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

RATIONALE AND OVERVIEW

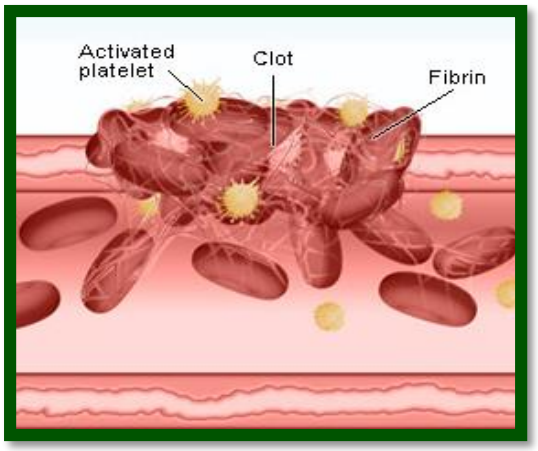
Protocol Code: ISRCTN11225767
Rationale and overview – version 3.0 date 08/10/2018

Gastrointestinal haemorrhage

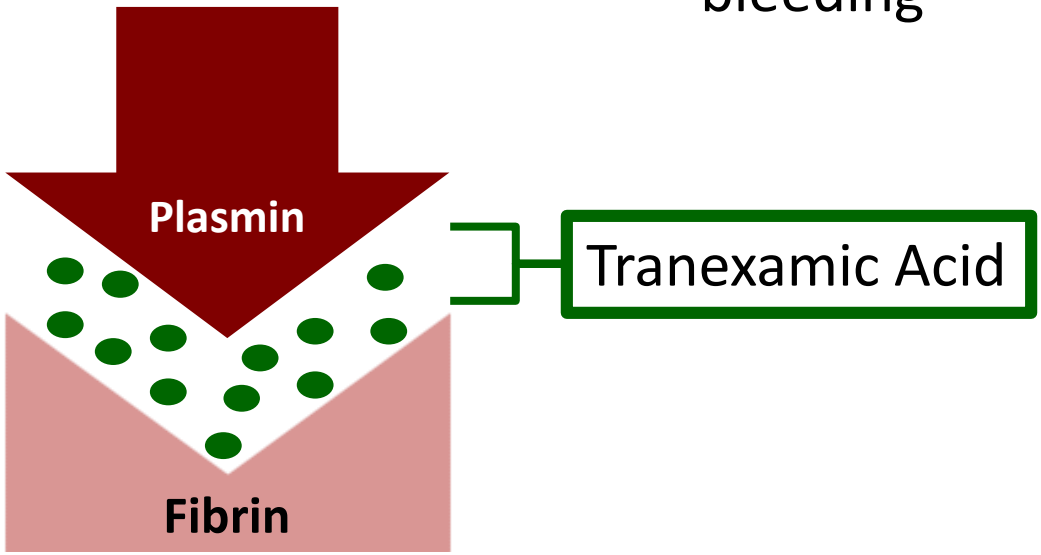
- A common emergency
- Important cause of mortality and morbidity
- Case fatality is high (10–20% in the UK)

- *Rockall TA et al. BMJ, 1995. 311(6999): p. 222-6.*
- *Williams JG et al. Gut, 2007. 56 Suppl 1: p. 1-113.*

Fibrinolysis & Tranexamic Acid (TXA)

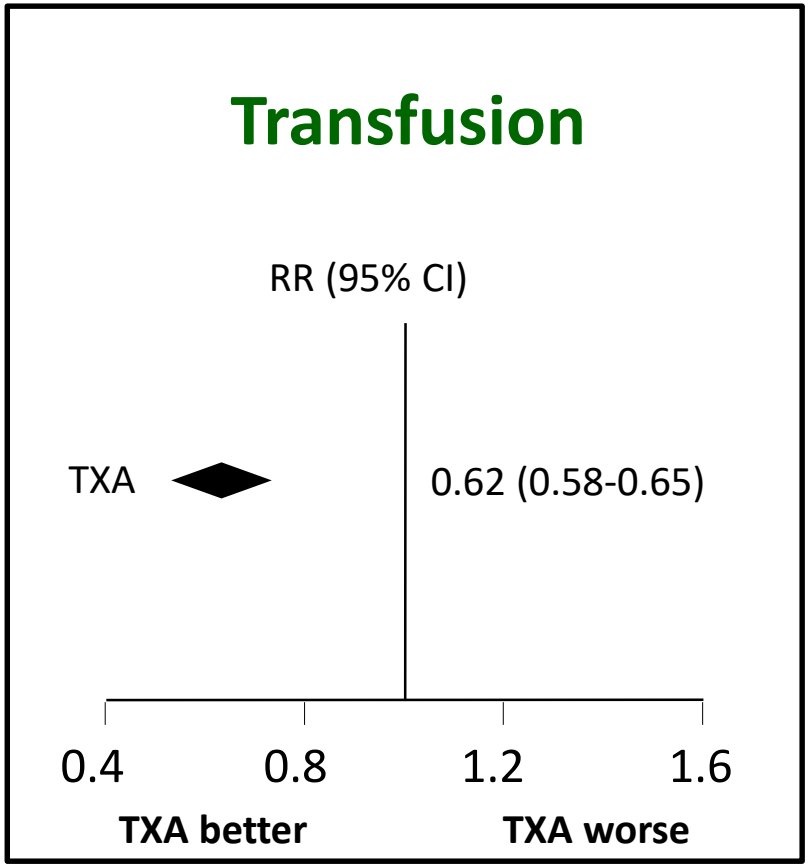


- At the site of damaged blood vessel, a fibrin blood clot forms
- Plasmin can impair clot stability and worsen bleeding
- TXA inhibits plasmin and reduces bleeding



TXA use in surgery

TXA reduces bleeding in surgery



95 trials

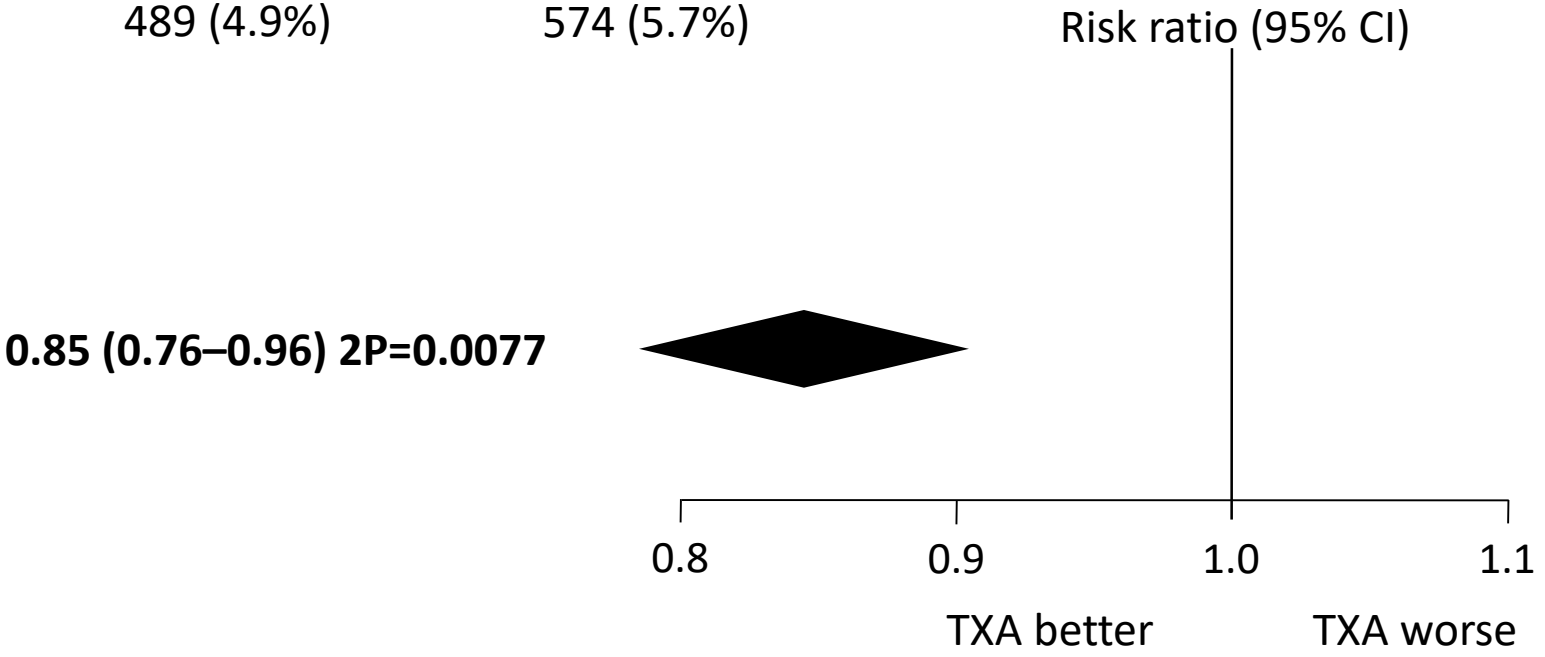
72 trials

Ker et al. BMJ 2012; 344:e3054

CRASH-2 trial results

TXA reduces death due to bleeding in trauma patients

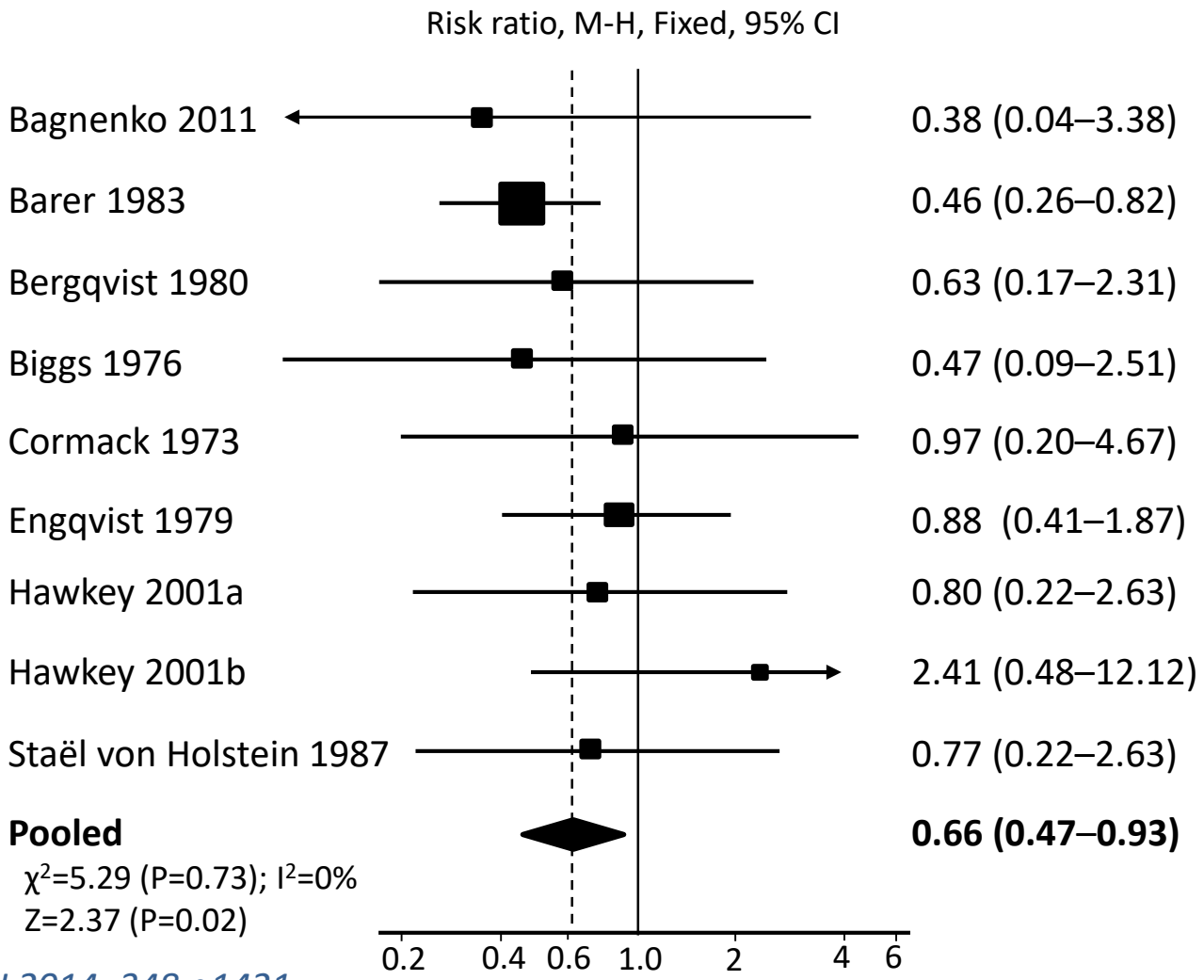
TXA-allocated	**Placebo-allocated**
(n=10,060)	**(n=10,067)**
489 (4.9%)	574 (5.7%)



The CRASH-2 Collaborators. The Lancet. 2010; 376(9734):23-32

TXA in upper GI bleeding

TXA may reduce death in GI bleeding but the quality of the trials is poor

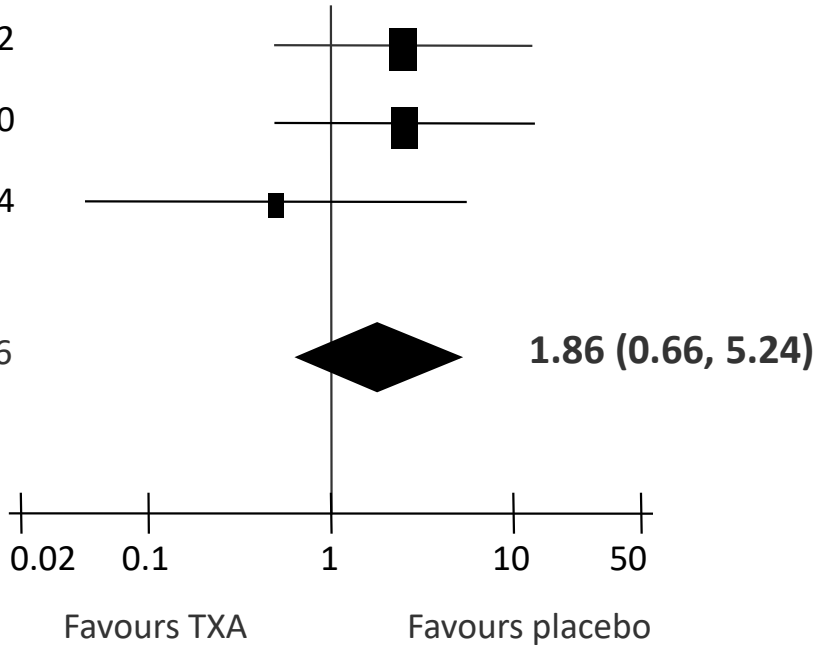


Manno D et al. BMJ 2014; 348:g1421

TXA in upper GI bleeding (2)

Trials are too small to assess the effect of TXA on thromboembolic events

	TXA		Placebo		Risk Ratio (95% CI)
	Events	*Total*	*Events*	*Total*	
Engquist 1979	5	102	2	102	
Barer 1983	5	256	2	260	
von Holstein 1987	1	164	2	164	
Total	11	522	6	526	**1.86 (0.66, 5.24)**



Rationale for HALT-IT

- GI bleeding is an important cause of death
- TXA reduces bleeding in surgery
- TXA reduces death due to bleeding in trauma patients
- TXA may reduce deaths in GI bleeding but the evidence is poor
- TXA could reduce death and morbidity in GI bleeding

Aims

To quantify the effect of TXA on mortality and morbidity

- **Primary outcome:** death in hospital within 28 days of randomisation (cause-specific mortality will also be recorded)

- **Secondary outcomes:**
  - Death from haemorrhage
  - Re-bleeding
  - Need for surgery or radiological intervention
  - Blood product transfusion
  - Thromboembolic events
  - Other adverse medical events
  - Patient's selfcare capacity
  - Days spent in ICU or HDU
  - Patient status (death, hospital readmission) at 12 months*

* England and Wales only

Study characteristics

- **Trial design:** randomised, double blind, placebo controlled
- **Target sample size:** 12,000 adults with acute significant upper or lower GI bleeding
- **Where?** Worldwide

Before the trial starts

- A completed Hospital & Principal Investigator CV Form
- GCP training certificate(s)
- Approval of your hospital (if required)
- Ethics Approval (local and/or national)
- Ministry of Public Health approval (if applicable)
- A signed Principal Investigator Agreement
- A copy of the approved Patient Information Sheet & Consent form (if different from the protocol sent to you)

Good Clinical Practice (GCP)

Good Clinical Practice (GCP) is an international standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

- Free online training via our website
- All staff should complete training before the study starts at your hospital

Create a trial team

Provide information and training to all team members

Identify people to be responsible for specific trial processes – they must be interested in the trial

Nominate someone to be responsible in your absence

Every specialty should be represented:

- emergency medicine
- gastroenterology
- intensive care
- general surgery
- nurses
- clerical staff
- pharmacy
- managers
- administrators

Roles may include:

- principal investigator
- sub-investigator
- data collection
- study coordinator

Overview

ELIGIBILITY (data collected on entry form)

✓Adults with significant acute upper or lower gastrointestinal bleeding

✓Responsible clinician is substantially uncertain as to the appropriateness of tranexamic acid in a patient

↓

Appropriate CONSENT PROCESS (patient, representative or waiver)

↓

RANDOMISE (tranexamic acid or placebo)
Entry form completed

↓

LOADING DOSE over 10 minutes

↓

MAINTENANCE DOSE over 24 hours

↓

Complete OUTCOME FORM at discharge, death or day 28
whichever is earlier

All clinically indicated treatment is given in addition to trial enrolment

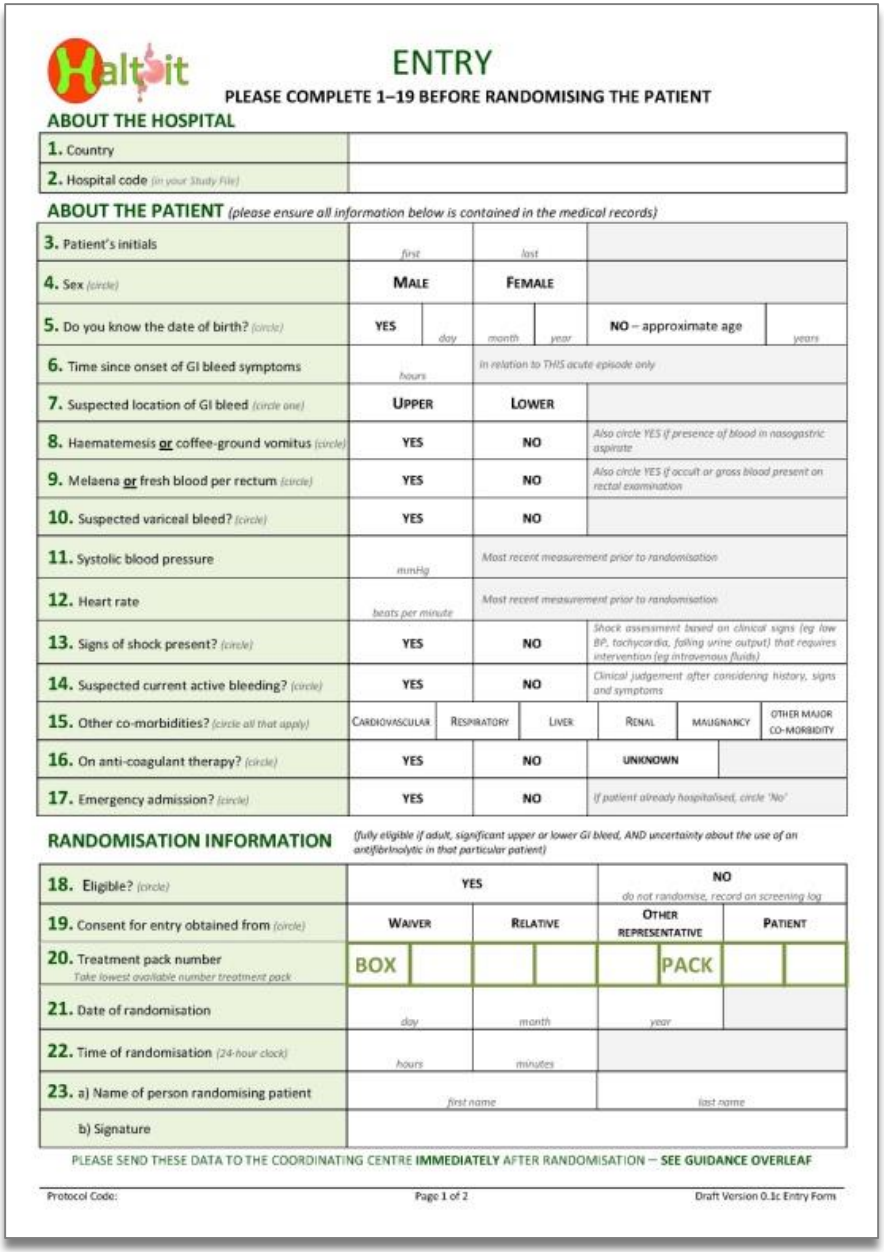
Adverse events are reported up to day 28

If prior consent waiver used, consent from patient or relative required after emergency is over

Consent

- Significant acute GI bleeding is an emergency and the priority is to provide appropriate emergency care.
- Eligible patients have a life threatening condition. Their physical, mental and emotional state may be affected by their condition.
- Consent procedures need to consider these factors.

Entry form



ENTRY

PLEASE COMPLETE 1–19 BEFORE RANDOMISING THE PATIENT

ABOUT THE HOSPITAL

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

ABOUT THE PATIENT *(please ensure all information below is contained in the medical records)*

3. Patient's initials	*first*		*last*						
4. Sex *(circle)*	MALE		FEMALE						
5. Do you know the date of birth? *(circle)*	YES	*day*	*month*	*year*	NO – approximate age		*years*		
6. Time since onset of GI bleed symptoms	*hours*		*In relation to THIS acute episode only*						
7. Suspected location of GI bleed *(circle one)*	UPPER		LOWER						
8. Haematemesis or coffee-ground vomitus *(circle)*	YES		NO		*Also circle YES if presence of blood in nasogastric aspirate*				
9. Melaena or fresh blood per rectum *(circle)*	YES		NO		*Also circle YES if occult or gross blood present on rectal examination*				
10. Suspected variceal bleed? *(circle)*	YES		NO						
11. Systolic blood pressure	*mmHg*		*Most recent measurement prior to randomisation*						
12. Heart rate	*beats per minute*		*Most recent measurement prior to randomisation*						
13. Signs of shock present? *(circle)*	YES		NO		*Shock assessment based on clinical signs (eg low BP, tachycardia, falling urine output) that requires intervention (eg intravenous fluids)*				
14. Suspected current active bleeding? *(circle)*	YES		NO		*Clinical judgement after considering history, signs and symptoms*				
15. Other co-morbidities? *(circle all that apply)*	CARDIOVASCULAR	RESPIRATORY	LIVER	RENAL	MALIGNANCY	OTHER MAJOR CO-MORBIDITY			
16. On anti-coagulant therapy? *(circle)*	YES		NO		UNKNOWN				
17. Emergency admission? *(circle)*	YES		NO		*If patient already hospitalised, circle 'No'*				

RANDOMISATION INFORMATION *(fully eligible if adult, significant upper or lower GI bleed, AND uncertainty about the use of an antifibrinolytic in that particular patient)*

18. Eligible? *(circle)*	YES		NO *do not randomise, record on screening log*	
19. Consent for entry obtained from *(circle)*	WAIVER	RELATIVE	OTHER REPRESENTATIVE	PATIENT
20. Treatment pack number *Take lowest available number treatment pack*	BOX		PACK	
21. Date of randomisation	*day*	*month*	*year*	
22. Time of randomisation *(24-hour clock)*	*hours*	*minutes*		
23. a) Name of person randomising patient	*first name*		*last name*	
b) Signature				

PLEASE SEND THESE DATA TO THE COORDINATING CENTRE **IMMEDIATELY** AFTER RANDOMISATION – **SEE GUIDANCE OVERLEAF**

Protocol Code: Page 1 of 2 Draft Version 0.1c Entry Form

One page only

- Complete questions 1–18 to assess eligibility
- If eligible, follow appropriate consent process – complete 19
- **RANDOMISE:**
  Use next lowest available pack number
  STRICT NUMERICAL ORDER

Randomisation

- Use next lowest available pack number
- Record on Randomisation log
- Record pack used on Drug Accountability Log

Entry form and Randomisation

RANDOMISATION INFORMATION *(fully eligible if adult, significant upper or lower GI bleed, AND uncertainty about the use of an antifibrinolytic in that particular patient)*

18. Eligible? *(circle)*	YES		NO *do not randomise, record on screening log*	
19. Consent for entry obtained from *(circle)*	WAIVER	RELATIVE	OTHER REPRESENTATIVE	PATIENT
20. Treatment pack number *Take lowest available number treatment pack*	BOX		PACK	
21. Date of randomisation	*day*	*month*	*year*	
22. Time of randomisation *(24-hour clock)*	*hours*	*minutes*		
23. a) Name of person randomising patient	*first name*		*last name*	
b) Signature				

- Use next lowest available pack number
- Record on Randomisation log
- Record pack used on Drug Accountability Log

Dose

Treatment	Dose TXA or placebo
Loading	1 gram / 10 minutes (IV infusion)
Maintenance	3 gram / 24 hours (IV infusion)

TRANEXAMIC ACID / PLACEBO IS AN ADDITIONAL TREATMENT TO THE ROUTINE MANAGEMENT OF GI BLEEDING

How to give the trial treatment

ALL AMPOULES ARE IDENTICAL AND CONTAIN 500mg OF EITHER TRANEXAMIC ACID OR PLACEBO

LOADING DOSE

2 ampoules over 10 minutes

Give immediately after randomisation

PRESCRIBE: *"HALT-IT Trial (1 gram of tranexamic acid/placebo) over 10 minutes"*

Draw up 10mL (2 ampoules) of tranexamic acid / placebo and add to 100 mL bag of Sodium Chloride 0.9% (provided) and infuse over 10 minutes.

MAINTENANCE DOSE

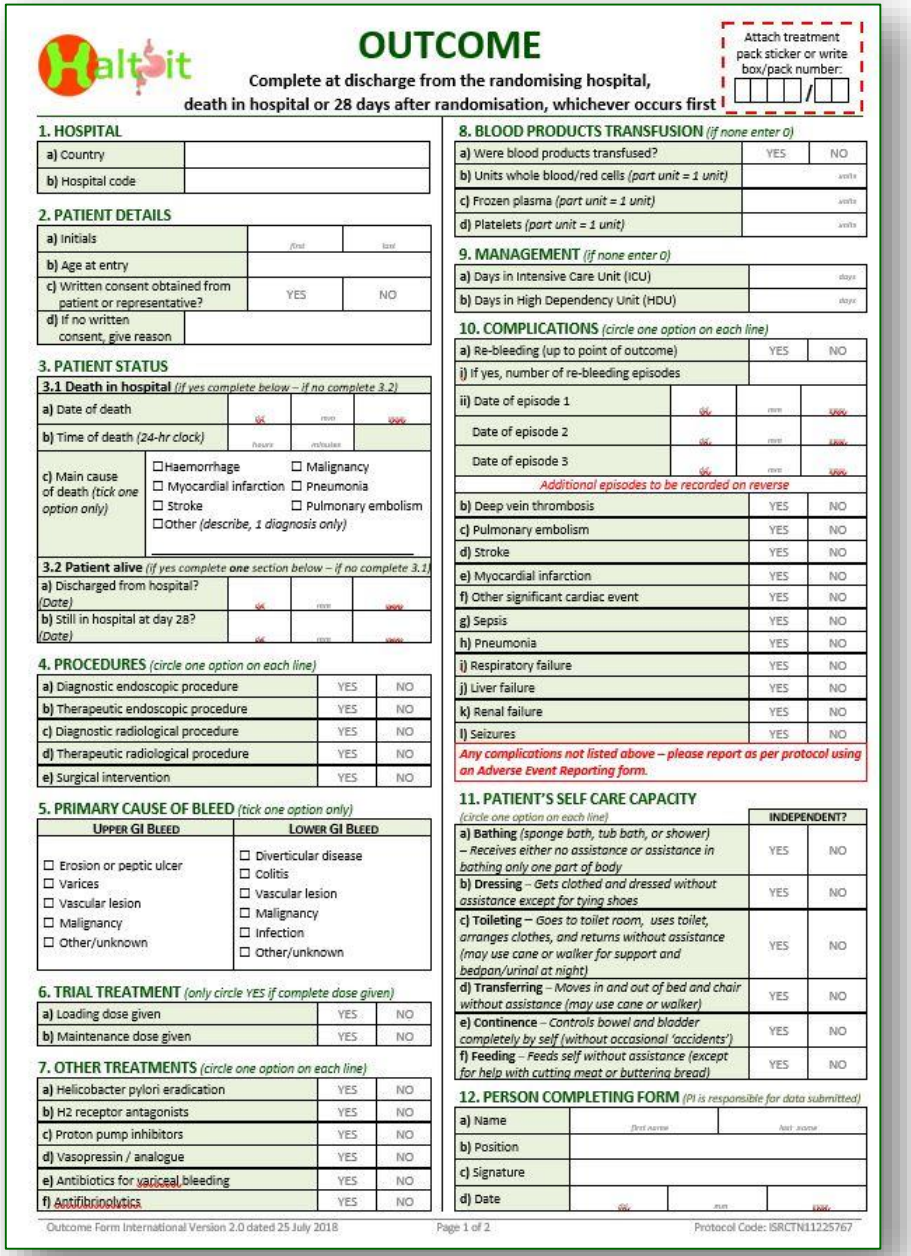
6 ampoules over 24 hours

Start immediately after completion of loading dose

PRESCRIBE: *"HALT-IT Trial (3 grams of tranexamic acid / placebo) in 1000 mL sodium chloride 0.9% or any isotonic intravenous solution. Infuse at 42 mL/hour"*

Draw up 30 mL (6 ampoules) of TXA/placebo and add to 1000 mL sodium chloride 0.9% or any isotonic intravenous solution and infuse over about 24 hours.

Outcome form



Halt it

OUTCOME

Complete at discharge from the randomising hospital, death in hospital or 28 days after randomisation, whichever occurs first

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

1. HOSPITAL

a) Country	
b) Hospital code	

2. PATIENT DETAILS

a) Initials		first	last
b) Age at entry			
c) Written consent obtained from patient or representative?	YES	NO	
d) If no written consent, give reason			

3. PATIENT STATUS

3.1 Death in hospital *(if yes complete below – if no complete 3.2)*

a) Date of death	dd	mm	yyyy
b) Time of death *(24-hr clock)*	hours	minutes	

c) Main cause of death *(tick one option only)*

☐Haemorrhage ☐ Malignancy
☐ Myocardial infarction ☐ Pneumonia
☐ Stroke ☐ Pulmonary embolism
☐Other *(describe, 1 diagnosis only)*

3.2 Patient alive *(if yes complete **one** section below – if no complete 3.1)*

a) Discharged from hospital? *(Date)*	dd	mm	yyyy
b) Still in hospital at day 28? *(Date)*	dd	mm	yyyy

4. PROCEDURES *(circle one option on each line)*

a) Diagnostic endoscopic procedure	YES	NO
b) Therapeutic endoscopic procedure	YES	NO
c) Diagnostic radiological procedure	YES	NO
d) Therapeutic radiological procedure	YES	NO
e) Surgical intervention	YES	NO

5. PRIMARY CAUSE OF BLEED *(tick one option only)*

UPPER GI BLEED	LOWER GI BLEED
☐ Erosion or peptic ulcer ☐ Varices ☐ Vascular lesion ☐ Malignancy ☐ Other/unknown	☐ Diverticular disease ☐ Colitis ☐ Vascular lesion ☐ Malignancy ☐ Infection ☐ Other/unknown

6. TRIAL TREATMENT *(only circle YES if complete dose given)*

a) Loading dose given	YES	NO
b) Maintenance dose given	YES	NO

7. OTHER TREATMENTS *(circle one option on each line)*

a) Helicobacter pylori eradication	YES	NO
b) H2 receptor antagonists	YES	NO
c) Proton pump inhibitors	YES	NO
d) Vasopressin / analogue	YES	NO
e) Antibiotics for variceal bleeding	YES	NO
f) Antifibrinolytics	YES	NO

8. BLOOD PRODUCTS TRANSFUSION *(if none enter 0)*

a) Were blood products transfused?	YES	NO
b) Units whole blood/red cells *(part unit = 1 unit)*		units
c) Frozen plasma *(part unit = 1 unit)*		units
d) Platelets *(part unit = 1 unit)*		units

9. MANAGEMENT *(if none enter 0)*

a) Days in Intensive Care Unit (ICU)	days
b) Days in High Dependency Unit (HDU)	days

10. COMPLICATIONS *(circle one option on each line)*

a) Re-bleeding (up to point of outcome)		YES	NO
i) If yes, number of re-bleeding episodes			
ii) Date of episode 1	dd	mm	yyyy
Date of episode 2	dd	mm	yyyy
Date of episode 3	dd	mm	yyyy
Additional episodes to be recorded on reverse			
b) Deep vein thrombosis		YES	NO
c) Pulmonary embolism		YES	NO
d) Stroke		YES	NO
e) Myocardial infarction		YES	NO
f) Other significant cardiac event		YES	NO
g) Sepsis		YES	NO
h) Pneumonia		YES	NO
i) Respiratory failure		YES	NO
j) Liver failure		YES	NO
k) Renal failure		YES	NO
l) Seizures		YES	NO

Any complications not listed above – please report as per protocol using an Adverse Event Reporting form.

11. PATIENT'S SELF CARE CAPACITY

(circle one option on each line)

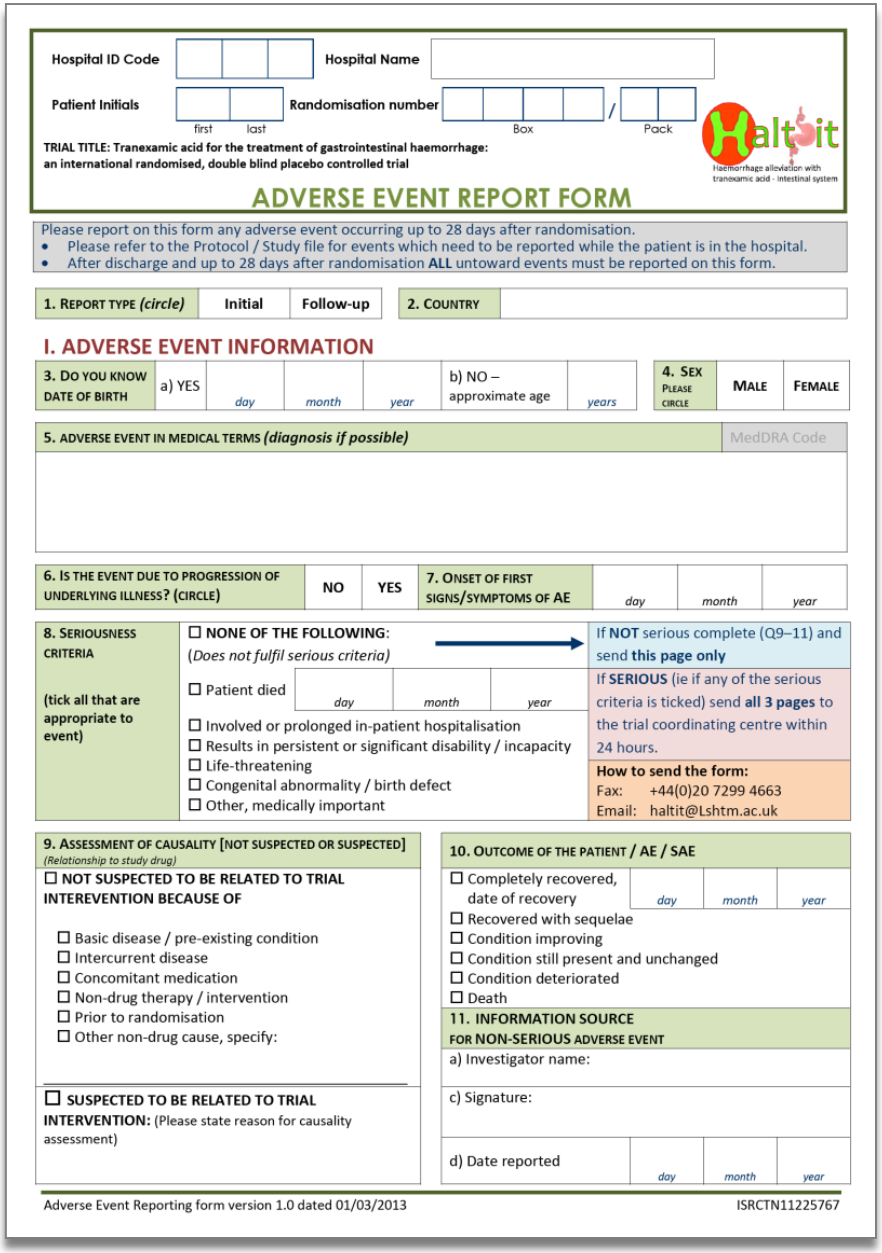
	INDEPENDENT?	
a) **Bathing** *(sponge bath, tub bath, or shower) – Receives either no assistance or assistance in bathing only one part of body*	YES	NO
b) **Dressing** – *Gets clothed and dressed without assistance except for tying shoes*	YES	NO
c) **Toileting** – *Goes to toilet room, uses toilet, arranges clothes, and returns without assistance (may use cane or walker for support and bedpan/urinal at night)*	YES	NO
d) **Transferring** – *Moves in and out of bed and chair without assistance (may use cane or walker)*	YES	NO
e) **Continence** – *Controls bowel and bladder completely by self (without occasional 'accidents')*	YES	NO
f) **Feeding** – *Feeds self without assistance (except for help with cutting meat or buttering bread)*	YES	NO

12. PERSON COMPLETING FORM *(PI is responsible for data submitted)*

a) Name	first name	last name
b) Position		
c) Signature		
d) Date	dd	mm yyyy

- No extra tests required – a short single page Outcome form completed 4 weeks (28 days) after randomisation, at discharge, or at death (whichever occurs first)
- Outcome to be collected even if the trial treatment is interrupted or is not actually given
- Form to be sent to the TCC as soon as possible

Adverse Event



Hospital ID Code | Hospital Name

Patient Initials (first, last) | Randomisation number (Box / Pack)

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

Haltit — Haemorrhage alleviation with tranexamic acid - intestinal system

ADVERSE EVENT REPORT FORM

Please report on this form any adverse event occurring up to 28 days after randomisation.
- Please refer to the Protocol / Study file for events which need to be reported while the patient is in the hospital.
- After discharge and up to 28 days after randomisation **ALL** untoward events must be reported on this form.

1. REPORT TYPE *(circle)* — Initial | Follow-up
2. COUNTRY

I. ADVERSE EVENT INFORMATION

3. DO YOU KNOW DATE OF BIRTH — a) YES (day, month, year) | b) NO – approximate age (years)
4. SEX (PLEASE CIRCLE) — MALE | FEMALE

5. ADVERSE EVENT IN MEDICAL TERMS *(diagnosis if possible)* — MedDRA Code

6. IS THE EVENT DUE TO PROGRESSION OF UNDERLYING ILLNESS? (CIRCLE) — NO | YES
7. ONSET OF FIRST SIGNS/SYMPTOMS OF AE (day, month, year)

8. SERIOUSNESS CRITERIA (tick all that are appropriate to event)
- ☐ NONE OF THE FOLLOWING: (*Does not fulfil serious criteria*) → If **NOT** serious complete (Q9–11) and send **this page only**
- ☐ Patient died (day, month, year)
- ☐ Involved or prolonged in-patient hospitalisation
- ☐ Results in persistent or significant disability / incapacity
- ☐ Life-threatening
- ☐ Congenital abnormality / birth defect
- ☐ Other, medically important

If **SERIOUS** (ie if any of the serious criteria is ticked) send **all 3 pages** to the trial coordinating centre within 24 hours.

How to send the form:
Fax: +44(0)20 7299 4663
Email: haltit@Lshtm.ac.uk

9. ASSESSMENT OF CAUSALITY [NOT SUSPECTED OR SUSPECTED] (*Relationship to study drug*)
- ☐ NOT SUSPECTED TO BE RELATED TO TRIAL INTEREVENTION BECAUSE OF
  - ☐ Basic disease / pre-existing condition
  - ☐ Intercurrent disease
  - ☐ Concomitant medication
  - ☐ Non-drug therapy / intervention
  - ☐ Prior to randomisation
  - ☐ Other non-drug cause, specify:
- ☐ SUSPECTED TO BE RELATED TO TRIAL INTERVENTION: (Please state reason for causality assessment)

10. OUTCOME OF THE PATIENT / AE / SAE
- ☐ Completely recovered, date of recovery (day, month, year)
- ☐ Recovered with sequelae
- ☐ Condition improving
- ☐ Condition still present and unchanged
- ☐ Condition deteriorated
- ☐ Death

11. INFORMATION SOURCE FOR NON-SERIOUS ADVERSE EVENT
a) Investigator name:
c) Signature:
d) Date reported (day, month, year)

Adverse Event Reporting form version 1.0 dated 01/03/2013 — ISRCTN11225767

- See Protocol (Section 2.9) and Investigator Study File section 7 for definition of adverse events and reporting procedures.

Sending your data

Internet: Data collection is to be done via internet.

A username and password to use this site will be sent to you by email before you start the trial.

Email: as scanned documents

Trial Materials

BEFORE YOU START THE TRIAL YOU WILL RECEIVE:

- a study file compiled specifically for your hospital, containing contact details, further information, guidance, spare forms and filing space for completed data forms
- training CD with PowerPoint presentations
- training DVD of the trial procedures and the scientific rationale
- randomisation posters with step by step guidance
- brief information leaflets and wall posters

PROTOCOLS

- protocol summaries
- pocket cards

TREATMENT PACKS

- Initially one box of 8 patient packs
- Stock level is monitored by patient entries received at the TCC
- We will send new boxes when you reach your minimum stock level, which is dependent on your randomisation rate
- With each box you will receive a document pack containing your hospital specific patient information sheets, consent forms, more alert cards and brief information leaflets

TRAINING AND PRESENTATIONS

Please contact the TCC if:

- you need more training materials for staff sessions
- you are presenting the trial at meetings or conferences

JOIN THE GLOBAL COLLABORATION

haltit.Lshtm.ac.uk

Trial Coordinating Centre
London School of Hygiene & Tropical Medicine
Room 180, Keppel Street, London WC1E 7HT

Tel +44(0)20 7299 4684
Fax +44(0)20 7299 4663
Email: haltit@Lshtm.ac.uk

UKCRC Registered Clinical Trials Units

Haltit
Haemorrhage alleviation with tranexamic acid - Intestinal system