	
Satisfaction	No. of participants who would have liked to continue trial treatment	(y)	Patient self-report/ Interview report	Proportion	Final visit	
Adverse events/ Safety						
Adverse events/ safety	Side effects of TXA listed on summary of product characteristics	y	Patient self-report and Interview report. Routinely collected as outcome events: gastro-intestinal symptoms, including diarrhoea, nausea, vomiting; colour vision disturbances; seizures; headache; stomach pain/cramps; thromboembolic events and allergic reactions.	Proportions	At all FU visits and between visits; Self-assessed during each menstrual period and recorded in participant diary	
“	Known side effects of iron/folic acid supplement	n	Patient self-report, Interview report Routinely collected as outcome events: gastro-intestinal symptoms, including diarrhoea, constipation, nausea, vomiting, stomach	Proportions	At all FU visits and between visits; Self-assessed during	

			pain/cramps, headache, dizziness, heartburn, darkened/black stools, metallic taste in mouth, loss of appetite and allergic reactions.		menstrual periods and recorded in participant diary	
“	Adverse Events not routinely collected/ SAEs/ SARs	(y)	Adverse event report form	Proportions by Meddra coding (Lower Level/Preferred term)	At all FU visits and between visits	
Other/ process						
Adherence	TXA adherence *[objective]*	n	Finger prick blood samples via Mitra® cartridges (based on Volumetric Absorptive Micro-sampling (VAMS™) technology) for TXA quantification	Mean TXA concentration and/or proportion of participant with positive TXA sample and detailed in SAP)	FU visits (Up to 600 participants only)	
“	Adherence (IMP)	n	Diary & tablet count (from returned packs), e.g. average number of tablets/ g TXA per cycle	Proportions and/or means to be detailed in SAP)	Recorded in participant diary and at FU and/or Final visit	
“	Adherence (iron & folic acid)		Questionnaire question and tablet count (from returned packs)	Proportions and/or means (to be detailed in SAP)	In person FU and/or Final visit	
“	Reasons for discontinuing/ reducing treatment	n	Self-reported by participants, interview reported	Numbers and/or proportions	In person FU and/or Final visit	

Concomitant treatment	Additional menstrual bleeding-related treatment during trial	n	Self-reported by participants, interview reported	Type by BNF coding. Numbers and/or proportions	Recorded in participant diary	
“	Additional anaemia-related treatment during trial	n	Self-reported by participants, interview reported	Type by BNF Coding. Numbers and/or proportions	Recorded in participant diary and/or FU and/or Final visit	

* COS = Core Outcome Set: This relates only to heavy menstrual bleeding and not the disease under investigation (anaemia) as currently there is no Core Outcome Set developed for anaemia – Y= Yes, included, N= not included, (Y)= Related to one of the COS

Acronyms: BNF=British National Formulary; Hb= Haemoglobin; FBC= Full blood count; FU= Follow up visit;; MB= Menstrual bleeding; MBL= Menstrual blood loss; PRO= Participant reported outcome (self-reported by participant); QoL= Quality of life; SAE= Serious adverse event; SAR= Serious adverse reaction; SAP= Statistical Analysis Plan, VAS= Visual analogue scale

11.8 APPENDIX VII - SAMPLE CASE REPORT FORMS (CRF)

11.9 APPENDIX VIII - SAMPLE PARTICIPANT DIARY

11.10 APPENDIX IX - BIOLOGICAL SAMPLE MANAGEMENT

None of the samples will be collected and processed at LSHTM and none of the samples will be stored for future research. All samples will be collected in participating countries after seeking informed consent. The types of samples collected at different trial stages varies for different cohorts/subgroups as described below. A detailed laboratory manual will be developed for each country which will include how to take samples, how to record samples taken, shipping of samples from site to laboratory, which laboratories will be used for analysis of samples, how results will be provided and recorded, and destruction of samples. The manual will also include normal values for each country.

Samples collected during screening (all persons screened)

After obtaining stage 1 consent for eligibility screening, trained staff will complete routine finger-prick tests for anaemia rapid testing. Samples will be immediately analysed at the study site using HemoCue® Hb testing devices. All used sharps, material and supply will be disposed of as clinical waste in line with relevant safety rules and regulations and as outlined in local SOPs/WPDs.

Samples collected at baseline (all participants)

All enrolled participants will have venous blood samples taken by an appropriately qualified staff.

Samples collected at baseline (subgroup/cause of anaemia cohort only)

A subgroup of 300 participants will have additional venous blood tests and self-collected stool and urine samples to assess the prevalence of main causes of anaemia. The samples will be transported to a local accredited laboratories for analysis. Samples will be kept until the results have been checked by the trial team and confirmed as complete. All samples will then be destroyed and disposed of in line with each country's rules and regulations. Each sample will be recorded in a specific trial register indicating when and where it was obtained. Laboratories will be asked to maintain a destruction log detailing who made the disposal and when it was disposed.

Country specific SOPs and WPDs will provide detailed guidance on the collection, shipment/transport and disposal of samples and relating record keeping in line with all relevant rules and regulations.

Samples collected during follow-up visits

For in-person follow-up visits, trained staff will repeat the HemoCue® finger prick tests following the same procedures described above. An additional small finger prick blood sample may be collected among up to 600 participants using Mitra® cartridges (based on Volumetric Absorptive Micro-sampling (VAMS™) technology). The trial staff will label the cartridges with the date and time the sample was taken and with the participant Study Identification number. They will then place the cartridges into suitable sealed biological sample shipping bags.

No special storage is required. The Mitra® sample is stable up to 50° Celsius for about 1 month. Samples obtained with the (Mitra® cartridges) for TXA testing can be kept in the sealed bags at room temperature. Approval for shipment of biological samples to France will be obtained where required. Samples will be shipped within one week of the sample date to Dr Stanislas Grassin-Delyle's laboratory at UFR Simone Veil – Santé, University Versailles Saint Quentin (2 avenue de la source de la Bièvre, 78180 Montigny le Bretonneux, France) for analysis and determination of TXA levels.

No participant identifiable data will be transferred to the laboratory. A log of samples shipped will be maintained at each site. A log of all samples received, analysed and destroyed will be maintained by Dr Grassin-Delyle or delegate. Samples will be destroyed once results have been verified and database is locked. To minimise risk of unblinding treatment allocation, results for individual participants will be kept by Dr Grassin-Delyle until database lock and a report using aggregate data on compliance will be produced as the trial is ongoing.

A Materials Transfer Agreement (MTA) will be in place for each participating country before transfer of the dried blood samples to France.

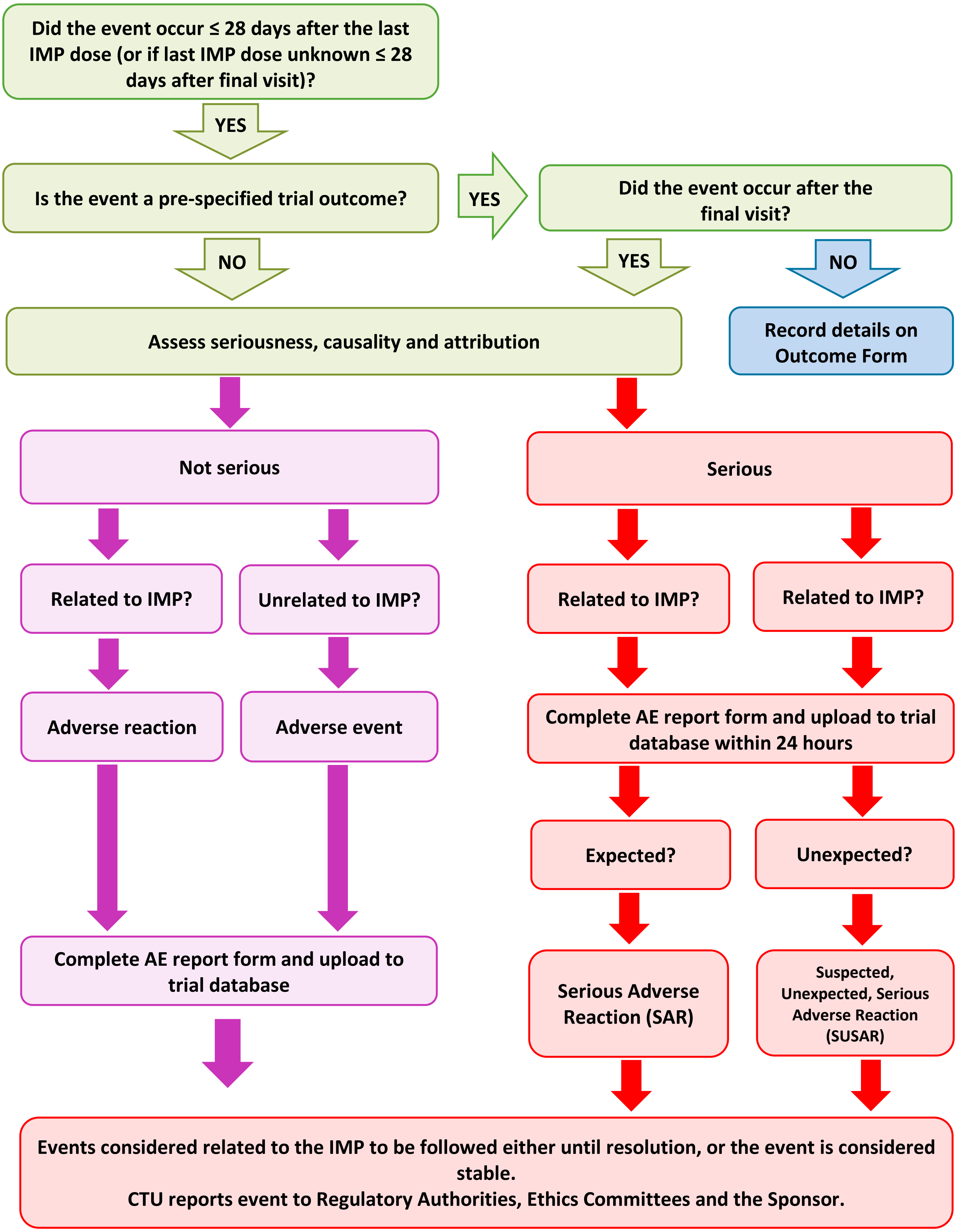
The National Coordinators in each country will ensure that the couriers and transport companies used to ship and deliver the blood samples are licensed and authorised as appropriate to handle such material.

Samples collected during final/early withdrawal visit (all participants)

Qualified staff will collect venous blood samples from all participants at early withdrawal / final study visit. The samples will be transported to local accredited laboratories for analysis and subsequent disposal in line with relevant rules and regulations. Samples will be kept until the results have been checked by the trial team and confirmed as complete. All samples will then be destroyed and disposed of in line with each country's rules and regulations. Each sample will be recorded in a specific trial register indicating when and where it was obtained. Laboratories will be asked to maintain a destruction log detailing who made the disposal and when it was disposed.

Country specific SOPs and WPDs will provide detailed guidance on the collection, shipment/transport and disposal of samples and relating record keeping in line with all relevant rules and regulations.

11.11 APPENDIX X - SAFETY REPORTING OVERVIEW



11.12 APPENDIX XI - TRIAL STEERING COMMITTEE

NAME (role)	AFFILIATION	RELEVANT EXPERTISE
Penelope Phillips-Howard (Independent Chair)	Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK	Professor of Public Health Epidemiology; Menstrual, sexual and reproductive health of adolescent girls and young women in low-income settings
Malcolm G. Munro (Independent expert)	Department of Obstetrics & Gynecology, University of California, Los Angeles, USA	Clinical Professor; Chair of the Women's Health Research Collaborative; Co-founder and past Chair of The International Federation of Gynecology and Obstetrics Menstrual Disorders Committee (FIGO-MDC).
Grasiana Festus Kimario (Independent expert)	Muhimbili University of Health and Allied Science, Tanzania	Public Health Professional; Project coordinator at Multilink Project, Liverpool School of Tropical Medicine; Youth, women's, and children's health, education and rights; Advocate for gender equality
Motunrayo Esan (Independent Stakeholder/ Lay member)	The EME Foundation, Ondo, Lagos, Ibadan and Abuja, Nigeria (A volunteer-run nonprofit committed to eradicating period poverty by increasing access to period products for disadvantaged females and comprehensive and positive menstrual education for everyone, including boys.)	Founder and Executive Director of EME Foundation; research interest in (in)security and social inequality; Lived experience of period shame inspired her commitment to advocate for research-driven solutions to period poverty and stigma
Ian Roberts (Co-Chief Investigator)	Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK	Professor of Epidemiology and Public Health; randomised controlled trials; large-scale international trials
Haleema Shakur-Still Co-Chief Investigator	Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK	Professor of Global Health Clinical Trials (Emeritus), maternal health trials, large-scale international trials
Sima Berendes	Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK	Assistant Professor; mixed-methods research, including international randomised controlled trials
Observers	May include delegates by the Funders and trial and data management experts	Grant oversight on behalf of the Funders and trial and data management input

11.13 APPENDIX XII - DATA MONITORING COMMITTEE

NAME	AFFILIATION	RELEVANT EXPERTISE
John Norrie (Independent Chair)	School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, UK	Professor of Health and Social Science Methodology; medical statistician and clinical trialist
Helen Weiss (Independent Expert)	Department of Infectious Disease Epidemiology and International Health, London School of Hygiene and Tropical Medicine	Professor of Epidemiology; medical statistician and epidemiologist; randomized controlled trials; menstrual health and adolescent health in low-income settings
Philip Ayieko (Independent Expert)	Mwanza Intervention Trials Unit (MITU), a collaborative health research unit established by the Tanzania National Institute for Medical Research and the London School of Hygiene and Tropical Medicine	Assistant Professor of Medical Statistics and Epidemiology; lead statistician at the MITU; randomised controlled trials

12 REFERENCES

1. WHO. *WHO Global Anaemia estimates, 2021 Edition Anaemia in women and children.* 2021 [cited 2022 June 25]; Available from: https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children.
2. Munro, M.G., et al., *The relationship between heavy menstrual bleeding, iron deficiency, and iron deficiency anemia.* Am J Obstet Gynecol, 2023. **229**(1): p. 1-9.
3. Nissenson, A.R., et al., *Economic burden of anemia in an insured population.* J Manag Care Pharm, 2005. **11**(7): p. 565-74.
4. Chavarro, J.E., et al., *Iron Intake and Risk of Ovulatory Infertility.* Obstetrics & Gynecology, 2006. **108**(5): p. 1145-1152.
5. Holzer, I., et al., *Iron status in women with infertility and controls: a case-control study.* Front Endocrinol (Lausanne), 2023. **14**: p. 1173100.
6. Stevens, R., A. Alvergne, and V.J. Vitzthum, *Low haemoglobin in arduous seasons is associated with reduced chance of ovulation among women living in the Bolivian altiplano.* Evolution, Medicine, and Public Health, 2024. **12**(1): p. 191-203.
7. Rahman, M.M., et al., *Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis.* Am J Clin Nutr, 2016. **103**(2): p. 495-504.
8. Georgieff, M.K., *Iron deficiency in pregnancy.* Am J Obstet Gynecol, 2020. **223**(4): p. 516-524.
9. Munro, M.G. and H.O.D. Critchley, *Our path from abnormal uterine bleeding and iron deficiency to impaired fetal development: A long and winding road.* International Journal of Gynecology & Obstetrics, 2023. **162**(S2): p. 3-6.
10. Say, L., et al., *Global causes of maternal death: a WHO systematic analysis.* The Lancet Global Health, 2014. **2**(6): p. e323-e333.
11. Mansukhani, R., et al., *Maternal anaemia and the risk of postpartum haemorrhage: a cohort analysis of data from the WOMAN-2 trial.* The Lancet Global Health, 2023. **11**(8): p. e1249-e1259.
12. Cresswell, J.A., et al., *Global and regional causes of maternal deaths 2009–20: a WHO systematic analysis.* The Lancet Global Health, 2025. **13**(4): p. e626-e634.
13. WHO. *Global nutrition targets 2025: stunting policy brief. World Health Organization*. 2014 [cited 2023 12 Sep]; WHO/NMH/NHD/14.3:[Available from: https://apps.who.int/iris/handle/10665/149019.

14. UN. *Global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development*. 2024 [cited 2024 26th March]; Available from: https://unstats.un.org/sdgs/indicators/indicators-list/.
15. WHO, *Global anaemia reduction efforts among women of reproductive age: impact, achievement of targets and the way forward for optimizing efforts*. 2020, World Health Organization: Geneva.
16. Stevens, G.A., et al., *National, regional, and global estimates of anaemia by severity in women and children for 2000-19: a pooled analysis of population-representative data.* Lancet Glob Health, 2022. **10**(5): p. e627-e639.
17. Haider, B.A., et al., *Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis.* Bmj, 2013. **346**: p. f3443.
18. Munro, M.G., *Heavy menstrual bleeding, iron deficiency, and iron deficiency anemia: Framing the issue.* International Journal of Gynecology & Obstetrics, 2023. **162**(S2): p. 7-13.
19. Auerbach, M., *Optimizing diagnosis and treatment of iron deficiency and iron deficiency anemia in women and girls of reproductive age: Clinical opinion.* International Journal of Gynecology & Obstetrics, 2023. **162**(S2): p. 68-77.
20. Fernández-Gaxiola, A.C. and L.M. De-Regil, *Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women.* Cochrane Database Syst Rev, 2019. **1**(1): p. Cd009218.
21. Harvey, L.J., et al., *Impact of menstrual blood loss and diet on iron deficiency among women in the UK.* Br J Nutr, 2005. **94**(4): p. 557-64.
22. Critchley, H.O.D., et al., *Menstruation: science and society.* Am J Obstet Gynecol, 2020. **223**(5): p. 624-664.
23. Thomas, S.L. and C. Ellertson, *Nuisance or natural and healthy: should monthly menstruation be optional for women?* The Lancet, 2000. **355**(9207): p. 922-924.
24. Konishi, T., et al., *Risk Factors for Postoperative Bleeding Following Breast Cancer Surgery: A Nationwide Database Study of 477,108 Cases in Japan.* World J Surg, 2022. **46**(12): p. 3062-3071.
25. Lv, M., et al., *A new model to predict the risk of major gastrointestinal bleeding in patients on direct oral anticoagulants (dabigatran and rivaroxaban).* Br J Clin Pharmacol, 2023. **89**(1): p. 253-260.
26. Tu, S.J., et al., *Associations of anemia with stroke, bleeding, and mortality in atrial fibrillation: A systematic review and meta-analysis.* J Cardiovasc Electrophysiol, 2021. **32**(3): p. 686-694.
27. Hellem, A.J., C.F. Borchgrevink, and S.B. Ames, *The role of red cells in haemostasis: the relation between haematocrit, bleeding time and platelet adhesiveness.* Br J Haematol, 1961. **7**: p. 42-50.
28. Ho, C.H., *Increase of red blood cells can shorten the bleeding time in patients with iron deficiency anemia.* Blood, 1998. **91**(3): p. 1094.
29. Valeri, C.R., et al., *Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss.* Transfusion, 2001. **41**(8): p. 977-83.
30. Weisel, J.W. and R.I. Litvinov, *Red blood cells: the forgotten player in hemostasis and thrombosis.* J Thromb Haemost, 2019. **17**(2): p. 271-282.
31. Boneu, B. and F. Fernandez, *The role of the hematocrit in bleeding.* Transfus Med Rev, 1987. **1**(3): p. 182-5.
32. Weiskopf, R.B., et al., *Heart rate increases linearly in response to acute isovolemic anemia.* Transfusion, 2003. **43**(2): p. 235-40.
33. Whittaker, S.R. and F.R. Winton, *The apparent viscosity of blood flowing in the isolated hindlimb of the dog, and its variation with corpuscular concentration.* J Physiol, 1933. **78**(4): p. 339-69.
34. Aarts, P.A., et al., *Blood platelets are concentrated near the wall and red blood cells, in the center in flowing blood.* Arteriosclerosis, 1988. **8**(6): p. 819-24.
35. Horne, M.K., 3rd, et al., *The effect of red blood cells on thrombin generation.* Br J Haematol, 2006. **133**(4): p. 403-8.
36. Peyrou, V., et al., *Contribution of erythrocytes to thrombin generation in whole blood.* Thromb Haemost, 1999. **81**(3): p. 400-6.
37. Taymor, M.L., S.H. Sturgis, and C. Yahia, *THE ETIOLOGICAL ROLE OF CHRONIC IRON DEFICIENCY IN PRODUCTION OF MENORRHAGIA.* Jama, 1964. **187**: p. 323-7.

38. Gleeson, N.C., et al., *The effect of tranexamic acid on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding.* Acta Obstet Gynecol Scand, 1994. **73**(3): p. 274-7.
39. Dockeray, C.J., et al., *The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid.* Eur J Obstet Gynecol Reprod Biol, 1987. **24**(4): p. 309-18.
40. Bryant-Smith, A.C., et al., *Antifibrinolytics for heavy menstrual bleeding.* Cochrane Database Syst Rev, 2018. **4**(4): p. Cd000249.
41. Schatz, F., et al., *The role of decidual cells in uterine hemostasis, menstruation, inflammation, adverse pregnancy outcomes and abnormal uterine bleeding.* Human reproduction update, 2016. **22**(4): p. 497-515.
42. Lockwood, C.J. and F. Schatz, *A biological model for the regulation of peri-implantational hemostasis and menstruation.* Journal of the Society for Gynecologic Investigation, 1996. **3**(4): p. 159-65.
43. Critchley, H.O.D., et al., *Physiology of the Endometrium and Regulation of Menstruation.* Physiol Rev, 2020. **100**(3): p. 1149-1179.
44. Gleeson, N., et al., *Endometrial fibrinolytic enzymes in women with normal menstruation and dysfunctional uterine bleeding.* Br J Obstet Gynaecol, 1993. **100**(8): p. 768-71.
45. Gleeson, N.C., *Cyclic changes in endometrial tissue plasminogen activator and plasminogen activator inhibitor type 1 in women with normal menstruation and essential menorrhagia.* American journal of obstetrics and gynecology, 1994. **171**(1): p. 178-83.
46. Hefnawi, F., et al., *Fibrinolytic activity of menstrual blood in normal and menorrhagic women and in women wearing the Lippes Loop and the Cu-T (200).* Int J Gynaecol Obstet, 1979. **16**(5): p. 400-7.
47. Ker, K., D. Prieto-Merino, and I. Roberts, *Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss.* British Journal of Surgery, 2013. **100**(10): p. 1271-1279.
48. Sentilhes, L., et al., *Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery.* New England Journal of Medicine, 2018. **379**(8): p. 731-742.
49. Shakur, H., 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, 2010. **376**(9734): p. 23-32.
50. 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**(10084): p. 2105-2116.
51. Callender, S.T., G.T. Warner, and E. Cope, *Treatment of menorrhagia with tranexamic acid. A double-blind trial.* British Medical Journal, 1970. **4**(5729): p. 214-6.
52. Edlund, M., et al., *Reduction of menstrual blood loss in women suffering from idiopathic menorrhagia with a novel antifibrinolytic drug (Kabi 2161).* British Journal of Obstetrics & Gynaecology, 1995. **102**(11): p. 913-7.
53. Freeman, E.W., et al., *A dose-response study of a novel, oral tranexamic formulation for heavy menstrual bleeding.* American Journal of Obstetrics and Gynecology, 2011. **205**(4): p. 7.
54. Lukes, A.S., et al., *Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial.* Obstetrics and gynecology, 2010. **116**(4): p. 865-875.
55. Nilsson, L. and G. Rybo, *Treatment of menorrhagia with an antifibrinolytic agent, Tranexamic acid (AMCA) - A double blind investigation.* Acta Obstetricia et Gynecologica Scandinavica, 1967. **46**: p. 572-580.
56. Peterson, K., et al., *[Treatment of hypermenorrhea with tranexamic acid]* Ugeskr Laeger, 1983. **145**(36): p. 2759-60.
57. Vermylen, J., et al., *A double blind study of the effect of tranexamic acid in essential menorrhagia.* Thrombosis et Diathesis Haemorrhagica, 1968. **20**(3): p. 583-7.
58. Government of Pakistan and UNICEF. *National Nutrition Survey 2018 - Full Report (3 Volumes) & Key Findings Report*. 2020; Available from: https://www.unicef.org/pakistan/reports/national-nutrition-survey-2018-full-report-3-volumes-key-findings-report.
59. National Population Commission, N.P.C. and Icf. *Nigeria Demographic and Health Survey 2018 - Final Report*. 2019; Available from: http://dhsprogram.com/pubs/pdf/FR359/FR359.pdf.

60. Habib, N., S.S. Abbasi, and W. Aziz, *An Analysis of Societal Determinant of Anemia among Adolescent Girls in Azad Jammu and Kashmir, Pakistan.* Anemia, 2020. **2020**: p. 1628357.
61. GBD 2021 Anaemia Collaborators, *Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990-2021: findings from the Global Burden of Disease Study 2021.* Lancet Haematol, 2023. **10**(9): p. e713-e734.
62. MOH, et al., *Tanzania demographic and health survey 2022 - final report*. 2022, Ministries of Health (MoH) [Tanzania Mainland and Zanzibar], National Bureau of Statistics (NBS), Office of the Chief Government Statistician (OCGS), and ICF.: Dodoma, Tanzania and Rockville, Maryland, USA.
63. Review, W.P. *Average Age of Having First Child by Country 2025.* 2025 [cited 2025 22nd May]; Available from: https://worldpopulationreview.com/country-rankings/average-age-of-having-first-child-by-country.
64. S, O. and O. U, *Amino-methyl-cyclohexane-carboxylic acid: AMCHA. A new potent inhibitor of the fibrinolysis.* Kelo Journal of Medicine, 1962. **11**(3).
65. EMC. *The electronic medicines compendium - tranexamic acid*. 2024 [cited 2024 25th Feb]; Available from: https://www.medicines.org.uk/emc/search?q=tranexamic+acid.
66. FDA. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*. 2024 [cited 2024 25th Feb]; Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.
67. NICE. *Menorrhagia (heavy menstrual bleeding): Tranexamic acid*. 2024 [cited 2024 27th Feb]; Available from: https://cks.nice.org.uk/topics/menorrhagia-heavy-menstrual-bleeding/prescribing-information/tranexamic-acid/#:~:text=Tranexamic%20acid%20is%20licensed%20for,women%20with%20severe%20renal%20impairment.
68. European Commission, *The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use - Annex 13: Investigational Medicinal Products*. 2010, European Medicines Agency (EMA): EU.
69. Maybin, J.A. and H.O. Critchley, *Medical management of heavy menstrual bleeding.* Womens Health (Lond), 2016. **12**(1): p. 27-34.
70. MacGregor, B., M.G. Munro, and M.A. Lumsden, *Therapeutic options for the management of abnormal uterine bleeding.* International Journal of Gynecology & Obstetrics, 2023. **162**(S2): p. 43-57.
71. Adawiyah, R., et al., *Randomized Controlled Trial of Tranexamic Acid's Effect on Bleeding Length: A Study on DMPA Users with Abnormal Uterine Bleeding Who Receive Low-Dose Oral Contraceptive Pill.* Journal of Biomedicine and Translational Research, 2020. **6**(1): p. 1-5.
72. Phupong, V., A. Sophonsritsuk, and S. Taneepanichskul, *The effect of tranexamic acid for treatment of irregular uterine bleeding secondary to Norplant use.* Contraception, 2006. **73**(3): p. 253-6.
73. Senthong, A.J. and S. Taneepanichskul, *The effect of tranexamic acid for treatment irregular uterine bleeding secondary to DMPA use.* Journal of the Medical Association of Thailand, 2009. **92**(4): p. 461-5.
74. Ylikorkala, O. and L. Viinikka, *Comparison between antifibrinolytic and antiprostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive devices.* British Journal of Obstetrics & Gynaecology, 1983. **90**(1): p. 78-83.
75. Muse, K., et al., *Long-term quality of life and safety of a new tranexamic acid menorrhagia treatment.* Fertility and Sterility, 2010. **94**(4): p. S13.
76. Muse, K., et al., *Tranexamic acid increases hemoglobin and ferritin levels in women with heavy menstrual bleeding.* J Womens Health (Larchmt), 2012. **21**(7): p. 756-61.
77. Chornenki, N.L.J., et al., *Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis.* Thromb Res, 2019. **179**: p. 81-86.
78. Devereaux, P.J., et al., *Tranexamic Acid in Patients Undergoing Noncardiac Surgery.* N Engl J Med, 2022. **386**(21): p. 1986-1997.
79. Taeuber, I., et al., *Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression.* JAMA Surg, 2021. **156**(6): p. e210884.

80. Murao, S., et al., *Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis.* Crit Care, 2021. **25**(1): p. 380.
81. WHO, *Guideline: Daily iron supplementation in adult women and adolescent girls*. 2016, Geneva: World Health Organization. 26.
82. WHO, *WHO Guidelines Approved by the Guidelines Review Committee*, in *Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women*. 2011, World Health Organization

Copyright © World Health Organization 2011.: Geneva.

83. Butcher, N.J., et al., *Guidelines for Reporting Outcomes in Trial Protocols: The SPIRIT-Outcomes 2022 Extension.* Jama, 2022. **328**(23): p. 2345-2356.
84. WHO. *Guideline on haemoglobin cutoffs to define anaemia in individuals and populations*. 2024 [cited 2024 23rd May]; Available from: https://www.who.int/publications/i/item/9789240088542.
85. Suchdev, P.S., et al., *Assessment of iron status in settings of inflammation: challenges and potential approaches.* Am J Clin Nutr, 2017. **106**(Suppl 6): p. 1626s-1633s.
86. WHO, *WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations*. 2020: World Health Organization. 82.
87. MacLean, B., et al., *Identification of women and girls with iron deficiency in the reproductive years.* International Journal of Gynecology & Obstetrics, 2023. **162**(S2): p. 58-67.
88. Hennegan, J., et al., *Menstrual health: a definition for policy, practice, and research.* Sex Reprod Health Matters, 2021. **29**(1): p. 1911618.
89. Cooper, N.A.M., et al., *Standardising outcome reporting for clinical trials of interventions for heavy menstrual bleeding: Development of a core outcome set.* BJOG: An International Journal of Obstetrics & Gynaecology, 2023. **130**(11): p. 1337-1345.
90. Perelló, J., et al., *Heavy Menstrual Bleeding-Visual Analog Scale, an Easy-to-Use Tool for Excessive Menstrual Blood Loss That Interferes with Quality-of-Life Screening in Clinical Practice.* Womens Health Rep (New Rochelle), 2022. **3**(1): p. 483-490.
91. Calaf, J., et al., *Development and Psychometric Validation of a Screening Questionnaire to Detect Excessive Menstrual Blood Loss That Interferes in Quality of Life: The SAMANTA Questionnaire.* J Womens Health (Larchmt), 2020. **29**(7): p. 1021-1031.
92. Acaster, S., et al., *Qualitative and quantitative validation of the FACIT-fatigue scale in iron deficiency anemia.* Health Qual Life Outcomes, 2015. **13**: p. 60.
93. Lee, E.J., et al., *Association between Patients' Self-Judgement, Coagulated Menstrual Blood, and Menorrhagia: Results from a Questionnaire Survey and Blood Test Analysis.* Medicina (Kaunas), 2023. **59**(5).
94. *Data Protection Act 2018, c. 12*. 2018 [cited 2024 28th March]; Available from: https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted.
95. Low, M.S., et al., *Daily iron supplementation for improving anaemia, iron status and health in menstruating women.* Cochrane Database Syst Rev, 2016. **4**(4): p. Cd009747.
96. VanderWeele, T.J. and M.J. Knol, *Interpretation of subgroup analyses in randomized trials: heterogeneity versus secondary interventions.* Ann Intern Med, 2011. **154**(10): p. 680-3.
97. Group., D.S., *A proposed charter for clinical trial data monitoring committees: helping them to do their job well.* Lancet, 2005. **365**(9460): p. 711-22.
98. Peto, R., 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): p. 1-39.
99. Haybittle, J.L., *Repeated assessment of results in clinical trials of cancer treatment.* Br J Radiol, 1971. **44**(526): p. 793-7.
100. Moretti, D., et al., *Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women.* Blood, 2015. **126**(17): p. 1981-9.
101. Sinharoy, S.S., et al., *Prevalence of heavy menstrual bleeding and associations with physical health and wellbeing in low-income and middle-income countries: a multinational cross-sectional study.* Lancet Glob Health, 2023. **11**(11): p. e1775-e1784.