Tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial

CLINICAL TRIAL PROTOCOL

Effect of tranexamic acid on coagulation in a sample of participants in the WOMAN trial:

WOMAN–ETAC study

Protocol Number: ISRCTN76912190

This Protocol is to be used in conjunction with the Full Protocol of the WOMAN Trial

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1. BACKGROUND

1.1. The WOMAN Trial Summary
Obstetric haemorrhage is the leading cause of maternal mortality globally. Of the 14 million mothers who have postpartum haemorrhage (PPH) each year, about 1–2% will die, with an average interval from onset to death of about 2–4 h. Even with appropriate management, about 3% of vaginal deliveries will result in severe PPH. Most of these deaths are in low-income and middle-income countries, but in the UK haemorrhage is one of the five leading causes of maternal mortality. The volume of blood lost, which affects mortality and the need for hysterectomy, can be reduced by direct methods when possible (eg, by treating uterine atony). However, supporting a patient’s haemostatic mechanisms by preventing clot breakdown by using tranexamic acid could offer additional benefit.

WOMAN is a large, pragmatic, randomised, double-blind, placebo-controlled trial in 15 000 women. It aims to determine the effect of early administration of tranexamic acid (TXA) on mortality, hysterectomy, and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events) in women with clinically diagnosed PPH. The use of health services and safety, especially thromboembolic effect, on breastfed babies will also be assessed. All legally adult women with clinically diagnosed PPH after vaginal delivery of a baby or caesarean section are potentially eligible. The fundamental eligibility criterion is the responsible clinician’s uncertainty as to whether or not to use an antifibrinolytic agent in a particular woman with PPH.

Women eligible for inclusion are randomised and treatment started as soon as possible. After assessment of eligibility and appropriate consent, the next consecutively numbered treatment pack is taken from a box of eight packs. After a patient has been randomised, the outcome in hospital must be collected even if the trial treatment is interrupted or not actually given.

Assuming a control group event rate of 2.5% for mortality and 2.5% for hysterectomy, with 1% of women having both a hysterectomy and then dying, a study with 15 000 women would have over 90% power (two-sided alpha=5%) to detect a clinically important 25% reduction from 4% to 3% in the primary endpoint of mortality or hysterectomy.

The primary outcome is the proportion of women who die or undergo hysterectomy, and the primary cause of death will be described. Secondary outcome measures include death, surgical interventions, blood transfusion, health status measured with the EQ-5D, thromboembolic and other relevant medical events, need for mechanical ventilation, and health status of breastfed baby/ies.

The main analyses will be intention-to-treat. Results will be presented as appropriate effect estimates with a measure of precision (95% CI). Subgroup analyses for the primary outcome will be based on: type of delivery (vaginal or caesarean section); administration or not of prophylactic uterotonics; and whether the clinical decision to consider trial entry was based mainly on estimated blood loss alone or on haemodynamic instability. Time from delivery to randomisation will also be explored. The full protocol of the WOMAN Trial is published at http://www.trialsjournal.com/content/11/1/40.

1.2. Background to the WOMAN–ETAC trial
Haemostasis has evolved in order to maintain the integrity of the vasculature. Normal haemostasis is the controlled activation of clot formation and clot lysis that stops haemorrhage without inappropriate thrombosis formation. This means that haemostasis is achieved by two systems working together, the coagulation system, ie the system that produces blood clots and the fibrinolytic system which dissolves clots.

The fibrinolytic system acts as a balance to the coagulation system, preventing excess clotting by breaking down fibrin. Fibrinolysis is mediated by tissue-type plasminogen activator, which activates plasmin which degrades fibrin. Fibrinolysis can be detected in blood samples using a variety of standard laboratory
measures such as fibrinogen level, fibrinogen degradation products, D-dimer levels and euglobulin lysis time.

In recent years, global coagulation tests, such as thromboelastometry or thromboelastography, have been developed, and it has been suggested that these tests have the advantage of rapid bedside diagnosis for fibrinolysis and therefore they provide the possibility of early initiation of treatment.\[1,2\] Thromboelastometry evaluates the viscoelastic properties during blood clot formation and lysis. Thromboelastometry defines various parameters; the clotting time (CT) is the period from the start of the analysis until the start of clot formation, normally until the 2mm amplitude is reached. The clot formation time (CFT) is defined as the period until an amplitude of 20 mm is reached. The maximum amplitude of the curve is defined as the maximum clot firmness (MCF). The clot lysis index (CLI) at 30 and 60 min (CLI30, CLI60) describes the ratio between the MCF and the amplitude 30 and 60 min after clotting time, and gives information about the fibrinolysis. The maximum lysis (ML) represents the maximum fibrinolysis detected during the measurement.\[3\]

Haemostatic changes during delivery and postpartum: During delivery, when the placenta separates from the uterine wall, sequences of physiologic and haemostatic changes occur aimed at reducing bleeding: strong myometrial contractions, increased platelet activity, a massive release of coagulant factors and a parallel increase in the fibrinolytic activity. Fibrin deposition over the placental site and clots within supplying vessels play a significant role in the hours and days following delivery. Increased levels of markers of fibrinolysis including platelet activators, fibrin-fibrinogen degradation products\[4] and D-dimer\[4-6] have been reported in the postpartum period. ROTEM results for pregnant and non-pregnant women have shown good correlation with those obtained from standard coagulation tests.\[7\] Although few studies have investigated the fibrinolytic enzyme system among pregnant Nigerian women, available reports indicate significant increase in levels of fibrinogen and other related enzymes during pregnancy\[8-9] consistent with those reported among Caucasians.\[8\]

Haemostatic changes during postpartum haemorrhage: The haemostatic changes which occur in women who develop PPH are relatively poorly understood. There is some evidence that massive PPH is associated with reduction in levels of platelets, fibrinogen, Factor V, and Factor VIII leading to prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) as well as consumption of antithrombin and increased levels of fibrin degradation products (D-dimer).\[10\] To the best of our knowledge there is no published data about the changes in ROTEM parameters during postpartum haemorrhage.

Antifibrinolytics and obstetric haemorrhage: There is a theoretical benefit to the use of TXA in obstetric haemorrhage. Fibrin is known to be an important structural component of uteroplacental blood vessels, and fibrinolytic activity is inhibited in the vicinity of trophoblast cells in the terminal sections of the spiral arteries.\[11,12\] Placental bleeding appears to result from structural weakness of and vascular defects in placental blood vessels. Placental abruption (abruption placentae) is characterised by activation of the fibrinolytic system\[13\], and TXA has been used to secure local haemostasis and to reduce the risk of premature labour as the drug is known to cross the placental barrier.

A systematic review\[14\] was conducted to review the evidence for the use of TXA in obstetric haemorrhage. The review identified three randomised controlled trials\[15-17\] of TXA, all concerning its use in postpartum haemorrhage. The three trials included a total of 461 participants of whom 235 were randomised to receive TXA and 226 were randomised to a control group. Of the three included trials, two were of women who had caesarean section delivery\[16-17\] and one was of women who had spontaneous vaginal delivery.\[15\]

In Gai 2004\[16\] and Gohel 2007\[17\]; one dose of 1 g TXA was administered intravenously 10 and 20 minutes, respectively, before incision. The trial by Yang 2001\[15\] compared four groups. One group (n=94) received a single dose of 1 g TXA intravenously, another group (n=92) received a single dose of 0.5 g TXA intravenously, the third group (n=92) received a single dose of 0.5 g aminomethylbenzoic acid intravenously and the fourth group (n=87) served as a control group. For the purpose of this review only the comparison of the group that received 1 g of TXA versus control was included in the analysis (a total of 181 out of 365 participants).
The primary outcome of the review was mortality. However, mortality was not reported in the trials by Yang 2001\textsuperscript{[15]} and Gai 2004\textsuperscript{[16]}. There were no deaths in the Gohel 2007 trial\textsuperscript{[17]} Gai 2004\textsuperscript{[16]} and Yang 2001\textsuperscript{[15]} did not report thrombotic events. Gohel 2007\textsuperscript{[17]} reported that no thrombotic events occurred and that no participants required blood transfusion.

Combining the results of the three trials, the use of TXA statistically significantly reduced mean blood loss by 92 mL, 95% CI 76 mL to 109 mL compared to no treatment. There was no evidence of heterogeneity between trials (I\textsuperscript{2}=0\%, \chi\textsuperscript{2}=1.44, degrees of freedom=2, p=0.49). Adverse reactions were reported in Yang 2001\textsuperscript{[15]}; two participants in the TXA group developed nausea (RR 4.63, 95\% CI 0.23–95.1). Gohel 2007\textsuperscript{[17]} reported no adverse reactions in any participant in the study. Gai 2004\textsuperscript{[16]} reported transient mild adverse reactions, but the number of participants affected and the type of adverse reactions were not described.

The authors concluded that the systematic review and meta-analysis of three randomised controlled trials provides some evidence that a single dose of 1 g of TXA given intravenously reduces mean blood loss within 2 hours postpartum. However, the included trials were of low methodological quality. The trials provided no data on maternal mortality which was the primary outcome measure of this systematic review. The duration of follow-up in the included trials was short and it is therefore possible for adverse events to have occurred after the study period. TXA is not completely eliminated from the blood until 9–18 hours after administration\textsuperscript{[18]}, although plasma concentration of 1 g of TXA is reduced by half after two hours.

The overall conclusion of the review was that there is currently no information from high quality randomised controlled trials on the effects of antifibrinolytic agents on obstetric haemorrhage. Although TXA is considered in some guidelines for the management of PPH as a treatment option the current evidence is unsuitable to make firm recommendations, and adequately powered, high quality randomised controlled trials are therefore needed.\textsuperscript{[19]}

1.3. **Aim, Hypothesis and Outcome of the WOMAN–ETAC trial**

**Aim:** The WOMAN trial aims to determine the effect of the early administration of tranexamic acid on clinical outcomes (mortality, hysterectomy and other morbidities) in women with clinically diagnosed postpartum haemorrhage. It will provide a reliable scientific basis for recommendations as to whether or not tranexamic acid should be used in the treatment of PPH. If TXA reduces mortality in women with PPH, this would be of considerable significance worldwide. However, it will not provide information on any changes in coagulation parameters which occur in women who develop PPH nor will it provide any insight into the mechanism of action of TXA in these women.

The proposed WOMAN-ETAC study will be nested in a cohort of the WOMAN trial participants and aims to evaluate the effect of TXA on markers of coagulation in a sample of WOMAN trial participants. Standard coagulation parameters (platelets, fibrinogen, PT and aPTT time and D-dimer) and ROTEM® parameters measured after in vitro activation with tissue factor (EXTEM) and inhibition with aprotinin (APTEM) will be determined (maximum lysis, maximum strength [Maximal Clot Firmness (MCF)], time from start to when the waveform reaches 2mm above baseline [Clotting Time (CT)], time from 2mm above baseline to 20mm above baseline [Clot Formation Time (CFT)], time to lysis [CLT (10\% difference from MCF)], time to Maximum strength [MCF-t], Clot elasticity [MCE]).

**Hypothesis:** The hypothesis is that the administration of tranexamic acid will reduce markers of fibrinolytic activity in women with a clinical diagnosis of postpartum haemorrhage.

**Outcome:** The primary outcome is to evaluate the effect of tranexamic acid on fibrinolysis 30 minutes after the first dose is given. Fibrinolysis will be measured with D-dimer, fibrinogen level and using ROTEM parameters previously reported to be associated with fibrinolysis (ie MCF, CA\textsubscript{10}, CA\textsubscript{15}, CLI\textsubscript{30} and CLI\textsubscript{60}).\textsuperscript{[20]}

As a secondary outcome we will evaluate the relationship between coagulation parameters and mortality. Other relevant clinical outcomes including mortality, hysterectomy and other surgical interventions will be reported, but the WOMAN trial will provide the most reliable estimates of the effect of TXA on these outcomes.
2. METHODS

2.1. Trial Design
The WOMAN-ETAC study is nested within the WOMAN trial and will include 200 of its participants. The WOMAN trial is a large, pragmatic, randomised, double blind, placebo controlled trial of adult women, who have clinically diagnosed postpartum haemorrhage and who fulfil the eligibility criteria. They will be randomised to receive either TXA or placebo. The eligibility criteria are based on the uncertainty principle.

Participating hospital: The study will be conducted at the University College Hospital, Ibadan, Nigeria. The University College Hospital fulfils the required criteria to host the study namely (1) the site is already actively recruiting for the WOMAN trial, (2) the burden of PPH is significant in the country where the hospital is located, (3) the site is able to provide routine laboratory services required in the WOMAN-ETAC study, (4) the laboratory will maintain a standardised method of analysis for the duration of the trial, (5) it will provide an investigator with overall responsibility for ensuring that the procedures are carried out as per protocol.

Number of patients needed: Assuming that the D-dimer mean and standard deviation values in the control group will be 9,000 ng/ml and 7,200 ng/ml respectively, taking into account that we will adjust for baseline measurement (ANCOVA) and assuming that the correlation between baseline and follow-up is 0.4, a study with 180 patients would have about 90% power (two sided alpha=5%) to detect a reduction of 30% in the mean D-dimer value in the tranexamic group.

Blinding: The blinding of the trial treatment will be as per the WOMAN trial. In summary, tranexamic acid and placebo ampoules will be indistinguishable. Tranexamic acid will be manufactured by Pharmacia (Pfizer, Sandwich, UK) and placebo by South Devon Healthcare NHS Trust, UK. The treatment packs will be prepared by an independent clinical trial supply company (Brecon Pharmaceuticals Limited, Hereford, UK). Correct blinding and coding of ampoules will be assured by independent random testing of each batch by high performance liquid chromatography to confirm the contents.

2.2. Eligibility Criteria
- All women who fulfil the eligibility criteria for the WOMAN trial are also eligible for this study. There are no additional eligibility criteria.
- All legally adult women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section.
- Where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in a particular woman with PPH.

2.3. Consent
Consent procedures will be as per the WOMAN trial protocol. In summary, following delivery of her baby, and once a woman has been diagnosed with PPH, a critical clinical emergency situation exists. The risk of death is highest early after delivery. The process by which information will be given and consent obtained will depend on the need for urgent clinical intervention and her physical, mental and emotional state. Informed consent will be obtained from patients if physical and mental capacity allows. If patients cannot give consent, proxy consent will be obtained from a relative or representative. If a proxy is unavailable, then consent can be deferred or waived. Where consent is deferred or given by a proxy, the woman will be informed about the trial as soon as possible and consent obtained for continuation. To minimise the need for multiple information sheets and consent forms, one form which combines the WOMAN trial and the WOMAN-ETAC study will be used (see Appendices 1, 2a and 2b).
2.4. Study Overview

All clinically indicated treatment is given.

Report adverse events as per protocol (up to day 42).

**WOMEN FULLY ELIGIBLE FOR THE WOMAN TRIAL ARE ALSO ELIGIBLE FOR THE ‘WOMAN-ETAC STUDY’**

All legally adult women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section

Where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in a particular woman with PPH

Follow appropriate consent process

1. N = 100 RANDOMISE to the WOMAN trial (TXA)
   Entry form completed
   OBTAIN VENOUS BLOOD SAMPLE IMMEDIATELY AFTER RANDOMISATION
   GIVE FIRST DOSE of randomised treatment IMMEDIATELY SAMPLE IS TAKEN
   Complete ROTEM analysis and routine coagulation parameters of venous sample;
   COMPLETE SUBSTUDY INITIAL DATA; COMPLETE OTHER LAB ANALYSIS
   AT 30 MINUTES AFTER 1ST DOSE: REASSESS, IF SECOND DOSE INDICATED
   OBTAIN VENOUS BLOOD SAMPLE
   GIVE SECOND DOSE of randomised treatment IF INDICATED
   Complete ROTEM analysis and routine coagulation parameters of venous sample;
   COMPLETE POST INITIAL TREATMENT DATA; COMPLETE ROUTINE LAB ANALYSIS

2. N = 100 RANDOMISE to the WOMAN trial (Placebo)
   Entry form completed

COMPLETE OUTCOME FORM AT DISCHARGE, DEATH OR DAY 42 (WHICHEVER IS EARLIER)
2.5. Randomisation

Women will be randomised in accordance with the WOMAN trial protocol. In summary, after eligibility has been confirmed using the Entry Form and the locally approved consent procedures has been completed, women will be randomly assigned. Randomisation will be balanced by centre, with an allocation sequence based on a block size of eight. A local pack system that selects the lowest numbered treatment pack from a box containing eight numbered packs will be used. Apart from the pack number, the treatment packs will be identical. Once the treatment pack is opened and confirmed as intact, the woman will be included in the trial whether the allocated treatment started is given or not and the Entry Form completed. All site investigators and trial coordinating centre staff will be masked to treatment allocation.

2.6. Procedures after randomisation, before and after first dose of treatment administration

Immediately a patient is randomised, a total of 15 mL of venous blood will be taken. Immediately after the blood is taken, the first dose of the trial treatment will be given. Administration of the trial treatment will follow the WOMAN trial protocol. The blood taken will be prepared and analysed as follows:

a) Blood sample collection

At baseline, 15 mL of blood will be collected from each patient.

- 2 tubes of 5 mL each will be obtained in 5 mL vacutainer tubes containing 0.5 ml sodium citrate (0.109mol/L) for routine coagulation tests and thromboelastometry (ROTEM) analysis.
- 5 mL will be obtained in a 5 ml vacutainer tube containing EDTA.K3 for platelet and haemoglobin.

b) Blood sample analysis

Blood for Activated Partial Thromboplastin Time (APTT), prothrombin time (PT) and International Normalized Ratio (INR), Fibrinogen, and D-dimer assays will be assayed using HumaClot Junior automated coagulation analyser (Human, GmBH, Germany). The blood sample will be centrifuged at 3000 g for 20 min and analysed.

Activated Partial Thromboplastin Time (APTT): The term ‘partial thromboplastin’ indicates that the reagent contains phospholipids (as a substitute for the platelet membrane) but no tissue factor, distinguishing it from the PT. All procoagulant factors except FVII and FXIII are measured by this assay. Platelet-poor plasma is ‘activated’ by a 3-minute pre-test incubation with the APTT reagent. In addition to the phospholipids, this reagent contains a contact activator that is a fine suspension of negatively charged particles (kaolin, celite or ellagic acid). The sample is then recalcified and the time taken to fibrin strand formation is the APTT.

Prothrombin time (PT) and International normalized Ratio (INR): is the time taken to fibrin strand formation when platelet-poor plasma is recalcified in the presence of thromboplastin (tissue factor and phospholipid). The PT result is expressed as an international normalised ratio or INR, which provides a result standardised for local reagents and methodology.

Fibrinogen assay: Fibrinogen will be assayed after sampling with a HumaClot Junior automated coagulation analyser (Human, GmBH, Germany) according to standard procedures.

Platelets and haemoglobin assay: Platelet and haemoglobin will be determined using a five parameter particle counter Sysmex XS 1000i (Sysmex Corporation, Kobe, Japan).

D-dimer assay: D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two crosslinked D fragments of the fibrinogen protein. Blood for D-dimer assays will be collected in 5 ml tubes containing 0.5 ml sodium citrate (0.109mol/L). The sample will be centrifuged and assayed with a HumaClot Junior automated coagulation analyser (Human, GmBH, Germany) following manufacturer’s instructions.

Thromboelastometry procedure (ROTEM®): Thromboelastometry (ROTEM coagulation analyzer [Pentapharm, Munich, Germany]) is a whole blood assay performed to evaluate the viscoelastic properties
during blood clot formation and lysis. It uses a ball-bearing system for power transduction, which makes it less susceptible to mechanical stress, movement, and vibration. In order to standardise the in vitro coagulation process and also to speed up the analysis for thromboelastography, coagulation is mildly activated with tissue factor from rabbit brain for the EXTEM test and for the APTEM test, aprotinin is added to inhibit fibrinolysis when using the ROTEM® analyser.

The ROTEM® analysis will be performed at 37°C, in parallel, on two of the four channels (INTEM, EXTEM). All pipetting steps and mixing is standardised by utilising an automated electronic program. The following ROTEM® parameters will be analysed:

- clotting time (CT)
- clot formation time (CFT)
- maximum clot firmness (MCF)
- amplitude of clot at 15, 30 and 60 minutes min (CA_{15}, CA_{30}, CA_{60})

Venous blood will be drawn immediately before the loading dose is given. A further sample of blood will be drawn after 30 minutes of the loading dose and before the second dose is given (if clinically indicated).

Blood samples will be collected for ROTEM analysis in 5 ml tubes containing 0.5 ml sodium citrate (0.109mol/L). Samples will be kept at 37°C after sampling procedure and during analysis procedure. EXTEM and APTEM assays will be carried out.

EXTEM test mildly activates haemostasis via the physiological activator tissue factor. The result is influenced by extrinsic coagulation factors, platelets and fibrinogen. EXTEM is a screening test for the (extrinsic) haemostasis system. This assay is not influenced by heparin (heparin inhibitor included in the EXTEM reagent).

APTEM test is an EXTEM based assay in which fibrinolysis is inhibited by aprotinin in the reagent. A significant improvement of the clot in APTEM compared to EXTEM allows detection of fulminant hyperfibrinolysis.

### 2.7. Procedures after treatment administration

**a) Blood sample collection**

Fifteen millilitres of blood will be collected from each patient 30 (± 15) minutes after administration of first dose of treatment and before a second dose is given if clinically indicated. 2 x 5 mL will be obtained in a vacutainer tubes containing 0.5 mL sodium citrate (0.109mol/L) ROTEM analysis, PT, aPTT, INR, Fibrinogen assay and D-dimer assay. 5 mL will be obtained in a 5 mL vacutainer tube containing EDTA.K3 for platelet and haemoglobin.

**b) Blood sample analysis**

Will be carried out as per baseline.

### 2.8. Data Collection

Data will be collected as per the WOMAN trial (ie relevant entry data to assess eligibility and randomisation details and outcome data at death in hospital or 42 days after randomisation, whichever occurs first). In addition, the following additional information will be collected (see Appendix 3):

- information on time blood sample is taken
- time trial treatment is administered
- time laboratory analysis started and completed
- treatment given which may affect coagulation
- adverse events
- technical problems with analysis
- treatment used which may affect coagulation
2.9. Preparation and Storage of ROTEM Reagents

All reagents should be considered as potentially hazardous and care must be taken in handling the reagents in order to minimise spillage. ROTEM reagents are to be stored at 2–8°C in a refrigerator where the temperature is routinely monitored. A temperature monitoring log for the refrigerator should be maintained. Once opened, ROTEM reagents have a limited shelf life (EXTEM, 8 days after opening; APTEM, 14 days after opening). When opening a new bottle of reagent, the expiry date indicating the life of the reagent after opening is to be written on the reagent label. Out of date reagents are not to be used. Full instructions will be provided in the Trial Study File.

a) Analysing quality control samples on the ROTEM analyser

Routine Quality Control (QC) analysis should be processed at least on a weekly basis by trained personnel. Full procedure for QC analysis will be provided in the Trial Study File.

b) Performing a measurement on the ROTEM

Only trained personnel can perform ROTEM measurements. All samples and reagents are to be handled as potentially infectious. Full procedure for performing the EXTEM and APTEM will be provided in the Trial Study File. Training for key personnel will be provided by TEM Innovations GmbH on site before the start of the trial. New team members may be trained by the site lead Investigator for the WOMAN-ETAC study.

c) Recording and back-up of ROTEM data

ROTEM analysis data will be stored on the machine. Back-up of all files must be done immediately after an analysis has been completed. Each back-up will be transferred to the TCC and a copy should be filed in the Trial Study File.

d) Quality control of standard laboratory tests recording and data collection

Quality Control of the HumaClot Junior (Human, Germany) will be done in accordance with manufacturer’s instructions. QC reports will be maintained in the site laboratory and made available to the trial team, monitors and auditors as required.

Data output will be produced on paper copies. Where thermal sensitive paper is used, these will be copied/scanned to prevent degradation of the output. Paper copies will be transferred to the TCC by email.

2.10. Adverse Events

Any untoward medical occurrence affecting a trial participant up to day 42 will be reported in line with the WOMAN trial protocol.

Potential risks associated with the WOMAN-ETAC study: The WOMAN-ETAC will involve two venepunctures about 30 minutes apart. This may cause pain and bruising at the puncture site. The results of the routine laboratory tests may be used to guide treatment options in line with local procedures. However, the ROTEM tests are being done for research purposes only and should not be used to guide treatment options.

2.11. Unblinding

In general there should be no need to unblind the allocated treatment. If some contraindication to antifibrinolytic therapy develops after randomisation, eg clinical evidence of thrombosis, the trial treatment should simply be stopped and all usual standard care given. Unblinding should be done only in those rare cases when the clinician believes that clinical management depends importantly upon knowledge of whether the patient received tranexamic acid or placebo. In those few cases when urgent unblinding is considered necessary, a 24-hour telephone service will be available and details provided in the Investigator’s Study File and wall posters. The caller will be told whether the patient received antifibrinolytic or placebo. An unblinding report form should be completed by the investigator.
2.12. Analysis

Both intention to treat and per-protocol analysis will be done. Demographic and other baseline characteristics will be tabulated. Descriptive statistics for continuous variables will include the mean, standard deviation, median, range, and the number of observations. Categorical variables will be presented as numbers, and as percentages of those patients who had the assessment. All statistics will be reported by treatment group.

The intention-to-treat data set will comprise all randomised patients, irrespective of treatment actually taken. Patients will be considered to be randomised at the point that the treatment allocation is made.

The per-protocol data set will comprise that subset of the randomised patients who satisfy the eligibility criteria and who received the first dose of treatment and where the baseline blood sample was taken before administration of trial treatment and follow-up blood sample was taken at 30 minutes (±15 minutes).

In the primary analysis the TXA group will be compared with the placebo group. Comparisons between groups at follow-up will be made after adjustment for baseline levels with adjustment for time between first and second blood samples.

We will evaluate the difference in mean value of D-dimer at 30 minutes after TXA administration. We will also evaluate the change in fibrinogen levels, and ROTEM parameters (EXTEM) which have been described to be associated with increased fibrinolysis (MCF, CA10, CA15, CLI30, CLI60). Secondary analyses will be conducted to describe the incidence of fibrinolysis in PPH. In addition, the ability of each of the coagulation parameters collected to predict mortality will be explored.

A detailed Statistical Analysis Plan setting out full details of the proposed analyses will be finalised before the trial database is locked for final analysis.
3. ORGANISATION

3.1. Sponsor
The WOMAN-ETAC trial is sponsored by the London School of Hygiene & Tropical Medicine (LSHTM) and its responsibilities coordinated by the Trial Coordinating Centre (TCC). The TCC may delegate responsibilities to third parties which will be outlined in relevant agreements.

3.2. Protocol Committee
The following people have had input into this protocol and have agreed the final version:

- Bukola Fawole (Consultant Obstetrician – overall responsible at site for WOMAN-ETAC study)
- Oladapo Olayemi (Consultant Obstetrician – Site Principal Investigator for WOMAN trial)
- Chris O Aimakhu (Consultant Obstetrician – Co-investigator, responsible for participant recruitment)
- Adenike Bello (Consultant Obstetrician – Co-investigator, responsible for data transfer)
- Olayinka Ogunbode (Consultant Obstetrician – Co-investigator, responsible for participant recruitment)
- Taiwo Kotila (Consultant Haematologist – Co-investigator, responsible for routine tests)
- Modupe Kuti (Consultant Chemical Pathologist – Co-investigator, responsible for routine tests)
- Ian Roberts (Chief Investigator of WOMAN trial)
- Pablo Perel (Statistical advisor)
- Haleema Shakur (Protocol development lead coordinator, trial and data management oversight)

Dr Olayinka Ogunbode will be involved in the organisation, conduct and analysis of this study as part of his Doctor of Medicine degree.

3.3. Trial Steering Committee (TSC)
A TSC for the WOMAN trial is in place and will be informed of this nested study. Decisions of the TSC may impact directly the continuation of the WOMAN-ETAC study. If required by the TSC, information about the WOMAN-ETAC study will be reported routinely.

3.4. Data Monitoring Committee (DMC)
Adverse events which are directly associated with the WOMAN-ETAC study will be reported to the DMC. Otherwise there will be no routine review of the accumulating data for the WOMAN-ETAC study by the DMC.

3.5. Trial Co-ordinating Centre Responsibilities
The TCC will act on behalf of the Sponsor and will be responsible for ensuring that all Sponsor’s responsibilities are carried out. The responsibilities will include (but not limited to):

- Maintain the Trial Master File;
- Identify trial site;
- Confirm all approvals are in place before start of the trial at a site;
- Provide training about the trial;
- Ensure study materials are available;
- Data management centre;
- 24-hour advice and unblinding service;
- Report about the progress of the study;
- Respond to any questions about the trial;
- Ensure data security and quality and observe data protection laws;
- Safety reporting;
- Ensure trial is conducted in accordance with the ICH GCP;
- Statistical analysis;
- Oversee publication of trial results.
3.6. Site Investigators Responsibilities

- Ensure all necessary approvals are in place prior to starting the trial;
- Delegate trial related responsibilities only to suitably trained and qualified personnel;
- Train relevant medical and nursing staff who see obstetric patients and ensure that they remain aware of the state of the current knowledge, the trial and its procedures (there are wall charts, pocket summaries and a set of slides to assist with this);
- Agree to comply with the final trial protocol and any relevant amendments;
- Ensure that all women with postpartum haemorrhage are considered promptly for the trial;
- Ensure consent is obtained in line with local approved procedures;
- Ensure that the patient entry and outcome data are completed and transmitted to the TCC in a timely manner;
- Ensure the Investigator’s Study File is up-to-date and complete;
- Ensure all Adverse Events are reported promptly to the TCC;
- Accountability for trial treatments at their site;
- Ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements;
- Allow access to source data for monitoring, audit and inspection;
- Be responsible for archiving all original trial documents including the data forms for five years after the end of the trial.

3.7. Publication

All efforts will be made to ensure that the trial protocol and results arising from the WOMAN trial are published in an established peer-reviewed journal. At least one publication of the main trial results will be made.

3.8. 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 as a result of participating 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.

3.9. Financial Support

LSHTM is funding the run-in costs for the WOMAN trial and up to 2,000 patients’ recruitment. The main phase is funded by the UK Department of Health and the Wellcome Trust. Funding for this trial covers meetings and central organisational costs only. Pfizer, the manufacturer of tranexamic acid, have provided the funding for the trial drug and placebo used for this trial. An educational grant, equipment and consumables for ROTEM analysis has been provided by Tem Innovations GmbH, M.-Kollar-Str. 13-15, 81829 Munich, Germany for use in the WOMAN-ETAC study. An application for funding to support local organisational costs has been made to University of Ibadan Senate Research Grant. The design, management, analysis and reporting of the study are entirely independent of the manufacturers of tranexamic acid and Tem Innovations GmbH.
4. REFERENCES

APPENDICES

1. Information sheet for patient and her representative
2a. Patient consent form
2b. Representative consent form
3. WOMAN–ETAC data collection form
APPENDIX 1 - Information sheet for the patient and her representative

THE WOMAN TRIAL PATIENT INFORMATION SHEET – NIGERIA UCH IBADAN
Dr Oladapo Olayemi
Department of Obstetrics and Gynaecology, University College Hospital
PMB 5116, Orita-Mefa, Ibadan, Oyo State
Telephone 0803 219 7300; email oladapo.olayemi@yahoo.com

INFORMATION SHEET FOR THE PATIENT AND HER REPRESENTATIVE(S)
THE WOMAN TRIAL AND WOMAN–ETAC

TITLE OF RESEARCH:
(1) Tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind, placebo controlled trial, and
(2) Effect of tranexamic acid on coagulation in a sample of participants in the WOMAN trial
TRIAL SITE NUMBER: 010
LEAFLET VERSION: Version 1.1 dated 25 July 2011

This hospital is taking part in an international research study to find ways to improve the
treatment of women who have severe bleeding after delivery of their baby.

(1) We would like to invite you to take part in this study
(2) When you were very unwell you were included in this study and we would like you to
continue to take part
(3) As a representative of the patient we are asking you to make a decision on her behalf
(Please circle the option that applies)

The Research Doctor has already checked to make sure you/the patient is medically suitable for
this research and you are being asked to make a decision about whether you/the patient can be
included in this study. This sheet gives information about the study, including the reasons why
the study is being done, and the risks and benefits of taking part.

PLEASE READ THE INFORMATION BELOW CAREFULLY AND ASK THE DOCTOR OR
MIDWIFE LOOKING AFTER YOU ANY QUESTIONS YOU MAY HAVE.

1) What is the purpose of the study?
In this hospital, women who have a very severe bleeding after childbirth (also called postpartum
haemorrhage) are given the best available treatments. The aim of this research study is to see if there
is a better treatment for women who have severe bleeding after childbirth. We hope that the
treatment (tranexamic acid) will help the blood to clot sooner, and so lessen the amount of blood lost
and reduce the need for a blood transfusion and other treatments. But it is also possible that the
study treatment may cause clots where they are not needed, and because the drug is not routinely
used after childbirth, we do not know all the likely side effects. We hope to find that the treatment
will do a little more good than harm but we don’t yet know this.

2) Why is this research being done?
Postpartum haemorrhage can be a very serious condition and sometimes requires surgery to control
the bleeding. Many thousands of women worldwide die each year from this condition and it is
important to find better ways of controlling excessive bleeding after childbirth.

Tranexamic acid is often used to reduce bleeding after major operations such as heart operations.
Some women who have heavy menstrual bleeding (periods) also use tranexamic acid. The WOMAN
study is being done to see if TXA can reduce bleeding in women with postpartum bleeding.

3) Why have you been invited?
You have been diagnosed with postpartum haemorrhage by your doctor. Your doctor has checked
that you are suitable for the study, but it is up to you whether or not you decide to take part.
4) **Who is doing the study and who can you call if you have any questions or problems?**

If you have any questions or problems, you should contact the doctor in charge of the trial at this hospital:

<table>
<thead>
<tr>
<th>Name of Doctor</th>
<th>Dr Oladapo Olayemi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>Department of Obstetrics and Gynaecology, University College Hospital PMB 5116, Orita-Meja, Ibadan, Oyo State</td>
</tr>
<tr>
<td>Telephone</td>
<td>0803 219 7300</td>
</tr>
</tbody>
</table>

This research has been approved by the UI/UCH Ethics Committee. If you have any questions regarding your rights, or feel that your rights as a participant have been violated, the Chairman can be contacted at the following address:

<table>
<thead>
<tr>
<th>Name of Chairman</th>
<th>Professor Adesola Ogunmiluyi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>UI/UCH Ethics Committee, Institute of Advanced Medical Research and Training, College of Medicine, University College Hospital, Ibadan</td>
</tr>
</tbody>
</table>

You may also contact the Chief Medical Director of the hospital:

<table>
<thead>
<tr>
<th>Name of Director</th>
<th>Professor AO Iliesanmi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>University College Hospital, PMB 5116, Orita-Meja, Ibadan, Oyo State</td>
</tr>
<tr>
<td>Telephone</td>
<td>0803 563 6650</td>
</tr>
</tbody>
</table>

The study is coordinated by doctors and a trial team at The London School of Hygiene & Tropical Medicine (University of London). They can be contacted at:

<table>
<thead>
<tr>
<th>Address</th>
<th>Room 180, Trials Coordinating Centre, London School of Hygiene &amp; Tropical Medicine, London, WC1E 7HT, United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone</td>
<td>+44 (0)20 7299 4684</td>
</tr>
</tbody>
</table>

You are also free to visit the trial website to keep up to date with the progress of the trial:  
www.thewomantrial.lshtm.ac.uk

5) **A patient cannot be in this study if:**

- The doctor thinks there is a particular reason why tranexamic acid definitely **should not** be given
- The doctor thinks there is a particular reason why tranexamic acid **definitely should** be given
- They are not an adult

6) **What will happen/has happened during this study?**

You will be given all the usual emergency treatments for severe bleeding after childbirth, including fluids to replace the blood that you have lost. You will also be given a dose of either the tranexamic acid or a placebo (a liquid which doesn’t contain tranexamic acid). This dose will be given as an injection into your vein. If after about 30 minutes you are still bleeding, or if the bleeding stops and starts again within 24 hours after the first dose, you may be given a second dose of the same. You will not receive more than two injections for the study.

You will also have two blood samples taken from your vein through a needle. The first sample will be taken before you are given any of the trial treatment, and the second sample thirty minutes later. You will not have to pay for any of the tests done on these two blood samples.

We do not know whether giving tranexamic acid on top of all the other treatments will help or not, so half the women in the study will receive tranexamic acid and the other half will receive a placebo. The choice of which treatment you receive is completely random (like a lottery) and you will have an equal chance of receiving either one. Neither you nor the doctor treating you will know which treatment you receive. This information is kept on a confidential list at an independent location in London.
The study involves no extra tests but your doctor/midwife will send brief details about your treatment and recovery to the Coordinating Centre in London. They will also send information about the health of your baby/ies. If after discharge from hospital and up to 42 days after treatment you develop any medical problems, please let the doctor named on this form know. This information will be used in strict confidence by the people working on the study and will not be released under any circumstances.

7) What are the possible risks of being in the study?
Tranexamic acid is NOT a new drug and it is widely used to reduce bleeding in conditions such as major heart surgery. There is no conclusive evidence of serious side effects with short term use. But the study treatment may cause clots where they are not needed and, because the drug is not routinely used after childbirth, we do not know all the likely side effects. Sometimes, taking the blood test and giving the trial treatment can cause pain and bruising. Your doctor will report to the trial organisers any unexpected problems you may have.

8) What are the possible benefits of being in the study?
We hope that tranexamic acid may help reduce blood loss. The knowledge that we gain from this study will help women with postpartum haemorrhage worldwide in the future. The routine laboratory tests done for this study can be used by your doctor to help guide your treatment. Tests which are not routine will not be used.

9) What information do we keep private?
All information about you and the reason for bleeding after childbirth will be kept private. The only people allowed to look at the information will be the doctors who are running the study, the staff at the Coordinating Centre and the regulatory authorities who check that the study is being carried out correctly. The Trial Coordinating Centre may want to collect or copy some trial documents which will have your name and will include the signed Consent Form. This will help them to ensure that the trial is being carried out correctly. Your details will remain confidential and will be held in secure storage at the Trial Coordinating Centre. Your confidential information will be kept separately from the trial data and will be destroyed within five years of the trial ending. We will publish the results of the study in a medical journal so that other doctors can benefit from the knowledge, but your personal information will NOT be included and there will be no way that you can be identified.

10) Can you change your mind about being in the study?
You can always withdraw from the study at any time. You just need to say for example “I’ve decided I don’t want to be in this study now”. We hope that you will let us use information about how you got on, but if you do not want us to use it please tell the doctor.

11) What else do you need to know?
- In the event that something goes wrong and you are harmed during the study, the London School of Hygiene & Tropical Medicine who are organising the study would be responsible for claims for any non-negligent harm suffered as a result of participating in this study.
- We will ask you to sign a separate consent form and give you a copy to keep and you can also keep this information sheet.
- This study has been reviewed and approved by a Research Ethics Committee.

12) What happens afterwards?
If after you leave this hospital you develop any problems at any time up to 42 days later you had your baby, we would definitely want to know about it. You will be given a card with the contact details of the research doctor at this hospital, which you should keep safely and show to anyone who may be treating you for any illness. If you would like to have a copy of the final results of this study, please let the research doctor know and s/he will ensure you receive a copy when it is published.
APPENDIX 2a – Patient consent form

THE WOMAN TRIAL PATIENT CONSENT FORM – NIGERIA UCH IBADAN
Dr Oladapo Olayemi, Department of Obstetrics and Gynaecology
University College Hospital, PMB 5116, Orita-Meja, Ibadan, Oyo State
Telephone 0803 219 7300; email oladapo.olayemi@yahoo.com

CONSENT FORM FOR THE PATIENT
THE WOMAN TRIAL AND WOMAN–ETAC

Title of Research: (1) WOMAN: Tranexamic acid for the treatment of postpartum haemorrhage: An international randomised, double blind, placebo controlled trial, and (2) WOMAN–ETAC: Effect of tranexamic acid on coagulation in a sample of participants in the WOMAN trial

<table>
<thead>
<tr>
<th>Hospital Code Number</th>
<th>Name of Local Principal Investigator</th>
<th>Randomisation Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>010</td>
<td>Dr Oladapo Olayemi</td>
<td>BOX / FACE</td>
</tr>
</tbody>
</table>

Name of Patient

Version Number: 1.1 / Version Date: 25 July 2011

1. I confirm that I have read and understood the information sheet Version Number 1.1, version date 25 July 2011, for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that sections of my medical notes and those of my baby(ies) may be looked at by responsible individuals involved in the study. I give permission for these individuals to have access to these records.

4. I give permission for a copy of this consent form, which contains my personal information, to be made available to the Trial Coordinating Centre in London for monitoring purposes only.

5. I give permission for my personal doctor to be given information about my participation in this trial.

6. I agree to take part in the above study, the WOMAN trial and WOMAN-ETAC.

<table>
<thead>
<tr>
<th>Name of Patient</th>
<th>Date</th>
<th>Signature / Thumbprint or other mark (if unable to sign)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of person taking consent</td>
<td>Date</td>
<td>Signature</td>
</tr>
<tr>
<td>Name of local principal investigator</td>
<td>Date</td>
<td>Signature</td>
</tr>
</tbody>
</table>

(Witness only if required) The patient is unable to sign and as a witness I confirm that the patient has been given all the information about the trial and has verbally consented to taking part.

<table>
<thead>
<tr>
<th>Name of witness</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
</table>

Original to be filed in the investigator’s Study File; 1 copy for patient; 1 copy to be kept with woman’s hospital records

Rational Health Research Ethics Committee Assigned Number: NHREC/01/01/2007-10/1/2009

PATIENT CONSENT FORM ENGLISH-ENGLISH
Protocol Code: RSIC-09512159

FINAL VERSION 1.0
3 August 2011 Page 18 of 21
# APPENDIX 2b – Representative consent form

## THE WOMAN TRIAL REPRESENTATIVE CONSENT FORM – NIGERIA UCH IBADAN

Dr Oladapo Olayemi, Department of Obstetrics and Gynaecology
University College Hospital, PMB 5116, Orita-Mefo, Ibadan, Oyo State
Telephone 0803 219 7300; email oladapo.olayemi@yahoo.com

## CONSENT FORM FOR THE PATIENT’S REPRESENTATIVE

**THE WOMAN TRIAL AND WOMAN-ETAC**

**Title of Research:** (1) Tranexamic acid for the treatment of postpartum haemorrhage: An international randomised, double blind, placebo controlled trial, and (2) WOMAN-ETAC: Effect of tranexamic acid on coagulation in a sample of participants in the WOMAN trial

<table>
<thead>
<tr>
<th>Hospital code number</th>
<th>010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Hospital ID Number</td>
<td></td>
</tr>
<tr>
<td>Name of Local Principal Investigator</td>
<td>Dr Oladapo Olayemi</td>
</tr>
<tr>
<td>Randomisation Number</td>
<td>BOX</td>
</tr>
</tbody>
</table>

### Version Number: 1.1 / Version Date: 25 July 2011

1. I confirm that I have read and understood the information sheet **Version Number 1.1, version date 25 July 2011**, for the above study and have had the opportunity to ask questions.

2. I confirm that I am not aware of any reason why this patient would have objected to taking part in this study.

3. I understand that my consent is voluntary and that I am free to withdraw it at any time without giving any reason and without the patient’s medical care or legal rights being affected.

4. I understand that sections of the patient’s medical notes and those of her babies may be looked at by responsible individuals involved in the study.

5. I give permission for a copy of this consent form which contains my personal information to be made available to the Trial Coordinating Centre in London for monitoring purposes only.

6. I give permission for the patient’s personal doctor to be given information about her participation in this trial.

7. I agree for the above named patient to take part in the WOMAN trial and WOMAN-ETAC.

---

**Signature / thumbprint or other mark of Representative**

**Date**

**Name of person taking consent**

**Date**

**Signature**

**Name of local principal investigator**

**Date**

**Signature**

(Witness only if required) The representative is unable to sign and as a witness I confirm that the representative has been given all the information about the trial and has verbally consented to taking part.

**Name of witness**

**Date**

**Signature**

Original to be filed in the investigator’s Study File, 1 copy for representative, 1 copy to be kept with woman’s hospital records

---

**National Health Research Ethics Committee Assigned Number:** NHREC/01/02/2007-10/10/2009

**Protocol Code:** ISRCTN76912150

---

**FINAL VERSION 1.0** 3 August 2011
# APPENDIX 3 – WOMAN–ETAC data collection form

**WOMAN–ETAC DATA FORM**

**PLEASE ENSURE ALL RELEVANT INFORMATION BELOW IS CONTAINED IN THE MEDICAL RECORDS**

## INITIAL DATA

**PLEASE ENTER ON THE FORM AS PROCESSES ARE COMPLETED**

1. Hospital code (for your study file)  
2. Patient's initials (first name/last name)

3. Fully eligible for WOMAN trial? YES NO

4. Time baseline venous blood sample taken (24-hour clock) hours minutes

5. Time ROTEM analysis started (24-hour clock) hours minutes

   Note: See overview for parameters to be measured – ROTEM data to be printed off and appended to this data form. Data to be transferred to the Coordinating Centre electronically.

6. Routine laboratory samples prepared for analysis (24-hour clock) YES NO

   Note: See overview for parameters to be measured – copy of data to be printed off, appended to this data form and transferred to the Coordinating Centre.

7. Any treatment which can affect coagulation, given up to 48 hours prior to first blood sample? (circle one) YES NO e.g. heparin, warfarin, aspirin, vitamin K, protamine, fibrinogen

## RANDOMISATION AND FIRST TREATMENT INFORMATION

**PLEASE ENTER ON THE FORM AS PROCESSES ARE COMPLETED**

8. Insert randomisation number here

9. Date of randomisation (24-hour clock) day month year

10. Time of randomisation (24-hour clock) hours minutes

11. Time first dose given (24-hour clock) hours minutes

## POST TREATMENT DATA

**PLEASE COMPLETE IMMEDIATELY AFTER 30 MINUTE ASSESSMENT FOR 2ND DOSE, IMMEDIATELY AFTER 2ND BLOOD SAMPLE AND IF 2ND DOSE IS GIVEN**

12. Time post-treatment venous blood sample (24-hour clock) hours minutes

13. Second dose given? (circle one) YES NO e.g. heparin, warfarin, aspirin, vitamin K, protamine, fibrinogen

14. Time post-treatment ROTEM analysis started (24-hour clock) hours minutes

   Note: See overview for parameters to be measured – ROTEM data to be printed off, appended to this data form and transferred to the Coordinating Centre

15. Any treatment which can affect coagulation, given between first and second blood samples? (circle one) YES NO e.g. heparin, warfarin, aspirin, vitamin K, protamine, fibrinogen

16. Any Adverse Event directly associated with the WOMAN-ETAC study? YES NO If YES, report using the WOMAN trial Adverse Event Reporting Procedure

17. Any technical problem with sampling or analysis of venous blood? (circle one) YES NO If YES, describe in Box 18

18.

19. a) Name of person completing this data form

   b) Date day month year

c) Signature

---

Protocol Code: SRT7NW9I2190  Page 1 of 2  Version 1.0_WOMAN-ETAC Data Form
PLEASE ENSURE THE PARAMETERS LISTED BELOW FOR ROTEM AND ROUTINE LABORATORY PARAMETERS ARE COMPLETED FOR BOTH FIRST AND SECOND BLOOD SAMPLES.

<table>
<thead>
<tr>
<th>ROTEM PARAMETERS TO BE MEASURED</th>
<th>ROUTINE LABORATORY PARAMETERS TO BE MEASURED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction Time [RT] – Measurement period</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Clotting Time [CT] – Time from start to when the waveform reaches 2mm above baseline</td>
<td>White blood cell count</td>
</tr>
<tr>
<td>Clot Formation Time [CFT] – Time from 2mm above baseline to 20mm above baseline</td>
<td>Differential white cell count</td>
</tr>
<tr>
<td>Alpha angle [°] a [angle of tangent at 2mm amplitude]</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Maximum angle (CRF)</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Maximal Clot Firmness [MCF] – Maximum strength</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Time to Maximum strength (MCF-t)</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Amplitude at a specific time (A5, A10...)</td>
<td>Basophils</td>
</tr>
<tr>
<td>Clot elasticity (MCE)</td>
<td>Platelets</td>
</tr>
<tr>
<td>Maximum lysis (CLF)</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Clot Lysis (CL) at a specific time [minutes] (LY30, LY45, LY60)</td>
<td>PT</td>
</tr>
<tr>
<td>Time to lysis (CLT [10% difference from MCF])</td>
<td>INR</td>
</tr>
<tr>
<td></td>
<td>APTT ratio</td>
</tr>
<tr>
<td></td>
<td>D-dimer</td>
</tr>
</tbody>
</table>

SENDING DATA TO THE TRIAL COORDINATING CENTRE
Data contained on this form: To be uploaded via web access directly onto the trial database by authorised personnel.

**ROTEM data:** the electronic output should be emailed to woman.data@lshtm.ac.uk

**Routine laboratory parameters:** If names are present on the reports, a copy should be made and the name censored on the copy. The randomisation number should be inserted on the form and emailed to woman.data@lshtm.ac.uk