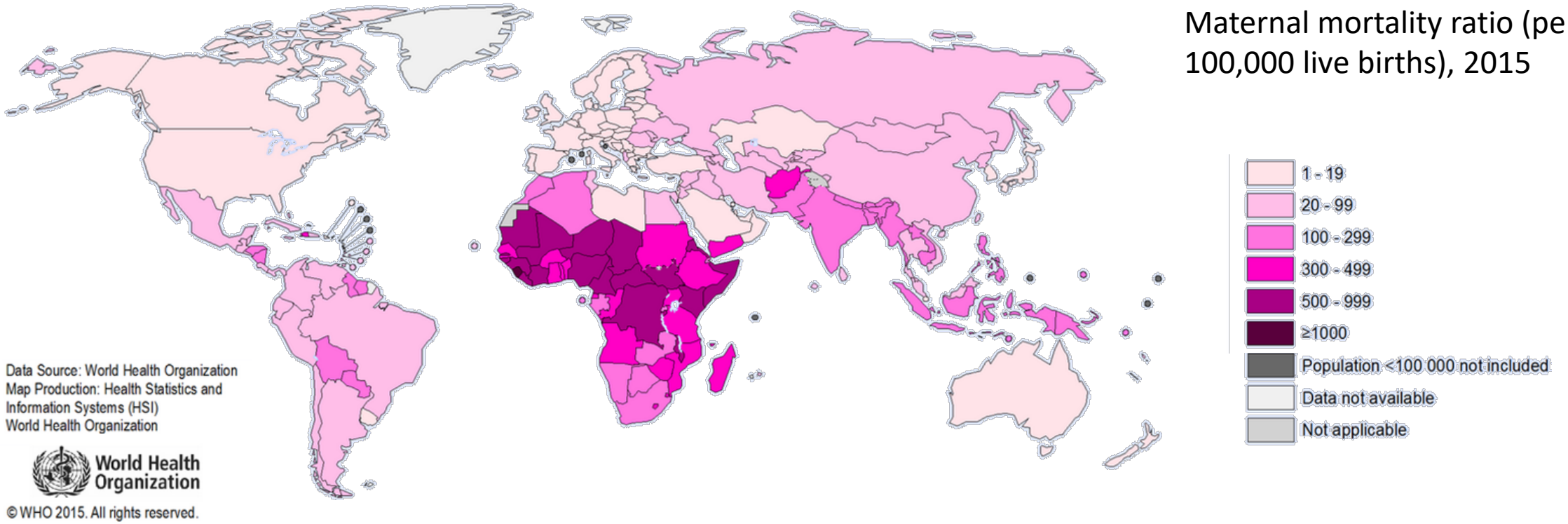
BACKGROUND, RATIONALE & OVERVIEW

Protocol number: ISRCTN62396133
Version 1.0; Date 05 April 2019

MATERNAL MORTALITY

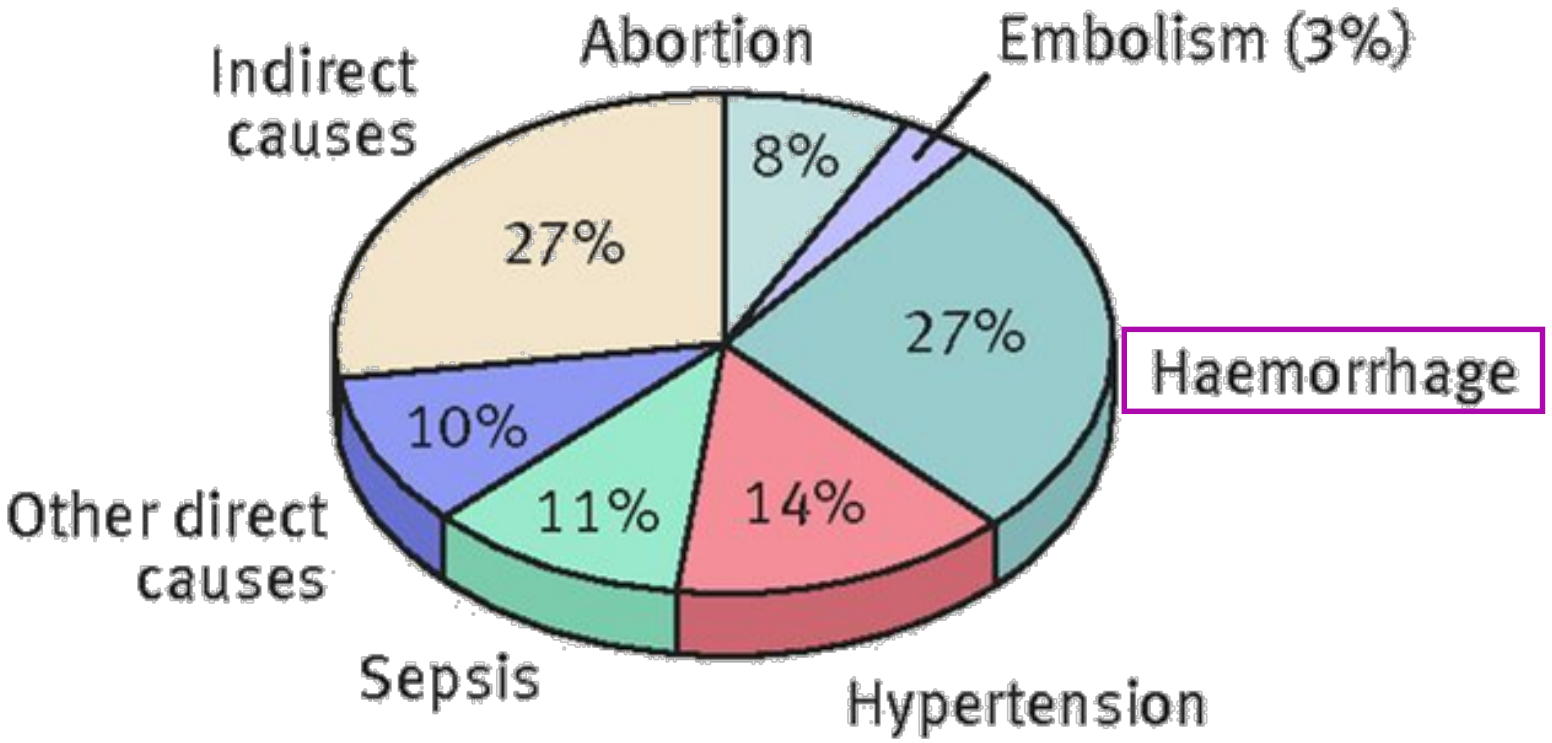
- Approximately 300,000 women die every year due to complications in pregnancy and childbirth
- 99% of deaths occur in low and middle income countries



Say L *et al.* BMC Reproductive Health 2004;1(3).
WHO, UNICEF, UNFPA and The World Bank estimates. 2015

CAUSES OF MATERNAL MORTALITY

- Postpartum haemorrhage (PPH) is a leading cause of mortality responsible for about 100,000 deaths every year

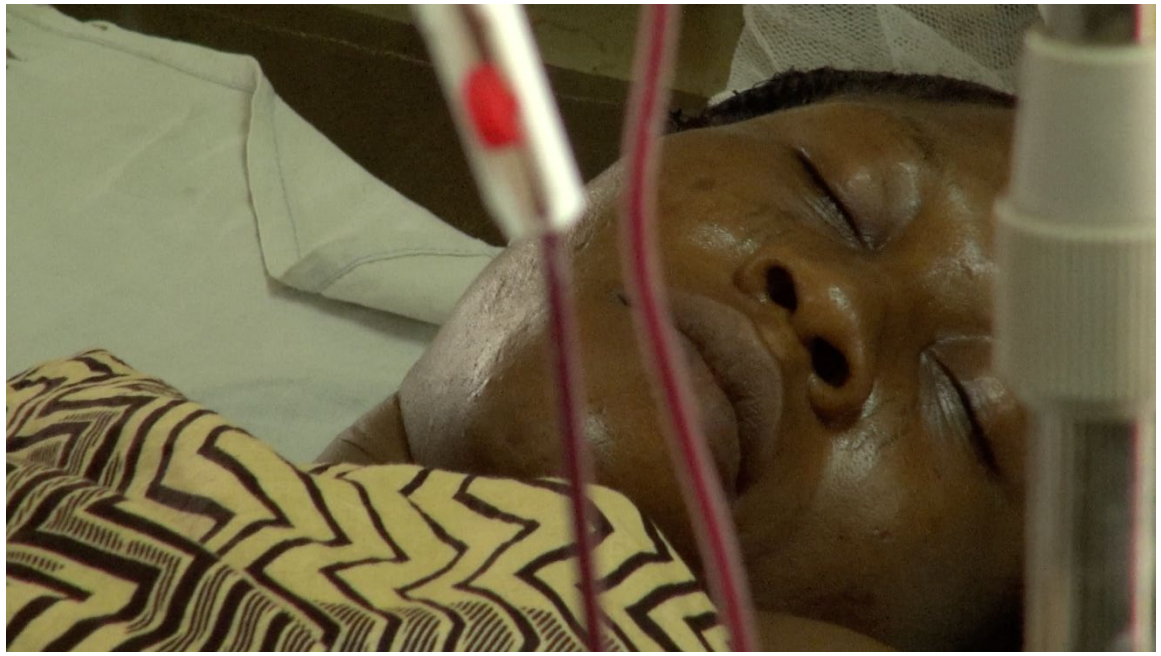


Chou *et al*. BMJ 2015;351:bmj.h4255

MATERNAL MORBIDITY

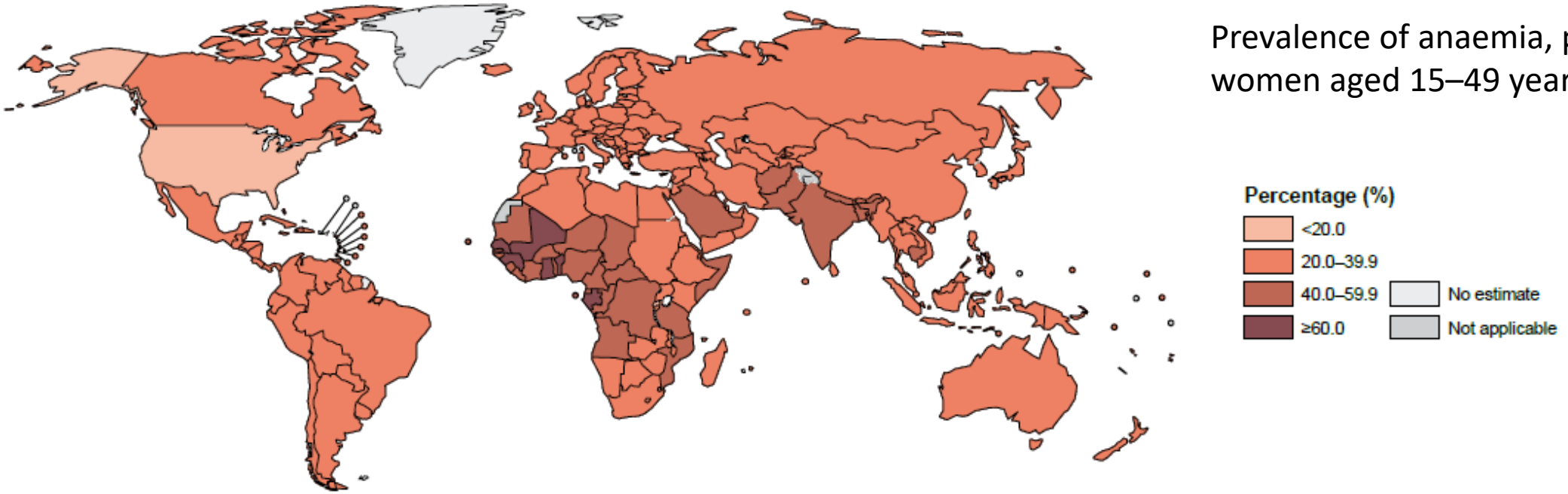
Many women who survive PPH suffer severe morbidity:

- Surgical intervention (e.g. uterine artery ligation, brace sutures)
- Hysterectomy
- Lead to or worsen existing anaemia
- Morbidity can interfere with breastfeeding and bonding
- Blood transfusion



MATERNAL ANAEMIA AND PPH

- Women with anaemia are more likely to have a PPH and to suffer worse outcomes
- Worldwide, over one third of pregnant women are anaemic

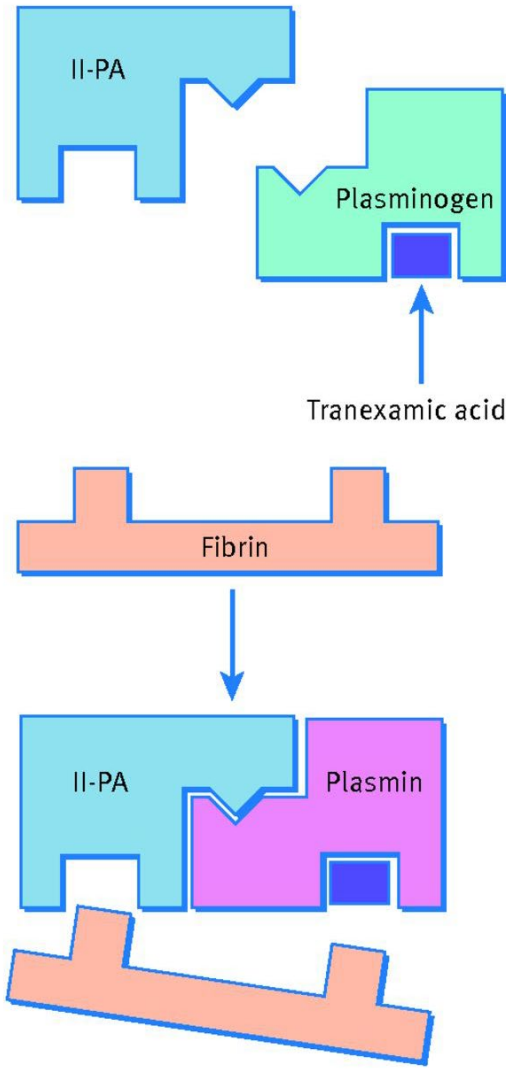


Prevalence of anaemia, pregnant women aged 15–49 years, 2011

- Prevalence is highest in countries in central and West Africa as well as in South Asia where about half of pregnant woman are anaemic

Nair *et al*. BMJ Global Health. 2016;1(e000026).
Sheldon *et al*. BJOG 2014;121, 1:5-13.
WHO. The global prevalence of anaemia in 2011. Geneva: WHO; 2015.

TRANEXAMIC ACID (TXA)



- TXA is a synthetic analogue of the amino acid lysine
- TXA exerts an antifibrinolytic effect by forming a reversible bond with the lysine binding site on the plasminogen molecule
- Plasmin is therefore prevented from interacting with fibrin and clot stability is achieved
- TXA is marketed in tablet and injection form as a treatment for a variety of chronic and acute bleeding conditions

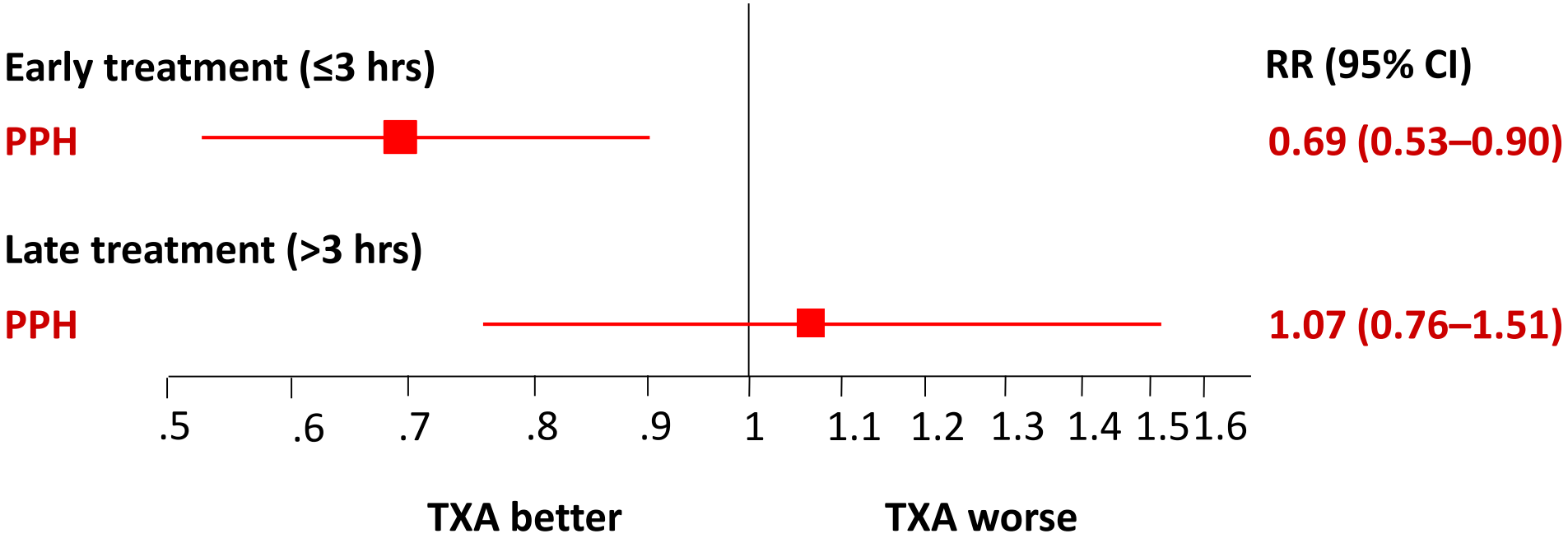
Mahmood *et al*. BMJ 2016;354:bmj.i4814

TXA FOR TREATING PPH

- 20,060 women with PPH haemorrhage after a vaginal birth or caesarean section were recruited from 193 hospitals in 21 countries
- Patients were randomised to receive either 1 g TXA or matching placebo in addition to usual care. If bleeding continued after 30 min, or stopped and restarted within 24 hr of the first dose, a second dose of 1 g of TXA or placebo could be given

The WOMAN trial Collaborators. Lancet. 2017 ; 389 (10084): 2105-16.

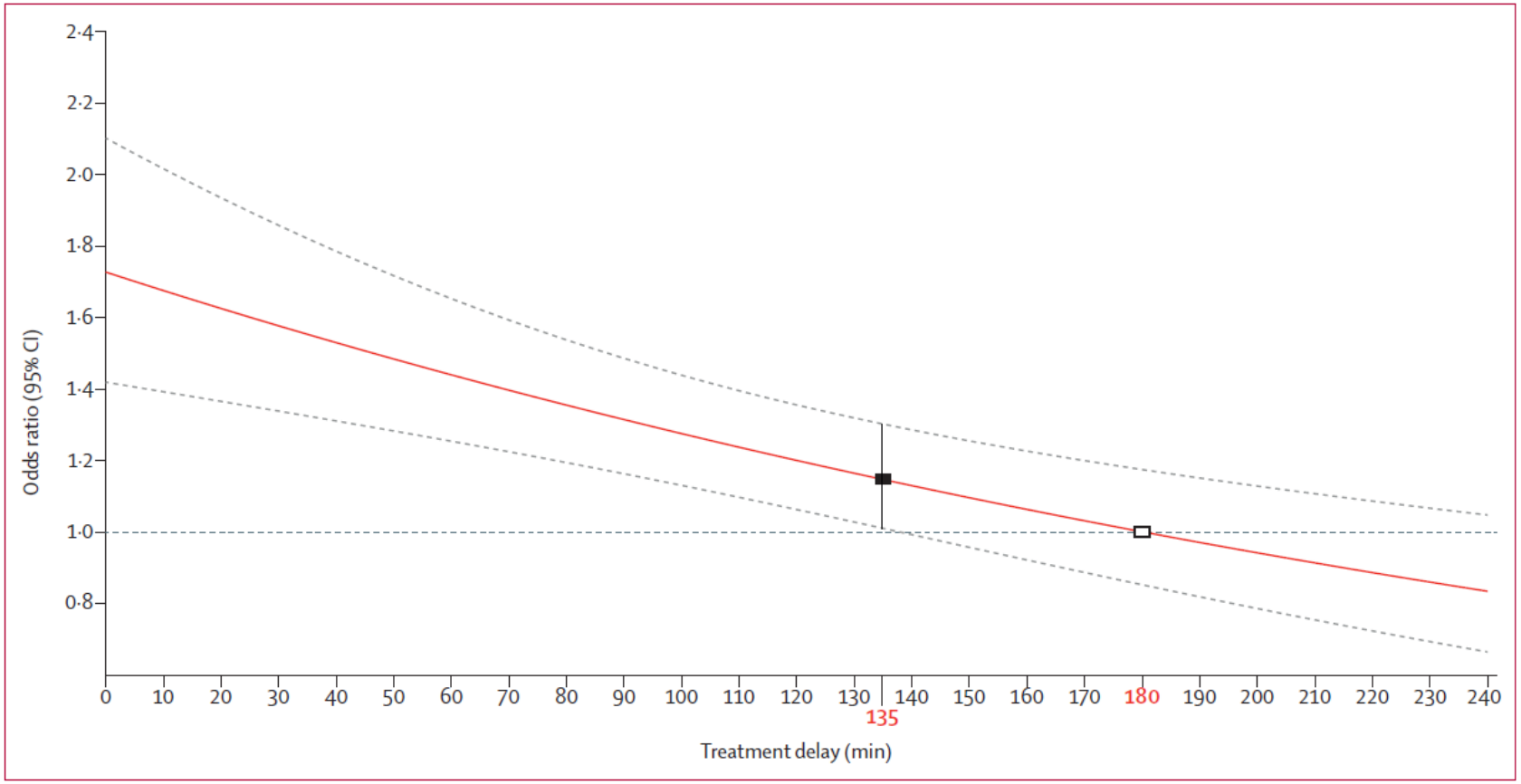
WOMAN TRIAL RESULTS



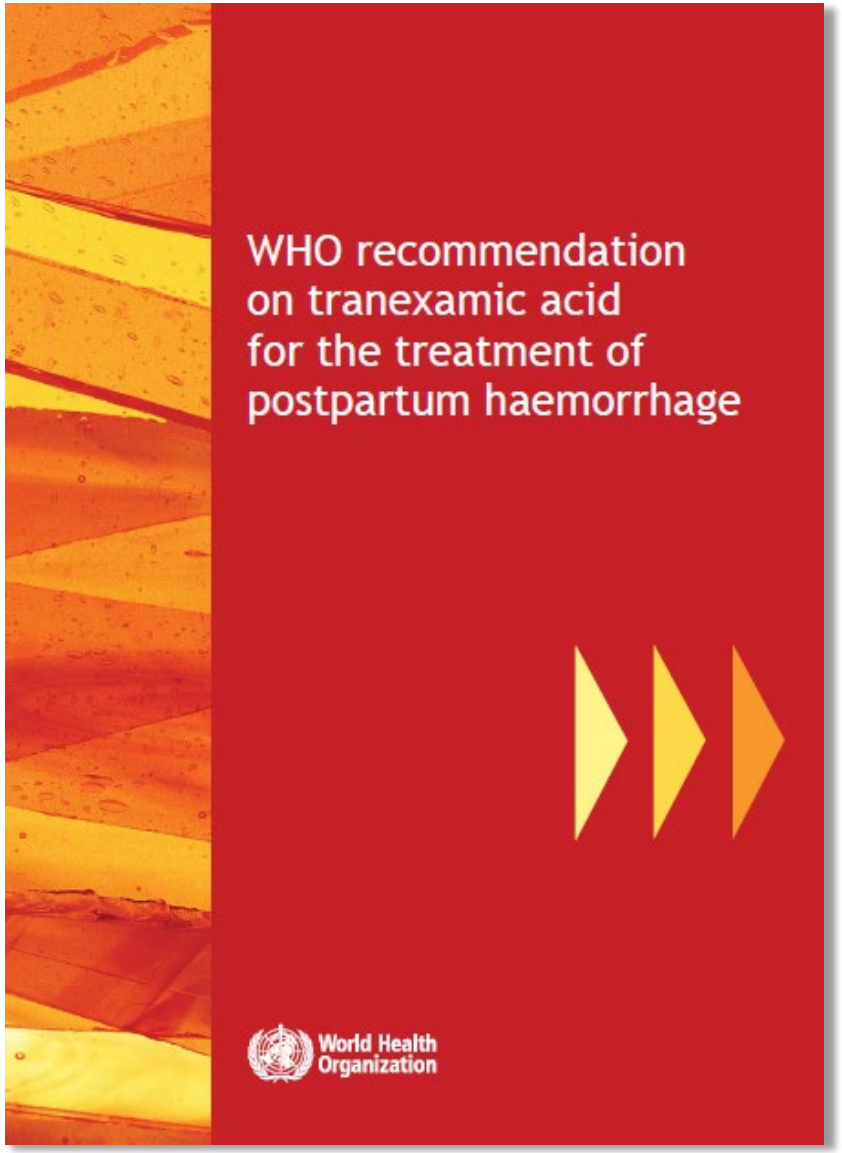
- TXA is most effective when given within three hours of birth
- TXA reduces death due to bleeding by one third
- No increase in adverse effects, including thromboembolic events

EARLY TREATMENT IS ESSENTIAL

Survival benefit decreased by 10% for every 15 min delay until 3 h, after which there was no benefit



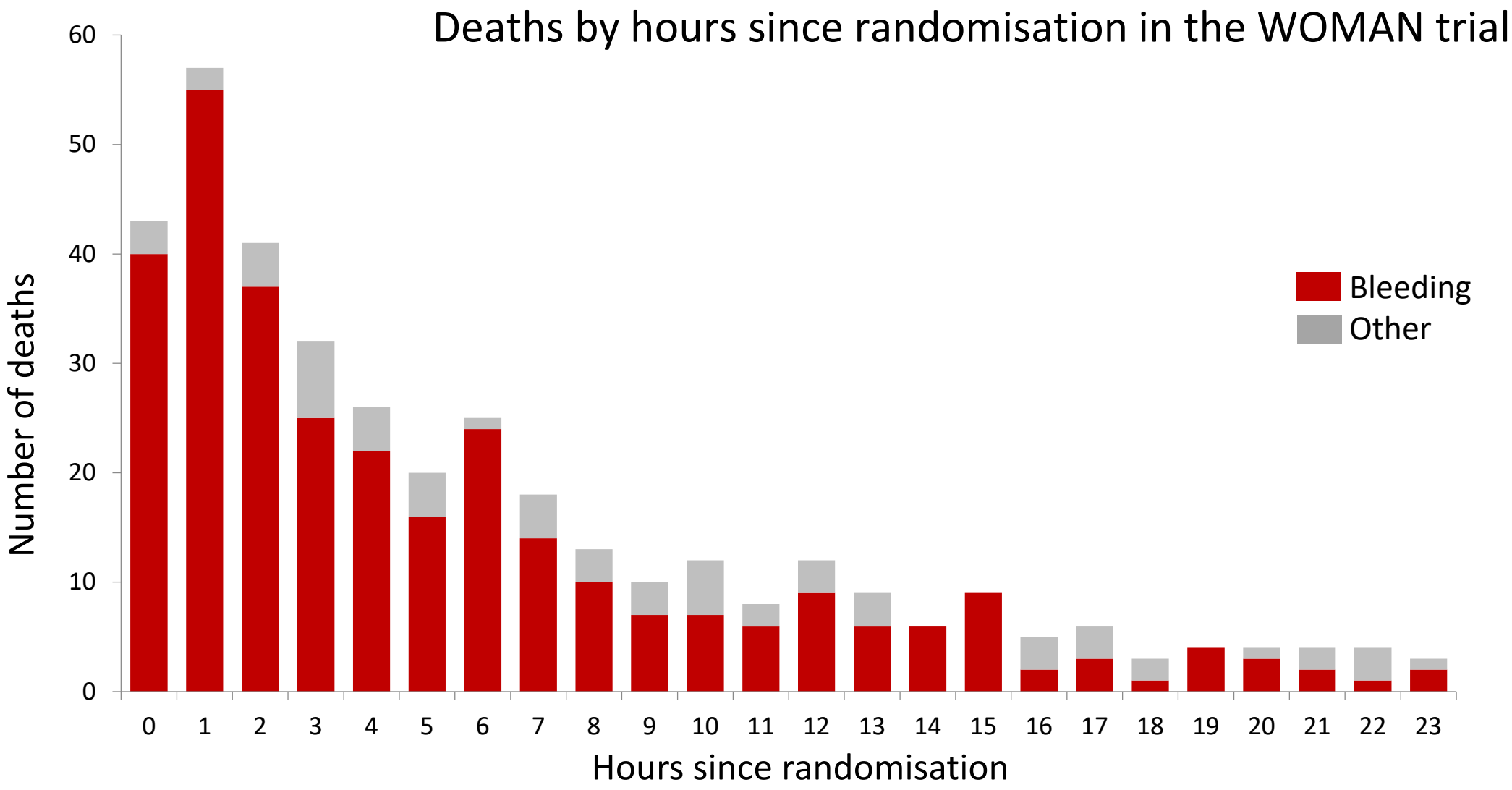
WOMAN TRIAL RESULTS



- Early use of intravenous TXA (within 3 hours of birth)

- Most deaths occur within the first two to three hours after birth, it is critical that TXA is given as soon as possible to save lives

FOR SOME WOMEN TREATMENT IS TOO LATE



The WOMAN Trial Collaborators. Lancet. 2017 ; 389 (10084): 2105-16.

TXA FOR PREVENTING PPH

- A systematic review including 26 trials assessing the effects of TXA for preventing PPH showed that many of the existing trials are small and unreliable

- The TRAAP trial is one exception

- In the TRAAP trial, 4079 women who were giving birth vaginally were randomised to receive 1 g TXA or matching placebo within two minutes after delivery

- Women who received TXA were less likely to experience blood loss of ≥500 mL but the difference was not statistically significant

Ker K *et al*. BJOG 2016;123(11):1745-52
Sentilhes L *et al*. Am. J. Obstet. Gynecol. 2018;218(1):S2-3.

IN SUMMARY

- PPH is a leading cause of maternal mortality and morbidity
- TXA reduces the risk of death in women with PPH
- For some women treatment of PPH is too late
- PPH may have a role in the prevention of PPH
- Currently there is insufficient evidence for the use of TXA to prevent PPH

TRANEXAMIC ACID FOR THE PREVENTION OF POSTPARTUM BLEEDING IN WOMEN WITH ANAEMIA: AN INTERNATIONAL, RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

WOMAN-2

Aim

To determine the effect of TXA on postpartum bleeding in women with moderate or severe anaemia

Trial design

- Randomised, double-blind, placebo controlled trial
- 10 000 women with moderate or severe anaemia who are giving birth vaginally in hospitals
- Randomised to receive 1 g of TXA or matching placebo (sodium chloride 0.9%) intravenously immediately and no later than 15 minutes after the umbilical cord is cut or clamped

Inclusion criteria

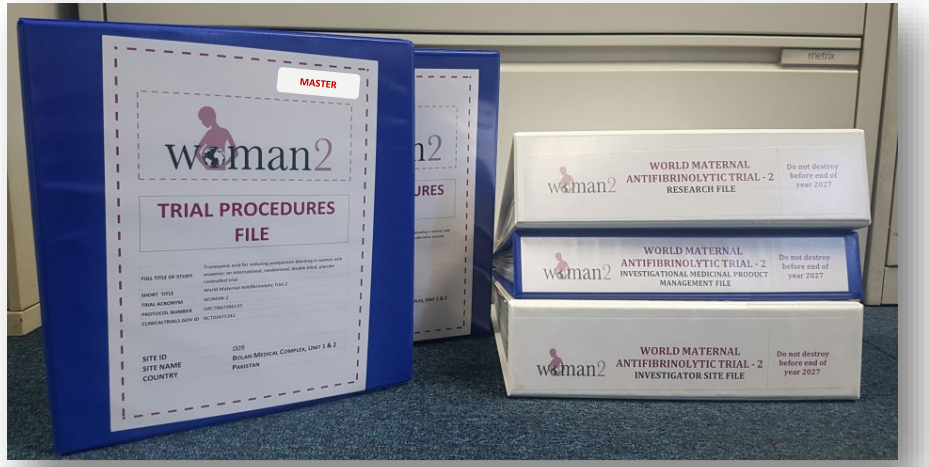
- Women with moderate or severe anaemia (Hb level <100 g/L or PCV <30%), who have given birth vaginally and for who the responsible clinician is substantially uncertain whether to use TXA

Exclusion criteria

- Women who are not legally adult (<18 years) and permission not provided by a guardian
- Women with a known allergy to TXA or its excipients
- Women who develop PPH before umbilical cord is clamped/cut

TRIAL MATERIALS: SITE FILES

- **The WOMAN-2 site files consist of five folders:**
  - Investigator Site File (ISF)
  - Investigational Medicinal Product (IMP) Management File
  - Trial Procedures File (x2)
  - Research File



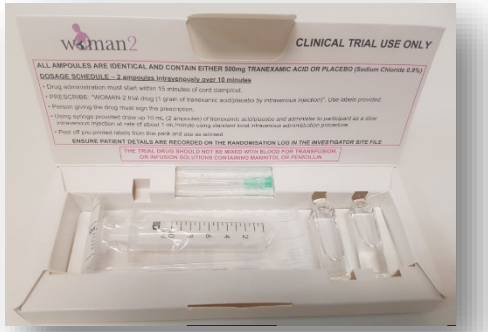
- **The site files are your record of the trial at your hospital**
  - Ensure the site files are kept up to date by regularly filing trial documents and updating trial logs and logbooks

- **The site files will need to be available for monitoring visits** by the CTU and inspections by the relevant regulatory authorities

TRIAL MATERIALS: DRUG BOX

- **Each trial drug box contains 20 drug packs**
- **Each drug pack contains:**
  - 2 x 500 mg ampoules of Tranexamic Acid (TXA)/Placebo
  - 1 x sterile 10 mL syringe and 1 x 21G needle for administering the drug

- **The PI/pharmacist should complete:**
  - Part 1 of the Drug Accountability Log (DAL) of each box and return a copy to the Clinical Trials Unit(CTU)
  - Part 2 of the DAL should be updated each time a drug box is used (or damaged, lost or destroyed)



- Your **minimum stock level** will depend on average monthly recruitment rate
  - Each time you randomise a patient and **submit the baseline data form**, one pack will automatically be deducted from your stock in the trial database

TRIAL OVERVIEW

HOSPITAL ADMISSION SCREENING FOR ANAEMIA (HemoCue)

Criteria: women in ACTIVE labour, planned vaginal birth

INITIAL ASSESSMENT OF ELIGIBILITY

Criteria: Hb <10 g/dL, planned vaginal birth, active labour, legally adult (if <18 guardian must be present), no indication or contraindication (allergy) to TXA

INFORMATION GIVING AND CONSENT PROCEDURE

BASELINE DATA COLLECTION

Complete Baseline Form sections A,B, D - G

FINAL ELIGIBILITY CHECK AND RANDOMISATION

Criteria: vaginal birth, no PPH

OUTCOME DATA COLLECTION

If discharged within 24 hours of randomisation

Complete Outcome Forms 1 and 2

If at hospital 24 hours post randomisation

At 24 hours: complete Outcome Form 1

At day 42,discharge, or death, whichever comes first, complete Outcome form 2

HOSPITAL ADMISSION SCREENING FOR ANAEMIA (HEMOCUE)

Criteria: women in ACTIVE labour, planned vaginal birth

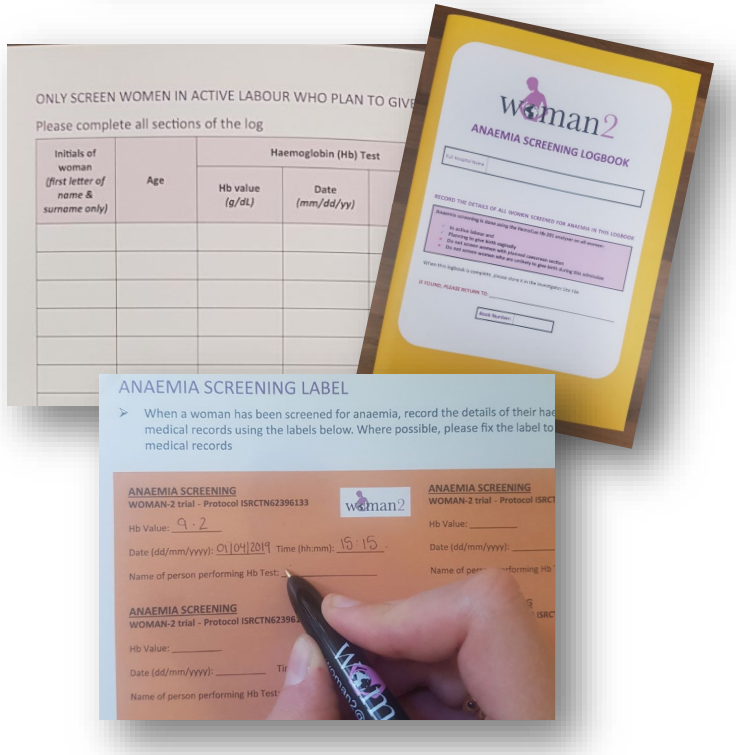
- On admission to hospital, offer woman a **free assessment of their haemoglobin** using the HemoCue if they meet the above criteria

- The HemoCue Hb 201 analyser is a handheld device used for standard point of care haemoglobin testing:
  - A small sample of blood, taken from the woman's finger
  - Tested in the analyser
  - Results available in 15 – 60 seconds

- The test is provided free of charge

- A woman has the right to accept or decline

- Enter results in the Anaemia Screening Logbook immediately after test is completed and record results in woman's medical record using the labels provided

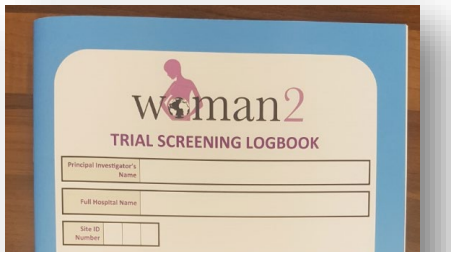


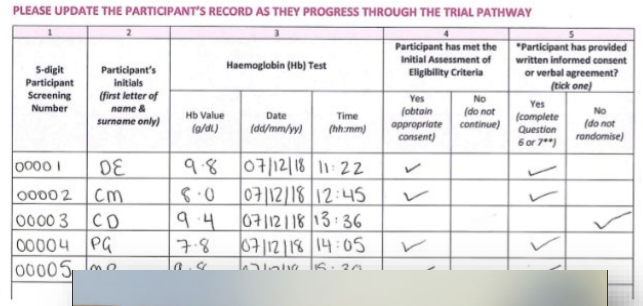
PLEASE INFORM TRIAL TEAM OF ALL WOMEN WITH A HB <10 G/DL

Initial assessment of eligibility

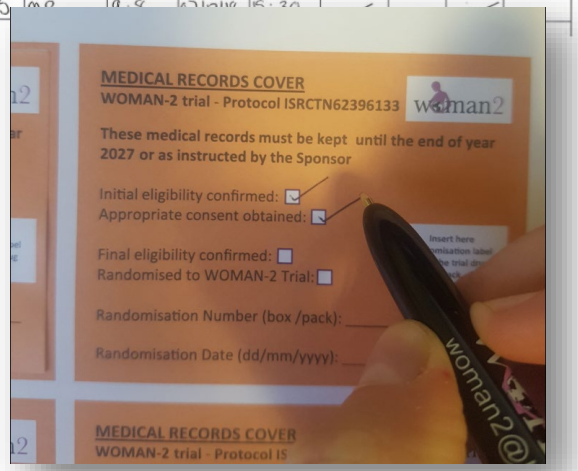
Criteria: Hb <10 g/dL, planned vaginal birth, active labour, legally adult (if <18 guardian must be present), no indication or contraindication (allergy) to TXA

- After a women as been admitted, an **initial assessment of eligibility** should be carried out
- Review woman's medical records and check the woman meets the above criteria
- If eligible, obtain agreement or consent as appropriate and record in medical records
- Record details in Trial Screening Logbook and assign them a 5-digit participant screening number in the format of **XXX – XXXXX:**
  - The first three digits correspond to the Site ID Number
  - The following 5-digits correspond to the Participant Screening Number. This number should be allocated to women in SEQUENTIAL ORDER
- Fix the WOMAN-2 medical records cover label to the **front** of the woman's medical records and complete accordingly




PLEASE UPDATE THE PARTICIPANT'S RECORD AS THEY PROGRESS THROUGH THE TRIAL PATHWAY

1	2	3			4		5	
5-digit Participant Screening Number	Participant's Initials (first letter of name & surname only)	Haemoglobin (Hb) Test			Participant has met the Initial Assessment of Eligibility Criteria		*Participant has provided written informed consent or verbal agreement? (tick one)	
		Hb Value (g/dL)	Date (dd/mm/yy)	Time (hh:mm)	Yes (obtain appropriate consent)	No (do not continue)	Yes (complete Question 6 or 7**)	No (do not randomise)
00001	DE	9·8	07/12/18	11:22	✓		✓	
00002	CM	8·0	07/12/18	12:45	✓		✓	
00003	CO	9·4	07/12/18	13:36				✓
00004	PG	7·8	07/12/18	14:05	✓		✓	
00005								



INFORMATION GIVING AND CONSENT PROCEDURE

Approach woman with clinician's permission
Clinician should assess woman's capacity to give consent

Woman in active labour, plans to give birth vaginally with Hb <10 g /dL. No indication or contraindication to TXA

Willing to be considered for inclusion in the trial & **fully competent** to give valid informed consent?

- Full information given to woman
- **Fully informed consent** obtained by researcher

IF UNWILLING, DO NOT INCLUDE

Willing to be considered for inclusion in the trial but **unable** to give fully informed consent?

- Brief verbal information given to woman
- **Verbal agreement obtained** by researcher in the presence of an impartial witness

- **When women regains capacity, obtain fully informed consent for continuing in the study**

INFORMATION GIVING AND CONSENT PROCEDURE

If woman is <18 years old:

- **Consent must be witnessed by a guardian.** A guardian is an appropriate responsible adult (e.g. her parents, husband, partner or other family member) who must also counter sign the form

If woman is unable to read or write:

- Explain trial in the presence of an **impartial witness** who must counter sign the consent form
  - **an impartial witness** cannot be a trial team member and must be able to read and write. An impartial witness is someone independent from the trial, i.e. not named on the Delegation Log. E.g. hospital staff member, or an adult accompanying the woman at hospital
- Obtain mark (e.g. thumbprint) in place of a signature if woman is unable to write

Documenting consent:

- A copy of PIS and signed ICF to should be given to the woman,
- A copy should be put in the medical records
- The **original should be stored in the Investigator Site File (ISF), box file 2**

Fully informed consent, or verbal agreement, must be obtained before baseline data collection and randomisation

BASELINE DATA COLLECTION

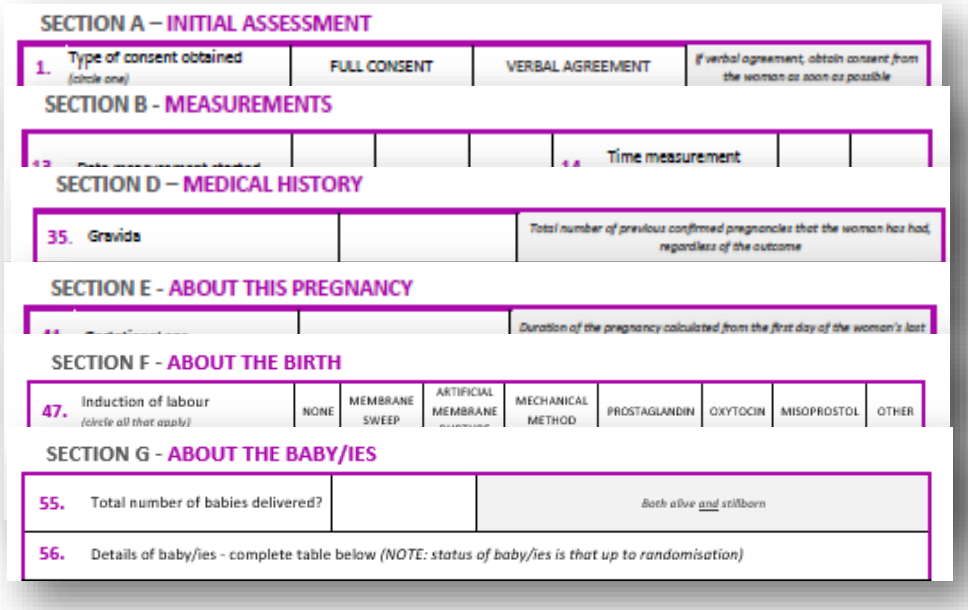
A Case Report Form (CRF) booklet should be completed for each participant. Each CRF contains a baseline form, outcome form and adverse event form

Complete the CRF baseline form after agreement/consent and before randomisation

- **Complete Sections A-B:**
  - Enter details of initial assessment of eligibility
  - Check IV cannula is inserted
  - Take temp, BP, HR, RR and other measurements

- **Complete as much of Sections D-G as time allows;**
  - If insufficient time (e.g. the woman gives birth rapidly) complete as soon as possible after randomisation. This must not delay randomisation
  - Obtain data from medical records or from woman

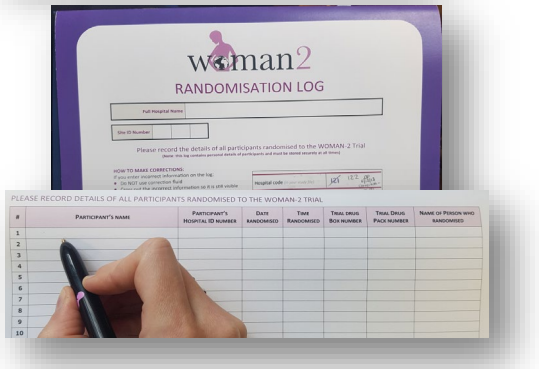
- **Complete Section C during final eligibility check, delivery and randomisation**



FINAL ELIGIBILITY CHECK AND RANDOMISATION

Criteria: vaginal birth, no PPH

- **Select and prescribe trial drug** immediately at delivery of anterior shoulder
  - Always take the NEXT LOWEST number drug pack. Do not skip numbers
- As cord is being cut or clamped, **prepare trial drug** by drawing the contents of both ampoules into the syringe provided
- **Randomise immediately after cord is cut/clamped**. NOT LATER THAN 15 MINUTES after
  - A single dose of 1 g of TXA or placebo by intravenous injection will be given
  - A participant is considered randomised to the trial as soon as the trial drug administration starts
- **Document randomisation** in Randomisation Logbook and participant's medical records (include all details required in CRF section C - WOMAN-2 labels are available)
- Upload completed CRF baseline form to trial database **within 24hrs of randomisation**



Women should receive all clinically indicated treatments.

OUTCOME DATA COLLECTION

If discharged within 24 hours of randomisation:

- Complete CRF outcome forms 1 and 2

If at hospital 24 hours post randomisation:

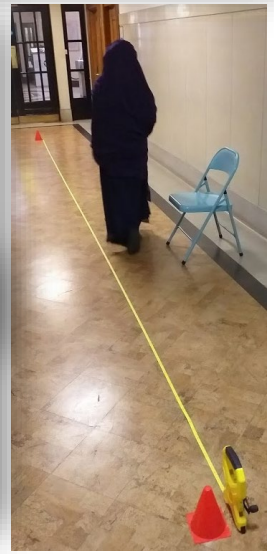
- At 24 hours: complete CRF outcome form 1
- At day 42, discharge or death (whichever comes first), complete outcome form 2

Outcome form 1:

- Repeat haemoglobin test using the HemoCue Hb 201 analyser
- Obtain other required data from medical records

Outcome form 2:

- Complete Participant Reported Outcome Questionnaire with participant
- Carry out 6 minute Walk Test with participant
- Obtain other required data from medical records



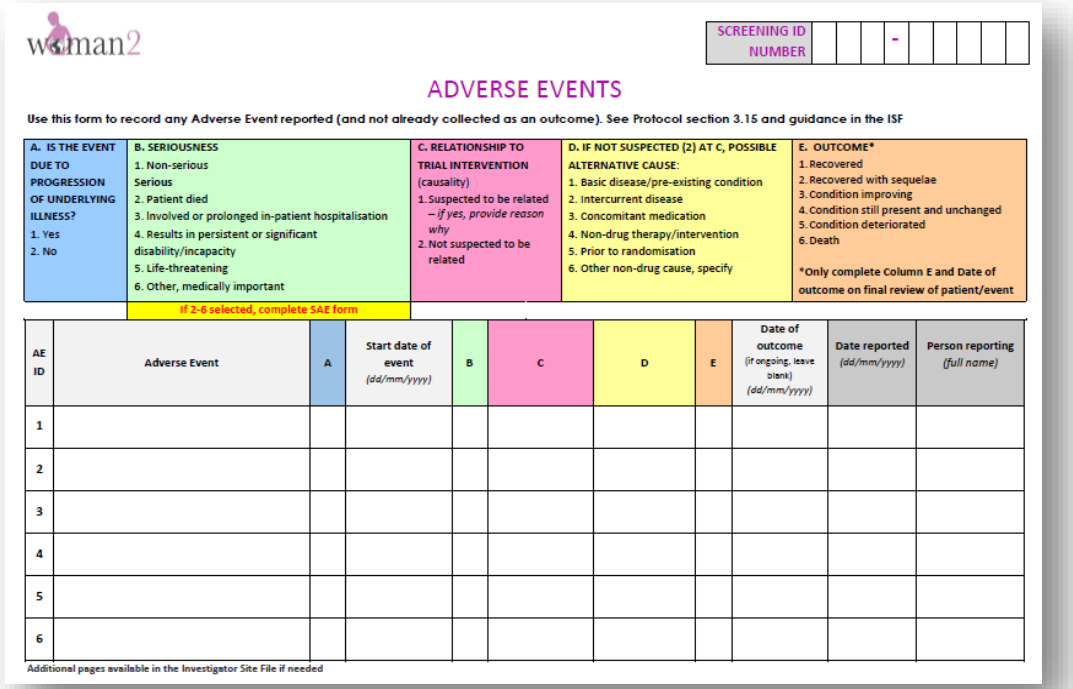
ADVERSE EVENT FORM

(1) While participant is <u>in hospital</u>: record any <u>untoward</u> medical events **NOT** collected on the outcome form that occur **up to 42 days** after randomisation.

(2) After participant has been <u>discharged</u> from hospital: record any <u>untoward</u> medical event, which **develops up to 42 days** after randomisation **(including those listed on the outcome forms)**

- Record any Adverse Event on the Adverse Event CRF immediately it occurs (see Protocol for definition)
- Complete all columns of each row
- **Column B: SERIOUSNESS** - if any Adverse Event fulfils one or more of the 'seriousness' criteria, a Serious Adverse Event form (found in Investigator Study File, section 4) must also be completed

All adverse events must be uploaded to the trial database **within 24 hours of occurrence**



woman2

SCREENING ID NUMBER | | | | - | | | | | | |

ADVERSE EVENTS

Use this form to record any Adverse Event reported (and not already collected as an outcome). See Protocol section 3.15 and guidance in the ISF

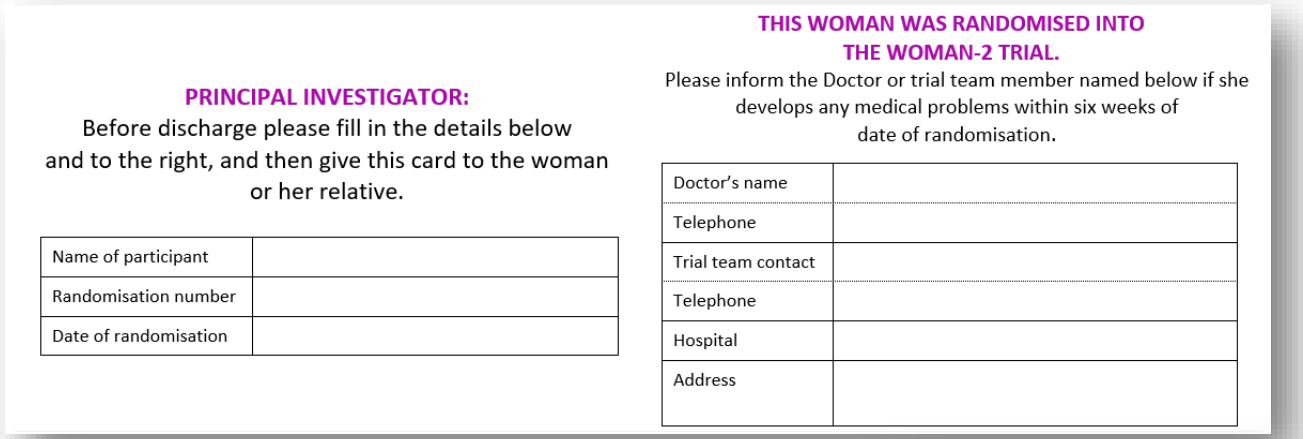
A. IS THE EVENT DUE TO PROGRESSION OF UNDERLYING ILLNESS?	B. SERIOUSNESS	C. RELATIONSHIP TO TRIAL INTERVENTION (causality)	D. IF NOT SUSPECTED (2) AT C, POSSIBLE ALTERNATIVE CAUSE:	E. OUTCOME*
1. Yes 2. No	1. Non-serious Serious 2. Patient died 3. Involved or prolonged in-patient hospitalisation 4. Results in persistent or significant disability/incapacity 5. Life-threatening 6. Other, medically important	1. Suspected to be related – *if yes, provide reason why* 2. Not suspected to be related	1. Basic disease/pre-existing condition 2. Intercurrent disease 3. Concomitant medication 4. Non-drug therapy/intervention 5. Prior to randomisation 6. Other non-drug cause, specify	1. Recovered 2. Recovered with sequelae 3. Condition improving 4. Condition still present and unchanged 5. Condition deteriorated 6. Death *Only complete Column E and Date of outcome on final review of patient/event
	If 2-6 selected, complete SAE form			

AE ID	Adverse Event	A	Start date of event (dd/mm/yyyy)	B	C	D	E	Date of outcome (if ongoing, leave blank) (dd/mm/yyyy)	Date reported (dd/mm/yyyy)	Person reporting (full name)
1										
2										
3										
4										
5										
6										

Additional pages available in the Investigator Site File if needed

ALERT CARD

- All participants should be given an **ALERT CARD at discharge** which contains information on who to contact if they develop any problems



PRINCIPAL INVESTIGATOR:

Before discharge please fill in the details below and to the right, and then give this card to the woman or her relative.

Name of participant	
Randomisation number	
Date of randomisation	

THIS WOMAN WAS RANDOMISED INTO THE WOMAN-2 TRIAL.

Please inform the Doctor or trial team member named below if she develops any medical problems within six weeks of date of randomisation.

Doctor's name	
Telephone	
Trial team contact	
Telephone	
Hospital	
Address	

The trial is sponsored and coordinated by a team at the University of London

Clinical Trials Unit,
London School of Hygiene & Tropical Medicine,
Keppel Street, London WC1E 7HT, UK

WOMAN2@LSHTM.AC.UK

Protocol number ISRCTN62396133
Version 1.1 : Date 30 April 2018

ALERT CARD

woman2

Please keep this card with you and show to anyone giving you medical treatment.

If you require any medical treatment within six weeks of having your baby, the doctor named overleaf must be informed.

Clinical Trials Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

Tel: +44(0)20 7299 4684
Email: woman2@Lshtm.ac.uk
Website: woman2.Lshtm.ac.uk