PROTOCOL 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 applicants 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 women 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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