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

CLINICAL TRIAL PROTOCOL
Tanzania

Protocol Number: ISRCTN76912190

	NUMBER	DATE
FINAL VERSION	Version 1.0	11 May 2009
AMENDMENT 1	Version 1.1	31 January 2014

TANZANIA COUNTRY INFORMATION (Edition 3)

PLEASE NOTE: This page of the WOMAN Trial Protocol is to provide country specific information and will be updated as required. These updates will not be considered as Global Protocol Amendments.

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RESEARCH ETHICS REVIEW

National Institute for Medical Research
Approval # NIMR/HQ/R.8c/Vol.II/174

Tanzanian Food and Drug Authority
Approval # DE.57/180/02/01

SUMMARY

FULL TITLE OF STUDY:	Tranexamic acid for the treatment of postpartum haemorrhage: An international, randomised, double blind, placebo controlled trial		
SHORT TITLE:	WORLD MATERNAL ANTIFIBRINOLYTIC TRIAL		
TRIAL ACRONYM:	**THE WOMAN TRIAL**		
PROTOCOL NUMBER:	ISRCTN76912190		
EUDRACT NUMBER:	2008-008441-38	**CLINICALTRIALS.GOV ID:**	NCT00872469

BACKGROUND: Each year, worldwide about 530,000 women die from causes related to pregnancy and childbirth. Almost all (99%) of the deaths are in low and middle income countries. Obstetric haemorrhage is the leading cause of maternal mortality accounting for between one quarter and one third of deaths, most of which occur in the postpartum period. About 14 million mothers develop postpartum haemorrhage (PPH) each year and about 2% of them will die, with an average interval from onset to death of about 2 to 4 hours. Obstetric haemorrhage is also an important cause of maternal mortality in high income countries where it accounts for about 13% of maternal deaths. Systemic antifibrinolytic agents are widely used in surgery to prevent clot breakdown (fibrinolysis) in order to reduce surgical blood loss. A systematic review of randomised controlled trials of antifibrinolytic agents in surgical patients identified 211 randomised controlled trials including 20,781 randomised participants. The results show that tranexamic acid (TXA) reduces the risk of blood transfusion by a relative 39% (RR=0.61, 95%CI 0.54 to 0.69). TXA reduces transfused volume by 1.1 units (95%CI 0.64 to 1.59). TXA also reduces the need for re-operation due to bleeding (RR= 0.67, 95%CI 0.41 to 1.09). There was no evidence of an increased risk of thrombotic events.

TXA significantly reduces uterine blood loss in women with menorrhagia and is "recommended for consideration" as a treatment in intractable postpartum haemorrhage in the UK. However, at present there is little reliable evidence from randomised trials on the effectiveness of TXA in the treatment of PPH. A systematic review of randomised trials of TXA in PPH conducted by the investigators identified three trials of the prophylactic use of TXA, including a total of 460 participants. Although there was a significant reduction in average postpartum blood loss in women treated with TXA, the quality of the trials was poor. None had adequate allocation concealment and even in aggregate the trials were too small to assess the effects of TXA on the clinically important end points of mortality, hysterectomy and thrombotic side effects. The most recently updated PPH treatment guidelines prepared by the World Health Organization (WHO) state that TXA may be used in the treatment of PPH if other measures fail, but points out that the quality of evidence on which this recommendation is based is low and recommends that further clinical trials of TXA in PPH are conducted.

AIM: The WOMAN Trial aims to determine the effect of the early administration of tranexamic acid on mortality, hysterectomy and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events) in woman with clinically diagnosed postpartum haemorrhage. The use of health services and safety, especially thromboembolic effect, on breastfed babies will also be assessed.

OUTCOME: Outcomes will be collected at 42 days after randomisation, at discharge from randomising hospital or at death (whichever occurs first).

PRIMARY OUTCOME: The primary outcome is the proportion of women who die or undergo hysterectomy. The primary cause of death will be described.

SECONDARY OUTCOMES:

(a) Death

(b) Surgical Interventions: including hysterectomy, brace suture (B-Lynch/Cho), selective arterial embolisation, laparotomy for other reasons, manual removal of placenta, intrauterine tamponade (packing or gauzing the uterine cavity, condom-catheter, any other method of intrauterine tamponade), artery ligation, to achieve haemostasis

(c) Blood transfusion – blood or blood component units transfused
(d) Health Status measured using the EQ-5D
(e) Thromboembolic events (myocardial infarction, strokes, pulmonary embolism, DVT)
(f) Other relevant medical events
(g) Length of stay at hospital/time spent at an intensive care unit
(h) Need for mechanical ventilation
(i) Status of breastfed baby/ies
(j) Cost-effectiveness

TRIAL DESIGN: A large, pragmatic, randomised, double blind, placebo controlled trial among 20,000 women with a clinical diagnosis of postpartum haemorrhage

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:

- All legally adult women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section. The clinical diagnosis of PPH may be based on any of the following:
  - estimated blood loss after vaginal delivery of a baby > 500 mL OR
  - >1,000 mL from caesarean section OR
  - blood loss sufficient to compromise the haemodynamic status of the woman
- 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 postpartum haemorrhage.
  - Women for whom the responsible doctor considers there is a clear indication for antifibrinolytic therapy should not be randomised.
  - Women for whom there is considered to be a clear contraindication to antifibrinolytic therapy should not be randomised.
- Where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in a particular woman with PPH.
- There are no other pre-specified exclusion criteria.

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: A dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation. If after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after the first dose, a second dose may be given.

SETTING: This trial will be coordinated from the London School of Hygiene & Tropical Medicine (University of London) and conducted worldwide in hospitals in low, middle and high income countries. It is likely that most patient recruitment will be in countries with high rates of mortality and morbidity from postpartum haemorrhage.

DURATION OF TREATMENT AND PARTICIPATION: The first dose will be given immediately after randomisation. If required, the second dose will be given up to 24 hours after the first dose. No further trial treatment will be given. Participation will end at discharge from randomising hospital, death or at 42 days post randomisation whichever occurs first.

CRITERIA FOR EVALUATION: All patients randomly assigned to one of the treatments will be analysed together, regardless of whether or not they completed or received that treatment, on an intention to treat basis.

CLINICAL PHASE:	3		
PLANNED TRIAL START:	May 2009		
PLANNED DATE OF LAST PATIENT ENROLMENT:	31 March 2016	**PLANNED DATE OF LAST OUTCOME**	12 May 2016

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1 INTRODUCTION

Each year, worldwide, about 530,000 women die from causes related to pregnancy and childbirth. Nearly all (99%) of these deaths are in low and middle income countries.[1] Haemorrhage, which usually occurs in the postpartum period, is responsible for between one quarter and one third of obstetric deaths.[2]

Postpartum haemorrhage (PPH) is commonly defined as blood loss of ≥500mL after vaginal delivery of a baby, or ≥1000mL after caesarean section. However, these thresholds do not take into account pre-existing health status, and blood loss of as little as 200mL can be life-threatening for a woman with severe anaemia or cardiac disease.[3]

Of the 14 million women who have PPH each year, about 2% die, with an average interval from onset of bleeding to death of 2 to 4 hours.[2] Although many deaths from PPH occur outside healthcare facilities, a significant number occur in hospital, where effective emergency care has the potential to save lives.[4,5] PPH is also an important cause of maternal mortality in high income countries, accounting for about 13% of maternal deaths.[6]

PPH also causes hospital morbidity. Many women require blood transfusion which sometimes can transmit blood borne viral infections. Approximately 1% of women with spontaneous vaginal deliveries require transfusion, but the figure increases to 5% or 6% for women with instrumental deliveries or caesarean sections.[7] The risk of infection from transfused blood is considerably higher in countries that do not screen all blood for transfusion.[8] In high income countries the risk of transfusion transmitted infection is low, but adverse reactions related to blood transfusion are common.[9]

Severe anaemia is a common consequence of PPH and affects about 11% of the 14 million women with PPH each year.[10] Severe anaemia can cause disabling fatigue and seriously reduce a woman's capacity to look after her children and to work.[11]

Systemic antifibrinolytic agents are widely used in surgery to prevent clot breakdown (fibrinolysis) in order to reduce surgical blood loss. A systematic review of randomised controlled trials of antifibrinolytic agents in surgical patients identified 211 randomised controlled trials including 20,781 randomised participants. The results show that tranexamic acid (TXA) reduces the risk of blood transfusion by a relative 39% (RR=0.61, 95%CI 0.54 to 0.69). In all patients, TXA reduces transfused volume by 1.1 units (95%CI 0.64 to 1.59). TXA may also reduce the need for re-operation due to bleeding (RR=0.67, 95%CI 0.41 to 1.09). There was no evidence of an increased risk of thrombotic events.[18]

TXA significantly reduces uterine blood loss in women with menorrhagia and is "recommended for consideration" as a treatment in intractable postpartum haemorrhage in the UK.[19] However, at present there is little reliable evidence from randomised trials on the effectiveness of TXA in the treatment of PPH. A systematic review of randomised trials of TXA in PPH conducted by the investigators identified three trials of the *prophylactic* use of TXA, including a total of 460 participants.[20] Although there was a statistically significant reduction in average postpartum blood loss in women treated with TXA [weighted mean reduction of approximately 100 mL] the quality of the trials was poor. None had adequate allocation concealment and even in aggregate the trials were too small to assess the effects of TXA on the clinically important end points of mortality, hysterectomy and thrombotic side effects. The most recently updated PPH treatment guidelines prepared by the World Health Organization (WHO) state that TXA may be used in the treatment of PPH if other measures fail, but points out that the quality of evidence on which this recommendation is based is low and recommends that further clinical trials of TXA in PPH are conducted.

1.1 NEED FOR A TRIAL

The WOMAN Trial 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. There is a global commitment to the Millennium Development Goal (MDG) of reducing maternal deaths by three-quarters by the year 2015, a commitment that requires a reduction of the maternal mortality ratio by 5.5% each year. Because maternal haemorrhage accounts for over a quarter of deaths, an effective treatment for PPH would contribute importantly to the MDG of reducing maternal mortality. TXA might also reduce the need for hysterectomy, decrease the risk of anaemia and avoid the need for blood transfusion. Blood is a scarce resource in many countries with a risk of transfusion transmitted infections. If TXA was effective in the hospital setting, further research could be conducted to evaluate its use in the community, possibly including the use of oral rather than intravenous administration.

The results of this trial will be disseminated by publication in peer reviewed medical journals, conference presentations, and in an updated version of the Cochrane systematic review of treatments for postpartum bleeding. There is evidence that hospitals participating in multi-centre trials are more likely to implement the trial results.[21] For this reason, a large international multi-centre trial like the WOMAN trial can be expected to have a substantial impact on clinical practice. The large network of collaborating sites will ensure that the results are disseminated worldwide.

1.2 TRANEXAMIC ACID AND ITS EFFECT ON BLEEDING

In the haemostatic process, coagulation occurs rapidly at the site of a damaged vessel building a tight net of fibrin, while at the same time, the fibrinolytic system removes the fibrin deposits that could cause permanent vascular occlusion once vascular repair has taken place.[22] The coagulation and fibrinolytic system are believed to be in a state of dynamic balance which maintains an intact vascular system. Tranexamic acid is a potent antifibrinolytic agent that exerts its effect by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own haemostatic mechanisms. Consequently, clot breakdown (fibrinolysis) is inhibited and excessive or recurrent bleeding is reduced.

During delivery, when the placenta separates from the uterine wall, a sequence of physiologic and haemostatic changes occur that reduce bleeding: strong myometrial contractions, increased platelet activity, a massive release of coagulant factors and a parallel increase in the fibrinolytic activity.[23] As a result, there is a theoretical rationale for the use of antifibrinolytic agents in the treatment of postpartum haemorrhage.[18,24,25]

1.3 POTENTIAL SIDE EFFECTS OF TRANEXAMIC ACID

As TXA inhibits the breakdown of fibrin deposits already formed, it might theoretically increase the risk of thromboembolism. However, the systematic review of TXA in surgery did not show statistically significant increases in the risks of any of the thromboembolic events assessed.[14]

Events	Effect of TXA	
	RR	95% CI
Myocardial Infarction	0.96	0.48-1.90
Stroke	1.25	0.47-3.31
Deep venous thrombosis	0.77	0.37-1.61
Renal failure	0.73	0.16-3.32

During pregnancy, women have an increased risk of thromboembolic events, compared with non-pregnant women. The absolute risk of symptomatic venous thrombosis during pregnancy has been estimated to be between 0.5 and 3.0 per 1,000 women based on studies using radiographic documentation.[26-28] Studies using objective criteria for diagnosis have found that ante-partum deep vein thrombosis (DVT) is as common as postpartum thrombosis and occurs with equal frequency in all three trimesters.[26]

A population-based cohort study estimated an incidence of thromboembolic events to be 200 per 100,000 woman-years.[29] DVT was three times more common than pulmonary embolism and thromboembolic events were five times more likely in the postpartum period than during the pregnancy. This was particularly evident with pulmonary embolism which was 15 times more likely to occur in the postpartum period than during the pregnancy. Thromboembolic events will be collected routinely as part of the data collection process for this trial.

TXA passes into breast milk in very low concentrations, approximately one hundredth of the concentration in the maternal blood. An antifibrinolytic effect in the infant is very unlikely at this low concentration.[30] The thromboembolic effects on breastfed babies will be assessed in this trial.

TXA is not a new drug and is generally well tolerated. Adverse events are uncommon and usually manifest as nausea or diarrhoea, or occasionally as orthostatic reactions.[18]

1.4 OBJECTIVE

The WOMAN trial will provide reliable evidence as to whether the antifibrinolytic agent tranexamic acid reduces mortality, hysterectomy and other morbidities in woman with clinically diagnosed postpartum haemorrhage. Thromboembolic effects on breastfed babies will be assessed.

2 TRIAL DESIGN

2.1 OVERVIEW

This trial is a large, pragmatic, randomised, double blind, placebo controlled trial to quantify the effects of the early administration of tranexamic acid on death, hysterectomy and other relevant outcomes. 20,000 adult women, who have clinically diagnosed postpartum haemorrhage and who fulfil the eligibility criteria, will be randomised to receive either TXA or placebo. The eligibility criteria are based on the uncertainty principle.

Pragmatic design and the uncertainty principle: The pragmatic design will allow us to find out how effective the treatment actually is in routine everyday practice. The eligibility criteria are based on the uncertainty principle. This approach to trial eligibility is well established.[31] A patient can be enrolled if, and only if, the responsible clinician is substantially uncertain as to which of the trial treatments would be most appropriate for that particular woman (see graph 1). A woman should not be enrolled if the responsible clinician or the woman (or her representative) are for any medical or non-medical reasons reasonably certain that one of the treatments that might be allocated would be inappropriate for this particular individual (in comparison with either no treatment or some other treatment that could be offered to the patient in or outside the trial). Using the uncertainty principle should allow the process of this trial to be closer to what is appropriate in normal medical practice. Clinicians, women and their representatives will be provided with information about the trial treatment to assist them in their judgement.

Randomisation: Women eligible for inclusion should be randomised, and the study treatment started, as soon as possible. The Entry form (Appendix 1) will be used to assess eligibility and collect baseline information. The next consecutively numbered treatment pack, taken from a box of eight packs, should be chosen. Once a patient has been randomised, the outcome in hospital needs to be collected even if the trial treatment is interrupted or is not actually given.

Follow-up: No extra tests are required for the trial but a short Outcome form (Appendix 2) must be completed directly from the medical records six weeks (42 days) after randomisation or on discharge from the randomising hospital or on death (whichever occurs first). Any adverse events which become known to the investigator will be reported up to 42 days after randomisation.

2.2 SETTINGS

The pragmatic nature of this trial will allow for the recruitment of women from a wide variety of health care facilities. Participating hospitals or maternal health facilities will be selected from high, middle and low income countries. Eligible women may have delivered their babies at the participating hospital or may have delivered outside the participating hospital and been admitted following the delivery of a baby. There is no limit to the maximum number of women to be recruited at each site.

2.3 NUMBER OF PATIENTS NEEDED

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

Estimated event rate: Review of the literature and data from hospital reports shows that there are wide variations in mortality after PPH worldwide, varying from about 0.6% in the United Kingdom to 2.6% in South Africa and 20% in some parts of Africa. The frequency of occurrence of peripartum hysterectomies also varies, from about 0.02% in the

United Kingdom to 2% in Nigeria or 14% in Congo-Brazzaville. Based on these ranges, a baseline event rate of 2.5% for mortality and 2.5% for hysterectomy might reasonably be expected.

Sample size and size of treatment effect that should be detectable:

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. A survey of baseline event rates among hospitals that have expressed interest in taking part shows that baseline event rates of this magnitude are realistic and that higher baseline event rates might reasonably be expected. Experience from the CRASH-1 and CRASH-2 clinical trials suggests that the anticipated rates of loss to follow-up (less than 1%) would not impact importantly on study power.

Additional information for justification to changes made in Version 1.1

Summary of amendment: As of December 2013, the trial has recruited 10,014 women, 261 of whom died. Because the effect of tranexamic acid on maternal mortality is of considerable public health importance, the sample size has been increase from 15,000 to 20,000 so that the trial has enough power to detect an effect on this important secondary outcome. This involves an additional 15 months of recruitment. On this basis, the Trial Protocol Version 1.0, dated 11 May 2009, has been modified as follows:

- Increase the sample size from 15,000 to 20,000
- Date of last patient recruitment: changes from 31 December 2014 to 31 March 2016
- Date of last patient follow up: changes from 11 February 2015 to 12 May 2016

Rationale: If the administration of tranexamic acid were shown reliably to reduce mortality and morbidity in women with postpartum haemorrhage (PPH), it would be a major obstetric advance with the potential to improve the lives of tens of thousands of women around the world. Tranexamic acid is inexpensive, heat stable and easy to use and could be rapidly implemented if shown to be effective. The challenge for research is to provide reliable evidence of effectiveness and safety. Although PPH is a leading cause of maternal mortality, the case-fatality rate is relatively low, which means that trials of treatments to reduce maternal mortality have to recruit thousands of patients in order to have enough power to detect a reduction in the risk of death. The primary end point in the WOMAN trial is a composite of death or hysterectomy. Use of a composite end point is justified by the assumption that the effect of the trial treatment on death and hysterectomy is likely to be similar and that patients will attach importance to each of the components. As of December 2013, the trial has recruited 10,014 women (261 of whom died). The primary end point (death or hysterectomy) occurs in approximately 6.3% of recruited women and a trial of 15,000 women should have enough power to reliably detect a 25% reduction in death or hysterectomy.

Although the use of a composite end point increases the statistical power of the trial, if the effect of TXA on death and hysterectomy are not similar, it could make the interpretation of the results more difficult. If the trial had enough power to detect a reduction in maternal mortality alone, this would be an important advantage. Because the case-fatality rate observed in the trial is higher than expected (3%), a modest increase in the sample size from 15,000 to 20,000 women will mean that the trial will have sufficient (90%) power to detect a 25% reduction in maternal mortality. Based on current recruitment, increasing the sample size from 15,000 to 20,000 women will involve an additional 15 months of recruitment. Given the global public health importance of reducing maternal mortality, we believe that this extra effort is justified.

2.4 RECRUITMENT OF COLLABORATING INVESTIGATORS

The trial will recruit collaborating sites from all countries worldwide and will continue to add sites to ensure the sample size is achieved. Suitable collaborating sites and investigators will be assessed on the level of obstetric service they provide and their ability to conduct the trial. In advance of the trial starting at a site the Principal Investigator must agree to adhere to Good Clinical Practice Guidelines and all relevant regulations in their country. In addition, all relevant regulatory and ethics approvals will need to be in place.

2.5 ELIGIBILITY

Immediately after delivery of the baby/ies, all usual care should be given for the prevention of PPH. Some bleeding is expected after delivery. However, if bleeding continues and a diagnosis of PPH is made, all usual treatments should be given and at the same time the assessment for inclusion in the trial should be made. It is important to consider inclusion as early as possible.

Inclusion criteria:

All legally adult women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section; women may have delivered their babies at a participating hospital or outside a participating hospital, with hospital admission following delivery:

- where the responsible clinician is substantially uncertain as to whether or not to use TXA
- when consent has been given according to approved procedures

The clinical diagnosis of PPH **may** be based on any of the following:

- estimated blood loss after vaginal delivery of a baby > 500 mL **OR**
- >1000 mL from caesarean section **OR**
- estimated blood loss enough to compromise the haemodynamic status of the woman

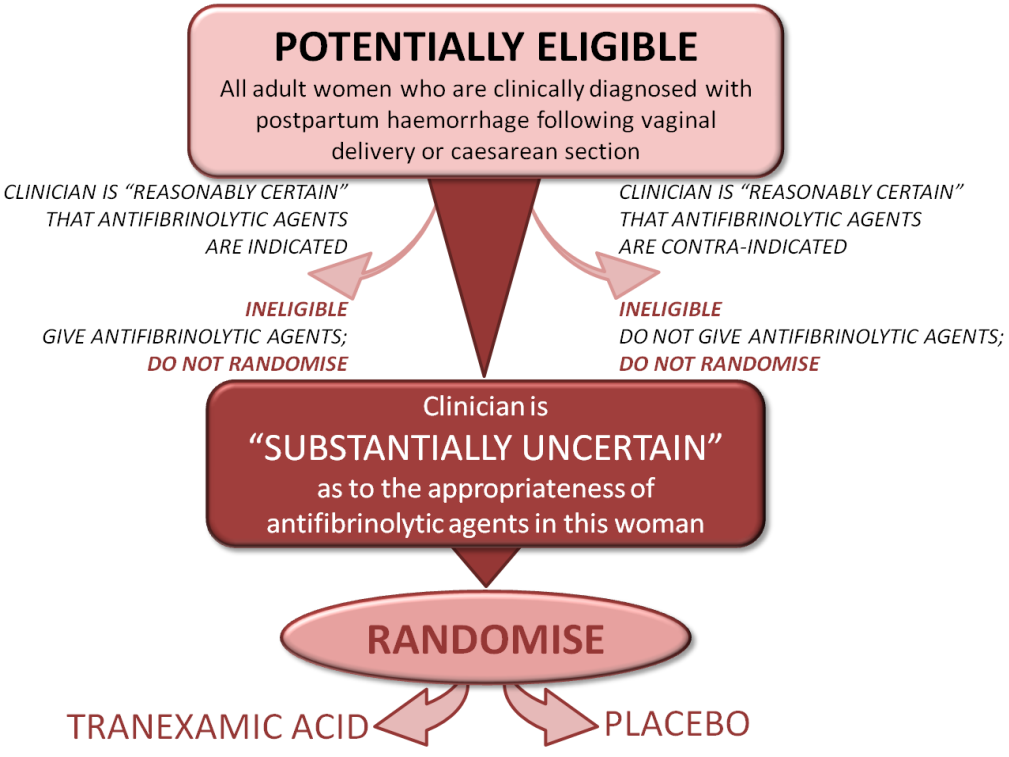
Exclusion criteria:

- Women for whom the responsible clinician considers there is a clear indication for TXA should not be randomised.
- Women for whom the responsible clinician considers there is a clear contraindication for TXA should not be randomised (e.g. a known thromboembolic event during pregnancy).

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 postpartum haemorrhage.

The TXA summary of product characteristics[30] and an Investigator's Brochure will be provided to investigators to ensure they have adequate information when considering the risk-benefit and the appropriateness of the trial for each woman.

Graph 1: Eligibility



2.6 CONSENT AND ETHICAL CONSIDERATIONS

This trial will be carried out worldwide and will include women soon after delivery of a baby. Postpartum haemorrhage is an emergency situation and clinical activities will be directed towards the provision of emergency care. Eligible women have a life threatening condition. Furthermore, their physical, mental and emotional state may be altered as a result of their blood loss or labour pains or by drugs administered during the labour. The consent process in this situation requires careful consideration bearing in mind applicable regulatory requirements, adherence to ICH-GCP and the requirements in the Declaration of Helsinki.

Advance Information: The majority of women deliver without complications and it would not be in the best interest of all pregnant women to cause undue concern by providing detailed information about this trial in the antenatal/delivery period. Also, it is not possible to identify in advance those women who will go on to develop PPH, and obtain advance consent. Therefore, where possible, a summary of the trial information will be provided to pregnant women (Appendix 3a). Refusal to be considered for participation will be documented in the woman's medical records and her decision respected.

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. Also, the availability and ability of a personal representative to make a decision on the woman's behalf will have to be taken into consideration. The approach which will allow the woman to have the most input into the decision making process without endangering her life will be utilised:

a) The woman is fully competent: The woman will be approached with the agreement of the primary carer (the midwife or doctor) at the time of diagnosis. Factors which may impair her decision making process including pain, altered level of consciousness due to drugs given and degree of blood loss, will be taken into consideration. An Information Sheet (Appendix 3c) will be provided and the study will be discussed with her and a written consent obtained (Appendix 3d). If the woman is unable to read or write, then the information sheet may be read to her and she may then mark the consent form with either a cross or thumbprint. In this event, a witness NOT associated with the trial, must provide a full signature confirming the mark.

b) The woman's mental capacity is impaired and either a Personal or Professional representative is available: Information should be given to the woman taking her level of mental impairment into consideration. Oral refusal by the woman should be respected and she should not be enrolled.

a. If a Personal Representative (PeR) who is knowledgeable about the woman's values and beliefs is available, an Information Sheet will be provided. Opportunity for questions should be given and written consent obtained. If the PeR is unable to read or write, then the information sheet may be read to him/her and a mark with either a cross or thumbprint made on the consent form. In this event, a witness NOT associated with the trial, must provide a full signature confirming the mark.
b. If a Personal Representative is not available and the woman is unable to provide valid informed consent, then an independent doctor / midwife / other site staff allowed to fulfil this role (ideally the primary carer if s/he is not part of the trial team) may be asked to consent as a Professional Representative (PrR). Informed consent given by a representative shall represent the woman's presumed will.

c) The woman's mental capacity is impaired and neither a Personal nor Professional representative is available: In situations where the woman is facing a clinical emergency and no PeR/PrR is available, the investigator and ONE independent person (doctor or midwife) who is not participating in this trial may enrol the woman into the trial by certifying in writing in the woman's medical records that:

- the woman is facing a life-threatening postpartum haemorrhage;

- the woman is unable to give her consent as a result of her medical condition;
- it is not feasible to contact the woman's PeR/PrR to obtain consent within the window period; and
- neither the woman nor the woman's PeR/PrR nor any member of the family has informed the investigator of any objections to the woman being used as a participant in this trial.

For women enrolled under such emergency consent procedure, the woman or her PeR or PrR should be informed about the trial as soon as it is possible and asked to consent for continuation of any trial procedure. A summary overview of the consent procedure is provided in Appendix 3b.

The requirements of the relevant ethics committee will be adhered to at all times.

2.7 RANDOMISATION

Randomisation codes will be generated and secured by an independent statistical consultant from Sealed Envelope Ltd (UK). The codes will be made available to Brecon Pharmaceuticals Limited (UK) explicitly for the treatment packs to be created in accordance with the randomisation list. Eligibility will be determined from the routinely collected clinical information and no trial-specific tests are required. Women eligible for inclusion should be randomised to receive either active (tranexamic acid) or placebo (sodium chloride 0.9%) treatment and the trial treatment started as soon as possible.

Baseline information will be collected on the trial entry form and the next lowest consecutively numbered pack will be taken from a box of eight treatment packs. When the treatment ampoule is confirmed as being intact, at this point the patient is considered to be randomised onto the trial. The entry form data will be sent to the Trial Coordinating Centre as soon as possible. Once a patient has been randomised, the outcome of the woman should be obtained even if the trial treatment is interrupted or is not actually given.

2.8 TREATMENT

Tranexamic acid will be compared with matching placebo (sodium chloride 0.9%).

2.8.1 DOSE SELECTION

In randomised trials of antifibrinolytic agents in surgery, TXA dose regimens vary widely. Loading doses range from 2.5 mg/kg to 100 mg/kg and maintenance doses from 0.25 mg/kg/hour to 4 mg/kg/hour given over periods of one to twelve hours. Studies examining the impact of different doses of tranexamic acid on bleeding and transfusion requirements showed no significant differences between a high dose and a low dose. Studies in cardiac surgery have shown that a 10 mg/kg initial dose of TXA followed by an infusion of 1 mg/kg/hour produces plasma concentrations sufficient to inhibit fibrinolysis in vitro. Horrow et al (1995) examined the dose-response relationship of TXA and concluded that 10 mg/kg followed by 1 mg/kg/hour decreases bleeding in cardiac surgery, but larger doses did not provide any additional haemostatic benefit.[32] Trials of the use of TXA for the prevention of obstetric haemorrhage used TXA at a dose of 1 gram without major complications.[20]

In the emergency situation, the administration of a fixed dose is more practicable since weighing women with PPH would be difficult. Therefore, a fixed dose of 1 gram of TXA initially followed by 1 gram if bleeding continues, which is within the dose range which has been shown to inhibit fibrinolysis and provide haemostatic benefit, has been selected for the WOMAN trial. On the basis of experience in surgery, the dose selected would be efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg), as the estimated dose/kg that the patients in the latter group would receive has been applied in other trials without significant adverse effects.

2.8.2 DRUG MANUFACTURE, BLINDING AND SUPPLY OF TRIAL TREATMENT

The active trial drug tranexamic acid (Cyklokapron® Injection) will be purchased on the open market in the UK. TXA is manufactured by Pfizer Ltd under Marketing Authorisation Number: PL 00032/0314. The Marketing Authorisation guarantees that the product has been manufactured and released in accordance with the United Kingdom's Good Manufacturing Regulations.

Placebo (sodium chloride 0.9%) will be manufactured specially to match the tranexamic acid by South Devon Healthcare NHS Trust, Kemmings Close, Paignton, Devon, TQ4 7TW, under UK Manufacturer's authorisation Number: MS13079 / MA(IMP) 13079.

Ampoules and packaging will be identical in appearance. The blinding process and first stage Qualified Person (QP) release will be done by Brecon Pharmaceuticals Limited, Wye Valley Business Park, Hay-on-Wye, Hereford HR3 5PG, under UK Manufacturer's authorisation Number MIA 11724/MIA IMP 11724. The blinding process will involve complete removal of the original manufacturer's label and replacement with the clinical trial label bearing the randomisation number which will be used as the pack identification. Other pack label text will be identical for both TXA and placebo treatments and will be in compliance with requirements for investigational medicinal products. Treatment packs containing TXA and placebo will be packed in balanced blocks of 8 (4 TXA: 4 Placebo) into a box in random order.

Brecon Pharmaceuticals Limited will also be responsible for maintaining the Product Specification File (PSF) until final database lock and unblinding of the trial data. Quality control checks to assure blinding process will be performed on a random sample of final QP released drug packs. High Performance Liquid Chromatography analyses (HPLC) separation of known tranexamic acid will be assessed against blinded samples to confirm which ampoule contains the placebo and active treatments. The tested samples will be unblinded to assure accuracy of blinding.

The Trials Coordinating Centre (TCC) will be responsible for assuring all relevant approvals are available at the TCC before release of the trial treatment to a site.

2.8.3 ADMINISTRATION OF TRIAL TREATMENT

Each treatment pack will contain:

- 4 x 500mg ampoules of tranexamic acid or placebo
- 2 x sterile 10mL syringe and 21FG needle
- Stickers (for attaching to data forms and patient medical records)

TREATMENT	AMPOULES	DOSE (TRANEXAMIC ACID OR PLACEBO)	ADMINISTRATION INSTRUCTION
DOSE 1	2	1 gram	To be administered by intravenous injection at an approximate rate of 1 mL/minute to all randomised women as soon as possible after randomisation.
DOSE 2	2	1 gram	If after 30 minutes bleeding continues, or if it stops and restarts within the 24 hours after the first dose, a second dose may be given. To be administered by intravenous injection at an approximate rate of 1 mL/minute.
The trial treatment injections should not be mixed with blood for transfusion, or infusion solutions containing penicillin or mannitol.			

2.8.4 OTHER TREATMENTS FOR PPH

There is a wide spectrum of first and second line treatments of postpartum haemorrhage. As the trial will be conducted worldwide, each participating site should follow its own clinical guidelines for the treatment of postpartum haemorrhage. Information on other treatments given will be collected on the outcome form. Tranexamic acid or placebo would be an additional treatment to the routine management of postpartum haemorrhage.

2.9 ADVERSE EVENTS (AEs)

TXA has a well documented safety profile. No increase in thromboembolic risks associated with its use has been shown to date. However, as discussed in Section 1.3 an expected complication of pregnancy is an increased risk of thromboembolic events. This trial will collect data on all thromboembolic events as secondary outcomes, and all such events are routinely reported to the independent data monitoring committee (DMC) for unblinded review.

Definitions:

Adverse event (AE)

Any untoward medical occurrence affecting a trial participant during the course of a clinical trial

Serious Adverse Event (SAE)

A serious adverse event (experience) is any untoward medical occurrence that at any dose

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Adverse Reaction (AR)

An adverse event when there is at least a possibility that it is causally linked to a trial drug or intervention

Serious Adverse Reaction (SAR)

SAE that is thought to be causally linked to a trial drug or intervention

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An *unexpected* occurrence of a SAR; there need only be an index of suspicion that the event is a previously unreported reaction to a trial drug or a previously reported but exaggerated or unexpectedly frequent adverse drug reaction.

Reporting of Adverse Events for this trial: Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes to be reported in this trial and also to the independent data monitoring committee. This clinical trial is being conducted in a critical emergency condition, using a drug in common use. It is important to consider the natural history of the critical medical event affecting each woman enrolled, the expected complications of this event and the relevance of the complications to TXA.

Adverse events to be reported using an adverse event reporting form will be limited to those NOT already listed as primary or secondary outcomes, yet, which might reasonably occur as a consequence of the trial drug. Events that are part of the natural history of the primary event of PPH or expected complications of PPH should not be reported as adverse events.

In addition, if a woman is discharged from the randomising hospital before day 42 and is readmitted to hospital, requires medical care for any reason or is known to have died, an 'adverse event form' should be completed irrespective of the cause.

If a Serious Adverse Event occurs, this should be logged by calling the Trial Coordinating Centre Emergency Helpline and a written report submitted within 24 hours. The TCC will coordinate the reporting of all SAEs to all relevant Regulatory Agencies, Ethics Committees and local investigators as per local legal requirements.

2.10 UNBLINDING

In general there should be no need to unblind the allocated treatment. If some contraindication to antifibrinolytic therapy develops after randomisation, e.g. 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 antifibrinolytic 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.

2.11 MEASURES OF OUTCOME

After a patient has been randomised, outcome in hospital will be collected even if the trial treatment is interrupted or is not actually given. No extra tests are required but a short single page Outcome Form will be completed 6 weeks (42 days) after randomisation, at discharge from the randomising hospital or at death (whichever occurs first).

Primary Outcome: The primary outcome is the proportion of women who die or undergo hysterectomy. The primary cause of death will be described.

Secondary outcomes:

(a) Death

(b) Surgical Interventions including hysterectomy; brace suture (B-Lynch/Cho); selective arterial embolisation; laparotomy for other reasons; manual removal of placenta; intrauterine tamponade (packing or gauzing the uterine cavity, condom-catheter, any other method of intrauterine tamponade); artery ligation, to achieve haemostasis.

(c) Blood transfusion – blood or blood component units transfused

(d) Health Related Quality of life (HRQoL) will be measured by the proxy version of the EQ-5D at discharge from the randomising hospital or in hospital at 42 days after randomisation. The EQ-5D includes single item measures of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item is coded using 3 levels (1 = no problems; 2 = some problems; 3 = severe problems). The instrument includes a global rating of current health using a visual analogue scale (VAS) ranging from 0 (worst imaginable) to 100 (best imaginable). The EQ-5D is a generic measure of health status that provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care.

(e) Thromboembolic events (myocardial infarction, strokes, pulmonary embolism, deep vein thrombosis)

(f) Medical events including renal failure, Adult Respiratory Distress Syndrome, hypertensive disorders of pregnancy (including HELLP Syndrome, eclampsia, toxaemia of pregnancy) and other adverse events reported

(g) Length of stay at hospital / time spent at an intensive care unit

(h) Receipt of mechanical ventilation

(i) Status of baby/ies: The health status of the baby/ies will be ascertained and information collected on any thromboembolic events in breastfed babies

(j) Cost-effectiveness analysis**:** An economic analysis will be relevant if TXA clearly demonstrates efficacy in achieving its clinical aims. In this case, the study will be undertaken in the form of a cost-effectiveness analysis with the aim of estimating the incremental cost-effectiveness ratio comparing the use of TXA with normal clinical practice. Analysis will be based on adjusted life years gained. A further analysis will explore the use of the EQ-5D data to quality adjust survival. In this study, the economic analysis is clearly bounded as virtually all significant resource use will occur in the initial period of hospitalisation. As such, neither a long-term resource analysis nor an analysis of out of hospital costs will be required. The trial use of TXA is likely to mirror its use in normal clinical practice, hence the cost-effectiveness estimated in the trial (adjusted for protocol driven costs) will closely approximate cost-effectiveness in actual clinical practice. Data on physical resource consumption (e.g. length and nature of hospital stay) will be collected for each patient and a common unit cost at a country level will be applied. A sensitivity analysis will be undertaken to assess the robustness of the economic analysis in response to variations in key variables such as drug prices. In all cases, the economic analysis will be integrated with the clinical trial procedures to optimise efficiency and minimise inconvenience to patients.

2.12 DATA COLLECTION

This trial will be coordinated from LSHTM and conducted in hospitals in low, middle and high income countries. Most recruitment will be in countries with high rates of mortality and morbidity from postpartum haemorrhage. Data will be collected at each site by local investigators and transmitted to the TCC. Only data outlined on the entry, outcome and adverse event forms will be collected for this trial.

Relevant data on an entry form will be collected before randomisation to assess eligibility and the form completed if randomised. The outcome form should be completed at death, discharge from the randomising hospital or 6 weeks (42 days) after randomisation whichever occurs first. This data should be collected from the woman's and her baby/ies routine medical records as no special tests are required.

If the woman (or her PeR or PrR) withdraws a previously given informed consent or refuses to consent for continuation in the trial, or if the woman dies and no consent is available from either a PeR/PrR, her data will be handled as follows:

- Data collected to the point of withdrawal of consent will be used as part of the intention to treat analysis
- All relevant adverse events identified will be reported as required to all relevant authorities

To allow for variation in available technology for data transfer a variety of methods will be used in this trial. Data will be collected by the investigator on paper case report forms (CRFs) and transmitted to the TCC either as a paper form (by fax or email) or by entering the data directly into the trial database. Data can also be transmitted by entry onto electronic data files which can be emailed or uploaded to the TCC secure web server. In cases where electronic data files are used, data stored on the investigator's computer(s) and data during transfer will be secured by encryption. The data will be used in accordance with local law and ethics committee approval.

2.13 MONITORING

GCP section 5.18.3 states in regard to monitoring, *"The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators*

training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."

This trial is a large, pragmatic, randomised placebo controlled trial. The intervention (tranexamic acid) has marketing authorisation in many countries and has been in clinical use for over 40 years. Its safety profile is well established and no significant serious adverse events associated with its use have been identified. The trial will routinely collect data on adverse events which may theoretically be associated with this product and the condition under investigation, and these will be reviewed routinely by the independent Data Monitoring Committee (DMC). Other than consent, the administration of the trial drug using a routine clinical procedure and collecting routine clinical information from the medical records, there are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in this research study has been assessed as low risk to participants in each of these categories. Based on the low risks associated with this trial, a Monitoring Plan to assure appropriate conduct of the trial will be developed which will incorporate 100% central monitoring in conjunction with procedures such as investigator training and meetings and written guidance. In addition, all data will be subject to statistical monitoring and at least 10% of data will be subjected to on-site monitoring.

Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial related and source documents must be kept for five years after the end of the trial.

2.14 END OF TRIAL FOR PARTICIPANTS

The trial ends either at death, discharge, or six weeks post-randomisation, whichever occurs first. If during the treatment phase a woman develops an adverse event the trial drug should be stopped, woman treated in line with local procedures and then followed up.

The trial may be terminated early by the Trial Steering Committee (TSC). The DMC may give advice/recommendation for the early termination of the trial but the TSC is responsible for the final decision.

2.15 ANALYSIS

The main analyses will compare all those allocated antifibrinolytic treatment versus those allocated placebo, on an 'intention to treat' basis, irrespective of whether they received the allocated treatment or not. Results will be presented as appropriate effect estimates with a measure of precision (95% confidence intervals). Subgroup analyses for the primary outcome will be based on type of delivery (vaginal or caesarean section); administration or not of prophylactic uterotonics; and on whether the clinical decision to consider trial entry was based primarily on estimated blood loss alone or on haemodynamic instability. Interaction test will be used to test whether the effect of treatment (if any) differs across these subgroups. Between-sites heterogeneity in effectiveness will be explored. All analyses will be conducted in STATA. 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 TRIAL ORGANISATION AND RESPONSIBILITIES

3.1 SPONSORSHIP AND TRIAL MANAGEMENT

The WOMAN 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. The responsibilities of the TCC will be overseen by the Trial Management Group.

3.2 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.

3.3 PROTOCOL DEVELOPMENT

The Protocol Committee consists of the following investigators who will be responsible for the development of and agreeing to the final protocol. Subsequent changes to the final Protocol will require the agreement of the Trial Steering Committee.

<table>
<tr><th>CHIEF INVESTIGATOR</th><th>CLINICAL EXPERTS</th></tr>
<tr><td>Professor Ian Roberts
Trials Coordinating Centre
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT, UK
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<tr><th>TRIAL MANAGEMENT</th><td rowspan="2">Dr Metin Gülmezoglu
Department of Reproductive Health and Research
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<tr><td>Ms Haleema Shakur, Senior Lecturer
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<tr><th>STATISTICIAN</th><td rowspan="2">Professor Carine Ronsmans
Infectious Diseases Epidemiology Unit
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<tr><td>Professor Diana Elbourne
Medical Statistics Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT, UK
Email: Diana.Elbourne@Lshtm.ac.uk</td></tr>
</table>

3.4 INDEPENDENT DATA MONITORING COMMITTEE (DMC)

Membership:

NAME	AFFILIATION	EXPERTISE
Professor Sir Iain Chalmers	James Lind Initiative, Oxford, UK	Large scale randomised controlled trials; Obstetric care
Professor Pisake Lumbiganon	Professor of Obstetrics & Gynaecology; Convenor, Thai Cochrane Network; Faculty of Medicine, Khon Kaen University, Thailand	Obstetric care
Dr Gilda Piaggio	Statistika Consultoria, São Paulo, Brazil	Statistician (Extensive experience of reproductive health and research at the World Health Organization)

Mortality and severe morbidity is expected within the target population. To provide protection for study participants, an independent DMC has been appointed for this trial to oversee the safety monitoring. The DMC will review on a regular basis accumulating data from the ongoing trial and advise the Trial Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial.

The DMC composition, name, title and address of the chairman and of each member, will be given in the DMC Charter which will be in line with that proposed by the DAMOCLES Study Group.[33] Membership includes expertise in the relevant field of study, statistics and research study design. The DMC Charter includes, but is not limited to, defining:

(a) the schedule and format of the DMC meetings
(b) the format for presentation of data
(c) the method and timing of providing interim reports
(d) stopping rules

Standard Operating Procedures: The Data Monitoring Committee (DMC) has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup), should be revealed to the TSC. The DMC Charter states that they will do this if, and only if, two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of, participants in terms of the major outcome; (2) The results, if revealed, would be expected to substantially change the prescribing patterns of clinicians who are already familiar with any other trial results that exist. Exact criteria for “proof beyond reasonable doubt” are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. DMC Charter is in agreement with the Peto-Haybittle[34,35] stopping rule whereby an interim analysis of major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure. An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgment.

3.5 TRIAL STEERING COMMITTEE

Membership:

NAME	AFFILIATION	EXPERTISE
Professor Adrian Grant (Chair)	Director, Health Services Research Unit, University of Aberdeen	Health Services Research; Randomised Control Trials
Professor Ian Roberts (Principal Investigator)	London School of Hygiene & Tropical Medicine	Epidemiology; Randomised Control Trials; Conduct of large scale international trials
Dr Metin Gülmezoglu	Dr Metin Gülmezoglu World Health Organization, Geneva	Obstetrician; Co-ordinating Editor of the WHO Reproductive Health Library; Randomised Control Trials
Dr Kaosar Afsana	BRAC Health Programme, Bangladesh	Reproductive & Sexual Health & Rights; Rural and Urban Maternal, Neonatal and Child Health Programme in BRAC
Dr Oladapo Olayemi	University College Hospital, Ibadan, Nigeria	Consultant Obstetrician; perspective on obstetrics in a developing country
Professor Beverley Hunt	Kings College, London	Professor of Thrombosis & Haemostasis, Randomised Control Trials

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC must be in agreement with the final Protocol and, throughout the trial, will take responsibility for:

(a) major decisions such as a need to change the protocol for any reason
(b) monitoring and supervising the progress of the trial
(c) reviewing relevant information from other sources
(d) considering recommendations from the DMC
(e) informing and advising the Trial Management Group on all aspects of the trial

The steering committee consists of experienced obstetric experts, clinical trialists as well as a Reproductive & Sexual Health & Rights representative. Face to face meetings will be held at regular intervals determined by need, but no less than once a year. A TSC Charter will be agreed at the first meeting which will detail how it will conduct its business.

When outcome data are available for 1,000 trial participants, the TSC will review the rate of recruitment into the trial and the overall event rates. The TSC will consider the extent to which the rate of recruitment and the event rates correspond to those anticipated before the trial and will take whatever action is needed in light of this information.

3.6 COLLABORATORS' RESPONSIBILITIES

Coordination within each participating hospital will be through a local Principal Investigator whose responsibility will be detailed in an agreement in advance of starting the trial and will include:

- 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 TRIAL MANAGEMENT GROUP (TMG) AND TRIAL COORDINATING CENTRE (TCC) RESPONSIBILITIES

- The Trial Management Group will consist of the Protocol Committee members (Section 3.3) plus a trial manager, data manager and trial administrator.
- The TCC will act on behalf of the Sponsor and will be responsible to the TMG to ensure that all Sponsor's responsibilities are carried out. The responsibilities will include (but not limited to):
  - Report to the Trial Steering Committee
  - Maintain the Trial Master File
  - Identify trial sites
  - Confirm all approvals are in place before release of the trial treatment and the start of the trial at a site
  - Provide training about the trial
  - Provide study materials
  - Data management centre
  - 24-hour advice and unblinding service
  - Give collaborators regular information about the progress of the study
  - Respond to any questions (e.g. from collaborators) 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
  - Publication of trial results

3.8 CONTACTING THE TCC IN AN EMERGENCY

For urgent enquiries, adverse event reporting and unblinding queries investigators can contact the 24-hour telephone service provided by the TCC. A central telephone number is given in the Investigator's Study File and posters.

3.9 PUBLICATION AND DISSEMINATION OF RESULTS

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. All publications will follow relevant external guidance such as the *'Uniform Requirements for Submission of Manuscripts to Biomedical Journals'* issued by the International Committee of Medical Journal Editors (ICMJE) (2008 update) and the CONSORT statement.[36,37] Links to the publication will be provided in all applicable trial registers. Dissemination of results to patients will take place via the media, trial website (www.thewomantrial@Lshtm.ac.uk) and relevant patient organisations. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients.
The success of the trial will be dependent entirely upon the collaboration of midwives, nurses and doctors in the participating hospitals and those who hold key responsibility for the trial. Hence, the credit for the study will be assigned to the key collaborator(s) from a participating site as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to trial collaborators.

3.10 FINANCIAL SUPPORT

The run-in costs for this trial and up to 2,000 patients' recruitment were funded by LSHTM. Funding to complete the recruitment of 15,000 patients is provided by the Health Innovation Challenge Fund (Wellcome Trust and Department of Health, UK). The recruitment of the additional 5,000 patients as well as dissemination and implementation planning is funded by Bill and Melinda Gates Foundation. 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. The design and management of the study are entirely independent of the manufacturers of tranexamic acid, which is not a new product.

Large trials of such drugs, involving many hospitals, are important for future patients, but are practicable only if those collaborating in them do so without payment (except for recompense of any minor local costs that may arise). Agreement for repayment of local costs will be made in advance.

4 ABBREVIATIONS USED

AE	Adverse Event
AR	Adverse Reaction
CONSORT	CONsolidated Standards of Reporting Trials
CRF	Case Report Form
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
FG	French Gauge
GCP	Good Clinical Practice
HELLP	Hemolytic anemia, Elevated Liver enzymes and Low Platelet count
HPLC	High Performance Liquid Chromatography
HRQoL	Health Related Quality of Life
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
ICMJE	International Committee for Medical Journal Editors
kg	Kilogram
LSHTM	London School of Hygiene & Tropical Medicine
MDG	Millennium Development Goal
mg	Milligram
mL	Millilitre
PeR	Personal Representative
PPH	Postpartum Haemorrhage
PrR	Professional Representative
PSF	Product Specification File
QP	Qualified person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Trials Coordinating Centre
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic Acid
UK	United Kingdom
VAS	Visual Analogue Score
WHO	World Health Organisation

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6 APPENDICES

Appendix 1: Entry form

Appendix 2: Outcome form

Appendix 3: Country/site specific documents

a) Brief information leaflet for pregnant women & family
b) Consent procedure overview
c) Information sheet for woman and her representative
d) Informed consent form for woman
e) Informed consent form for representative

APPENDIX 1 – ENTRY FORM (page 1)

World Maternal Antifibrinolytic Trial

ENTRY FORM

PLEASE COMPLETE BEFORE RANDOMISING THE WOMAN

ABOUT YOUR HOSPITAL *(please ensure all information below is contained in the medical records)*

1. Country	
2. Hospital code *(in your Study File)*	

ABOUT THE PATIENT

3. Patient's initials *(first name/last name)*		**4.** Patient Hospital identification number					
5. Do you know her date of birth? *(circle)*	a) YES	*day*	*month*	*year*	b) NO – approximate age		*years*

ABOUT THE DELIVERY

6. Delivery of the baby in this hospital? *(circle)*	YES	NO				
7. Type of delivery *(circle)*	VAGINAL	CAESAREAN SECTION				
8. Date of delivery	*day*	*month*	*year*			
9. Time of delivery *(24-hour clock)*	*hours*	*minutes*				
10. Placenta fully delivered? *(circle)*	YES	NO				
11. Primary cause of haemorrhage? *(circle)*	UTERINE ATONY	PLACENTA PRAEVIA/ACCRETA	SURGICAL TRAUMA/TEARS	OTHER	UNKNOWN	
12. Systolic Blood Pressure		*mmHg (most recent measurement prior to randomisation)*				
13. Estimated volume of blood loss		*Millilitres (estimated from delivery of baby to immediately prior to randomisation)*				
14. Any uterotonic prophylaxis given?	YES	NO	UNKNOWN			
15. Clinical signs of haemodynamic instability?	YES	NO	*Haemodynamic instability assessment based on clinical signs (e.g.low BP, tachycardia, falling urine output) that requires an intervention (e.g. intravenous fluids)*			

RANDOMISATION INFORMATION

16. Eligible? *(circle)*	**YES** *(Get the lowest available number treatment pack and follow instructions)*		**NO** *(Do not randomise, record on screening log)*	
17. Consent obtained from? *(circle)*	Woman	Relative	Other representative	Waiver
18. Insert treatment pack number here	**BOX**		**PACK**	
19. Date of randomisation	*day*	*month*	*year*	**20.** Time of randomisation *(24-hour clock)* *hours* *minutes*
21. a)Name of person randomising patient		b) Signature		

PLEASE SEND THIS FORM TO THE COORDINATING CENTRE **IMMEDIATELY** AFTER RANDOMISATION

SEE GUIDANCE OVERLEAF

Protocol Code: ISRCTN76912190 Page 1 of 2 FINAL Version 1.0_Entry Form

APPENDIX 1 – ENTRY FORM (page 2)

DATA FORMS GUIDANCE

AFTER COMPLETING THIS PAPER FORM, YOU CAN:

- Enter these data directly into the trial database (username and password required)

  www.thewomantrial.Lshtm.ac.uk
- Complete an Electronic Data Form (EDF) and send by email or upload to the trial intranet at *www.thewomantrial.Lshtm.ac.uk*
- Send as a secure scanned document by email to *woman.data@Lshtm.ac.uk*
- Fax to +44 20 7299 4663
- Store original form in the Investigator's Study File
- **PLEASE GIVE A COPY OF THIS COMPLETED FORM TO THE PERSON RESPONSIBLE FOR COMPLETING THE OUTCOME FORM AT YOUR HOSPITAL**

NOTES:

FOR ADVERSE EVENTS, UNBLINDING AND OTHER URGENT ENQUIRIES PLEASE TELEPHONE +44(0)7768 707500

PLEASE NOTE: IF YOUR QUERY IS NOT URGENT PLEASE USE THE NORMAL CONTACT DETAILS IN THE INVESTIGATOR'S STUDY FILE.

World Maternal Antifibrinolytic Trial

OUTCOME FORM

COMPLETE AT DISCHARGE FROM THE RANDOMISING HOSPITAL, DEATH IN HOSPITAL OR 42 DAYS AFTER RANDOMISATION, WHICHEVER OCCURS FIRST

Attach treatment pack sticker here or write box/pack number below: ☐☐☐☐ / ☐☐

1. HOSPITAL CODE

2. PATIENT

a) Patient initials		b) Patient hospital ID number			
c) Date of birth	DAY (DD)	MONTH (MM)	YEAR (YYYY)	d) If not known, estimated age	

3. OUTCOME

3.1 DEATH IN HOSPITAL

a) Date of death			
DAY (DD)	MONTH (MM)	YEAR (YYYY)	

b) Primary Cause of death *(tick one option)*

- ☐ Bleeding
- ☐ Pulmonary embolism
- ☐ Other – describe here:_____

3.2 WOMAN ALIVE

a) Discharged home - Date of discharge		
DAY (DD)	MONTH (MM)	YEAR (YYYY)
b) Transferred to another hospital - Date of transfer		
DAY (DD)	MONTH (MM)	YEAR (YYYY)
c) Still in this hospital now *(42 days after randomisation)* - Date		
DAY (DD)	MONTH (MM)	YEAR (YYYY)

3.3 IF ALIVE *(at 42 days or prior discharge):*

EQ-5D Questions as follows, to be rated by the Doctor/Midwife based on their knowledge of the woman. Read instructions overleaf before completing.

a) MOBILITY ☐ no problems in walking about ☐ some problems in walking about ☐ confined to bed	**b) SELF-CARE** ☐ no problems with self-care ☐ some problems with washing or dressing ☐ unable to wash or dress	**c) USUAL ACTIVITIES** *(e.g. care for baby, work, study, housework, family or leisure activities)* ☐ no problems with performing usual activities ☐ some problems with performing usual activities ☐ unable to perform usual activities
d) PAIN / DISCOMFORT ☐ no pain or discomfort ☐ moderate pain or discomfort ☐ extreme pain or discomfort	**e) ANXIETY / DEPRESSION** ☐ not anxious or depressed ☐ moderately anxious or depressed ☐ extremely anxious or depressed	**f) VALUE RECORDED ON VISUAL ANALOGUE SCALE** *(see reverse)* ☐☐☐

4. MANAGEMENT

a) DAYS IN INTENSIVE CARE UNIT *(if no ICU or not admitted to ICU, write '0' here)*	

b) MANAGEMENT *(Circle one box on every line)*		
Hysterectomy	YES	NO
Manual removal of placenta	YES	NO
Intrauterine tamponade	YES	NO
Embolisation	YES	NO
Laparotomy for other reasons	YES	NO
Brace sutures of the uterus	YES	NO
Artery ligation	YES	NO
Mechanical ventilation *(exclude use in general anaesthetic for surgery)*	YES	NO

5. COMPLICATIONS *(Circle one box on every line)*

Pulmonary embolism	YES	NO
Deep vein thrombosis	YES	NO
Stroke	YES	NO
Myocardial infarction	YES	NO
Renal failure	YES	NO
Cardiac failure	YES	NO
Respiratory failure	YES	NO
Hepatic failure	YES	NO
Sepsis	YES	NO
Seizure	YES	NO

SEE GUIDANCE NOTES ON REVERSE

6. OTHER TREATMENTS FOR PPH

a) BLOOD PRODUCTS TRANSFUSION *(transfused in 42 days) (part unit = 1unit)*	YES	NO
Units whole blood/packed cells		units
Fresh frozen plasma		units
Other blood products		units
b) UTEROTONICS ADMINISTERED (after PPH diagnosed) *(Circle one box on every line)*	YES	NO
Oxytocin	YES	NO
Ergometrine	YES	NO
Misoprostol	YES	NO
Prostaglandins (injectable)	YES	NO

7. TRIAL TREATMENT

a) Dose 1 given	YES	NO
b) Dose 2 given	YES	NO

8. ABOUT THE BABY *(please complete a separate form for each baby delivered alive: Sections 1, 2 and 8 only)*

a) Number of live babies from this pregnancy		b) Initials of baby on this form	

c) THIS BABY *(Circle one box on each line)*		
Alive	YES	NO
Healthy	YES	NO
Any confirmed thromboembolic event?	YES	NO
Breastfed at anytime after randomisation?	YES	NO

9. PERSON COMPLETING FORM ***THE PI IS RESPONSIBLE FOR ALL DATA SUBMITTED***

a) Name			
b) Position			
c) Signature			
d) Date	DAY (DD)	MONTH (MM)	YEAR (YYYY)

Protocol Code: ISRCTN76912190 **Page 1 of 2** **FINAL Version 1.0_OUTCOME FORM**

DETAILED GUIDANCE ABOUT COMPLETING THIS FORM CAN BE FOUND IN YOUR INVESTIGATORS STUDY FILE	**SECTION 3.3: EQ-5D© INSTRUCTIONS** **THIS SECTION OF THE OUTCOME FORM IS TO BE COMPLETED BY A DOCTOR/MIDWIFE WHO HAS PERSONAL KNOWLEDGE OF THE WOMAN. THE RESPONSE YOU GIVE SHOULD BE *YOUR* PERSPECTIVE OF THIS WOMAN'S STATUS COMPARED TO A NORMAL WOMAN POSTPARTUM.**

SECTION 3.3
Please follow the EQ-5D guidance on the right.

SECTION 8
If more than one baby delivered alive from this pregnancy, please complete Sections 1, 2 and 8 on a separate outcome form for each baby. Remember to write the randomisation number in the box on the top right hand corner of each form.

HOW TO SEND
Please see detailed guidance in your investigators study file

AFTER COMPLETING THIS PAPER FORM, YOU CAN:

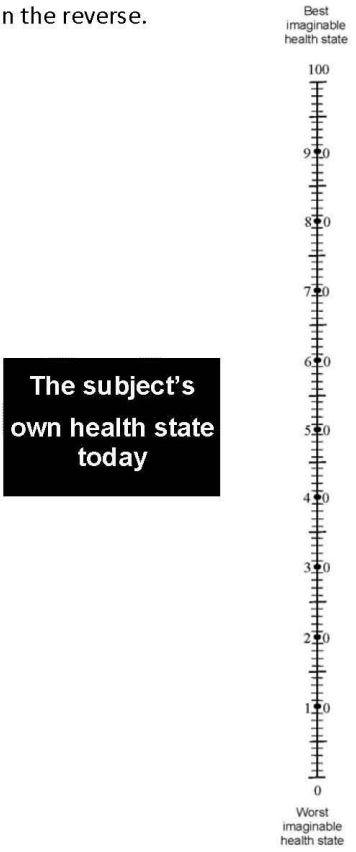
- Enter these data directly into the trial database (username and password required)
  www.thewomantrial.Lshtm.ac.uk
- Complete an Electronic Data Form (EDF) and send by email or upload to the trial intranet at *www.thewomantrial.Lshtm.ac.uk*
- Send as a secure scanned document by email to *woman.data@Lshtm.ac.uk*
- Fax to +44 20 7299 4663

STORE THIS ORIGINAL FORM IN YOUR SITEFILE

Questions a–e: By placing a tick in one box in each group, please indicate which statement best describes this woman's health state today. Do not tick more than one box in each group.

Question f: To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) below on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad the woman's health is today, **in your opinion**. Please do this by drawing a line from the black text box below to whichever point on the scale indicates how good or bad you think the woman's health is today.
Record the value on the reverse.



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APPENDIX 3a
Brief information leaflet for pregnant women & family

This hospital, like many others in this country and around the world, is involved in a research study to try and find better ways of treating women who develop severe bleeding soon after having a baby. Thank you for taking time to read this leaflet.

What is the Woman Trial about?

The WOMAN trial is a study being done to see whether using a drug called tranexamic acid will help women with severe bleeding soon after having a baby (postpartum haemorrhage) by reducing the amount of blood lost and therefore preventing them becoming too ill. This study will involve about 20,000 women worldwide. As severe bleeding is not a common problem and it is not possible to predict in advance exactly who will develop this condition, we are giving this information to all pregnant women to inform them of our plans.

What is Postpartum Haemorrhage?

Most women who give birth have no problems during or after the delivery of their baby. Following every birth there will be a small amount of bleeding from the mother – this is normal and usually nothing to worry about. However, occasionally after the baby is born there is much more bleeding. This extra bleeding is called postpartum haemorrhage (PPH). When this happens the doctors, nurses and midwives will do everything they can to stop the bleeding, because if too much blood is lost the mother may become very ill.

What causes Postpartum Haemorrhage?

Once a baby is delivered, the womb (uterus) normally continues to contract (tightening of muscles of the uterus) and this expels the placenta. After the placenta is expelled, these contractions help compress the bleeding vessels in the area where the placenta was attached. If the uterus does not contract strongly enough, these blood vessels bleed freely and haemorrhage occurs. There are many other causes of postpartum haemorrhage but this is the most common.

What is Tranexamic Acid and why use it?

Tranexamic Acid (TXA) is a drug that is used to slow down and reduce bleeding. For example, it is often used when people go for major heart surgery to stop them losing too much blood. It is also sometimes used for women who have very heavy periods. Because TXA is known to reduce blood loss in these situations, it is possible that if it is given to a woman with PPH, it may help to reduce the bleeding. But at the moment we do not know if it will help for PPH or not.

What does the study involve?

If a woman develops postpartum haemorrhage, the doctor will examine her, look at her medical records and decide whether she is suitable for the study. If she is suitable and well enough, the doctor will discuss the study with her and ask if she would be willing to take part in the WOMAN Trial. Otherwise her suitability for the trial will be discussed with her representative or the doctor/midwife primarily responsible for her, to see if she can join the trial.

If she does take part, she will receive an injection of either the TXA or a placebo (a liquid which does not contain TXA) directly into the vein. If after a while the bleeding still does not stop, the doctor may decide to give another injection of the TXA or placebo.

After six weeks, or when the woman leaves hospital, the doctor or midwife will collect some more information from the medical records of the woman and her baby/ies to let the trial team know how she is getting on.

Making a decision

Please discuss this with family and friends and if you need more information the research team at this hospital will be happy to discuss the WOMAN trial with you.

woman
World Maternal Antifibrinolytic Trial

PLEASE CONTACT:

Name of doctor or midwife	
Address	
Telephone	
Email	

Women do not have to make a decision now about taking part in this study. This information sheet is to allow them to consider carefully their wishes in the event they are asked to take part. However, if after reading this and discussing it with others you feel that you definitely do NOT want to be involved in this study, please tell your doctor or midwife and ask them to make a note in your medical records.

The study is organised by the London School of Hygiene & Tropical Medicine (University of London) and you can also contact them directly for information about the trial.

woman
World Maternal Antifibrinolytic Trial

Website	www.womantrial.Lshtm.ac.uk
Address	Trials Coordinating Centre, Room 180 London School of Hygiene & Tropical Medicine Keppel Street, London WC1E 7HT United Kingdom
Tel	+44(0)20 7299 4684
Fax	+44(0)20 7299 4663
Email	thewomantrial@Lshtm.ac.uk

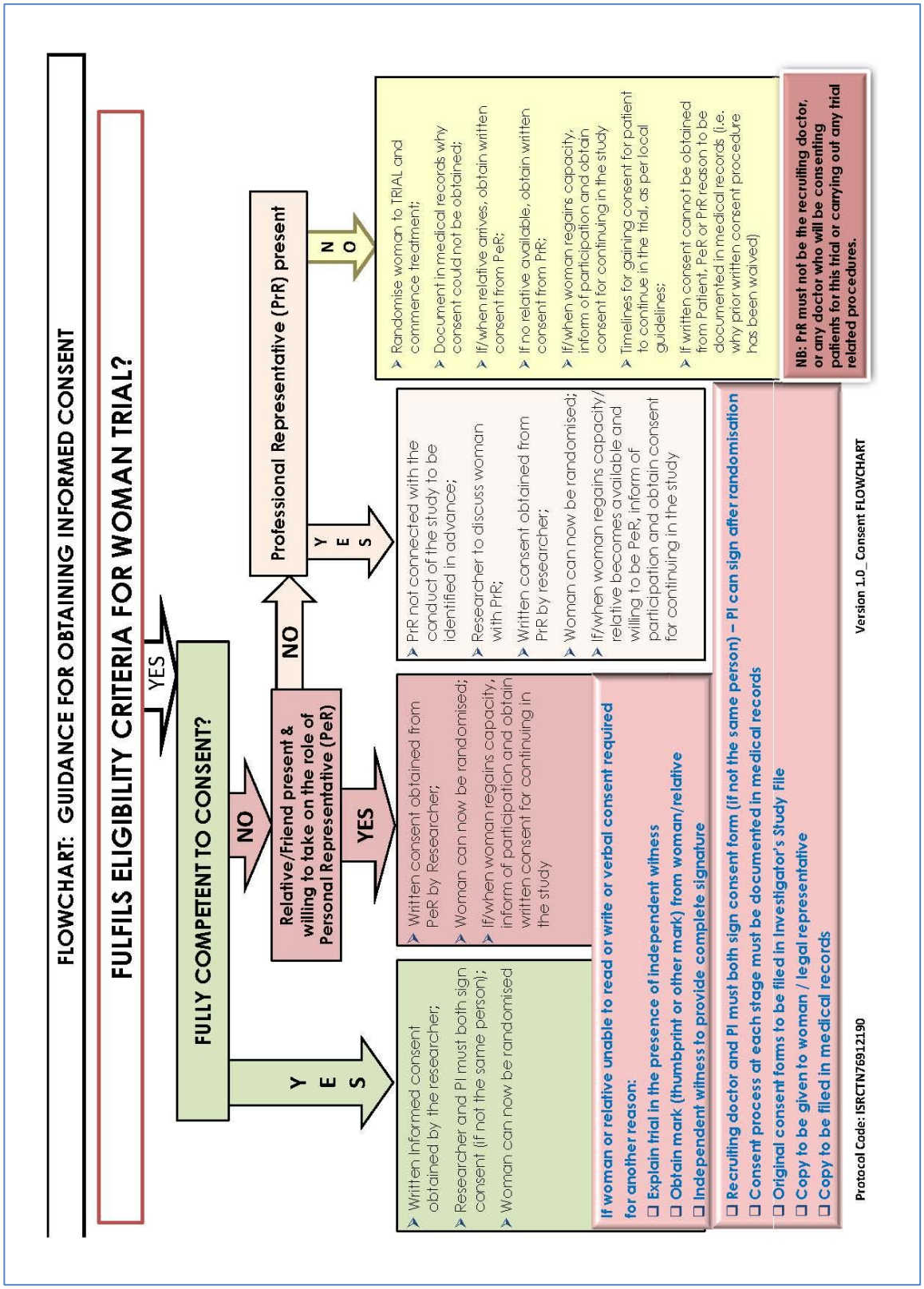
GENERAL INFORMATION LEAFLET ABOUT THE WOMAN TRIAL

woman
World Maternal Antifibrinolytic Trial

Please take a copy

MASTER Version 1.1; Protocol ISRCTN76912190; [NAME OF HOSPITAL]

APPENDIX 3b
Consent procedure overview



APPENDIX 3c
Information sheet for woman and her representative, page 1

(HOSPITAL LETTERHEAD)

INFORMATION SHEET FOR THE PATIENT AND HER REPRESENTATIVE(S)

THE WOMAN TRIAL

TITLE OF RESEARCH: TRANEXAMIC ACID FOR THE TREATMENT OF POSTPARTUM HAEMORRHAGE: AN INTERNATIONAL RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL

TRIAL SITE NUMBER: [ID from database]

LEAFLET VERSION: VERSION 1.0 DATED: 11 MAY 2009

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?

Dr _____ is in charge of this study at this hospital. The study is coordinated by doctors and a trial team at The London School of Hygiene & Tropical Medicine (University of London). If you have any questions you can contact the doctor at:

Address:	
Telephone:	

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.

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 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. 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.

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 does go 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 after 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 3d
Informed Consent Form for woman

Principal Investigator name, Hospital name
Hospital address
Telephone contact number, email for PI

CONSENT FORM FOR THE PATIENT

THE WOMAN TRIAL

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

Hospital Code Number		Name of Local Principal Investigator	
Patient Hospital ID Number		Randomisation Number	BOX / PACK
Name of Patient			

Version Number: 1.0 / Version Date: 11 May 2009 **PLEASE INITIAL BOXES**

1. I confirm that I have read and understood the information sheet Version Number_____, version date _____, 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. ☐

_____	_____	_____
Name of Patient	Date	Signature / Thumbprint or other mark (if unable to sign)
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____
Name of local principal investigator	Date	Signature

(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.

_____	_____	_____
Name of witness	Date	Signature

Original to be filed in the Investigator's Study File, 1 copy for patient,

1 copy to be kept with woman's hospital records

APPENDIX 3e
Informed Consent Form for representative

THE WOMAN TRIAL REPRESENTATIVE CONSENT FORM

Principal Investigator name, Hospital name
Hospital address
Telephone contact number, email for PI

CONSENT FORM FOR THE PATIENT'S REPRESENTATIVE

THE WOMAN TRIAL

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

Hospital code number		Name of Local Principal Investigator	
Patient Hospital ID Number		Randomisation Number	BOX / PACK
Name of Patient			
Name of Representative		Relationship of representative to patient	

Version Number: 1.0 / Version Date: 11 May 2009

PLEASE INITIAL BOXES

1. I confirm that I have read and understood the information sheet Version Number_____, version date_____, 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 baby/ies 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. ☐

_____ _____
Signature / thumbprint or other mark of Representative (if unable to sign) 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

REPRESENTATIVE CONSENT FORM [MASTER] [ENGLISH] **Protocol Code: ISRCTN76912190**