Haemorrhage alleviation with tranexamic acid - Intestinal system

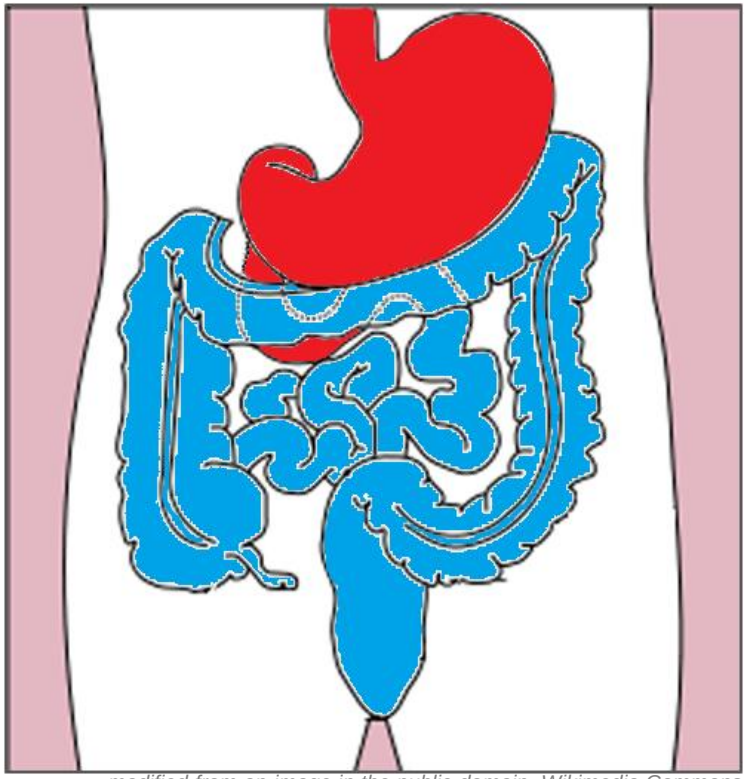
Gastrointestinal haemorrhage

- 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.*

Most common causes

- Cause varies by country, but in general:
- **Upper GI haemorrhage:**
  - Peptic ulcer
  - Oesophageal varices
- **Lower GI haemorrhage:**
  - Diverticular disease
  - Colitis
  - Cancer



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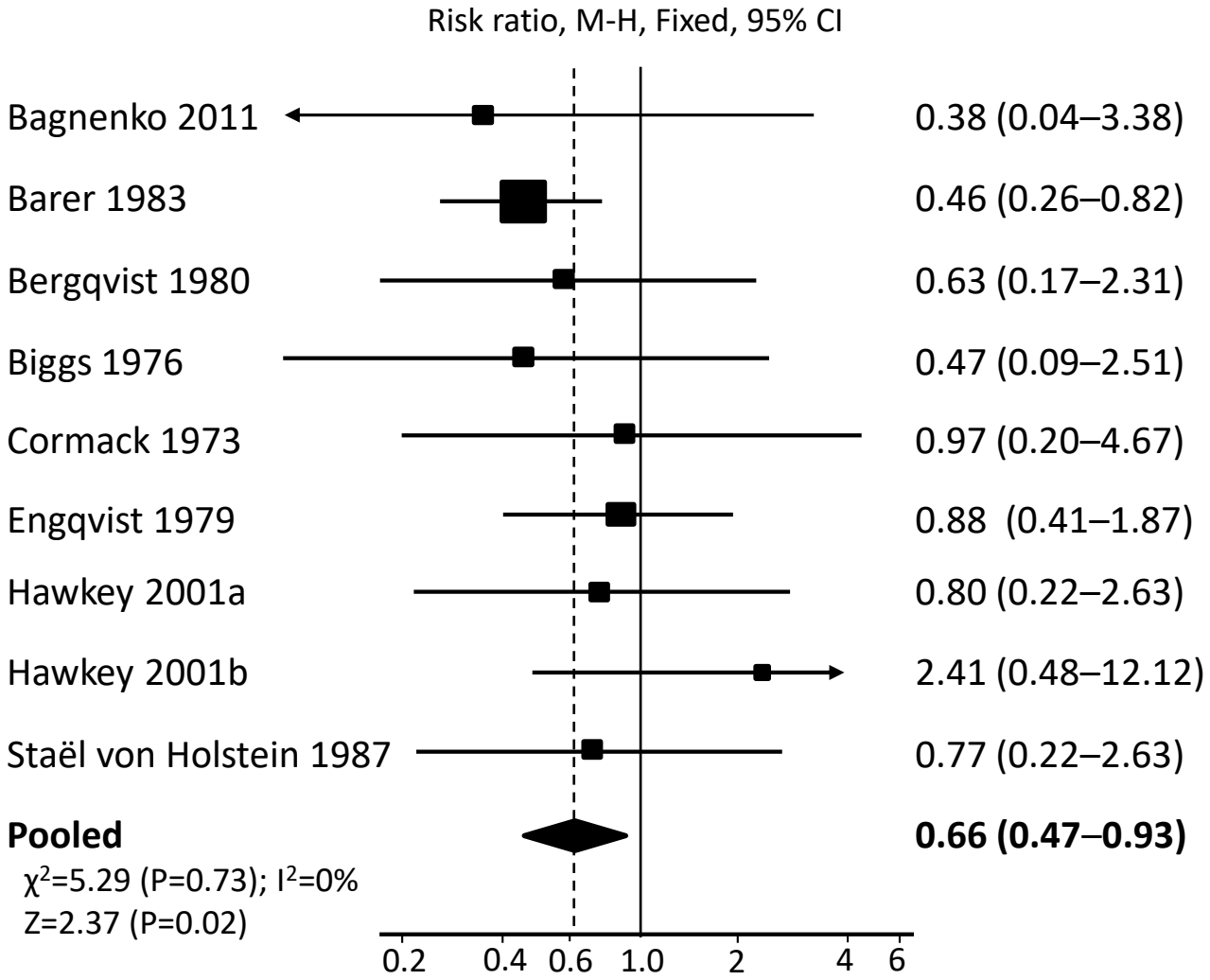
TXA in upper GI bleeding

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

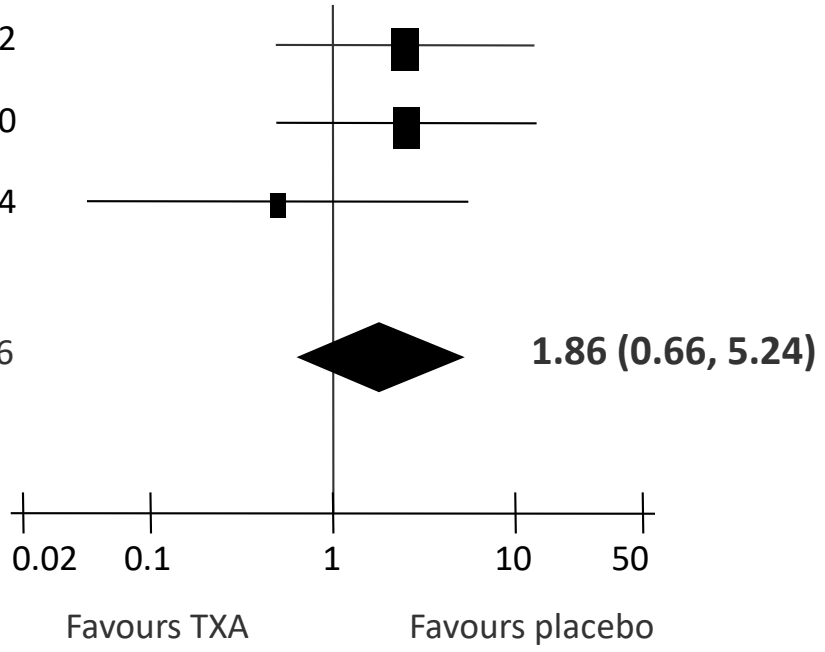


Manno D et al. BMJ 2014; 348:g1421

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

- The HALT-IT trial will provide reliable evidence about the effect of tranexamic acid on mortality and morbidity in patients with significant gastrointestinal bleeding.
- The effect of TXA on the risk of thromboembolic events will also be assessed.

Study characteristics

- **Trial design:** randomised, double blind, placebo controlled
- **Target sample size:** 8,000 adults with acute significant upper or lower GI bleeding
- **Where?** Worldwide: Egypt, Georgia, Malaysia, Nigeria, Pakistan, Papua New Guinea, Romania, United Kingdom

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:**
  - 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

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 (1g) over 10 minutes

↓

MAINTENANCE DOSE (3g) over 24 hours

↓

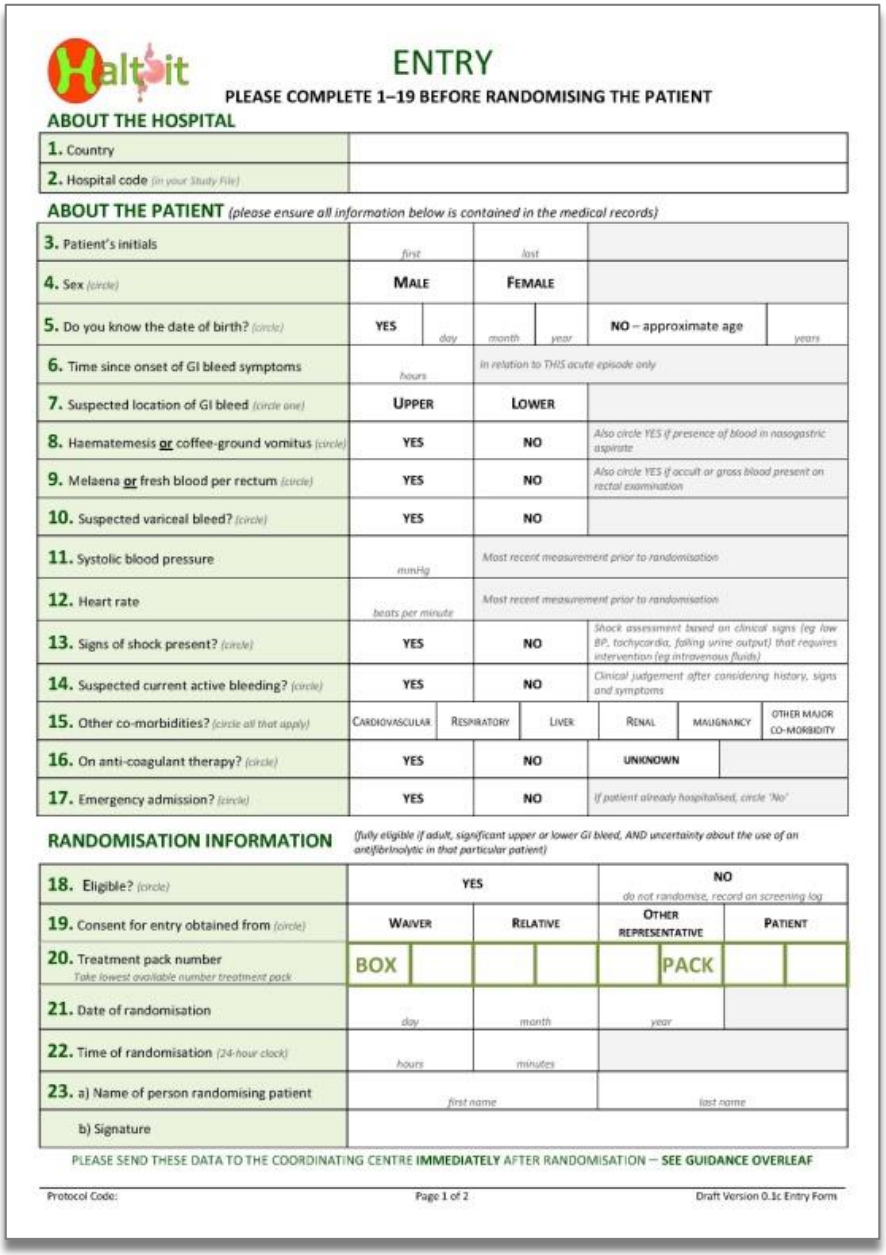
Complete OUTCOME FORM at discharge, death or day 28
whichever is earlier

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

Entry form



Halt it

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				

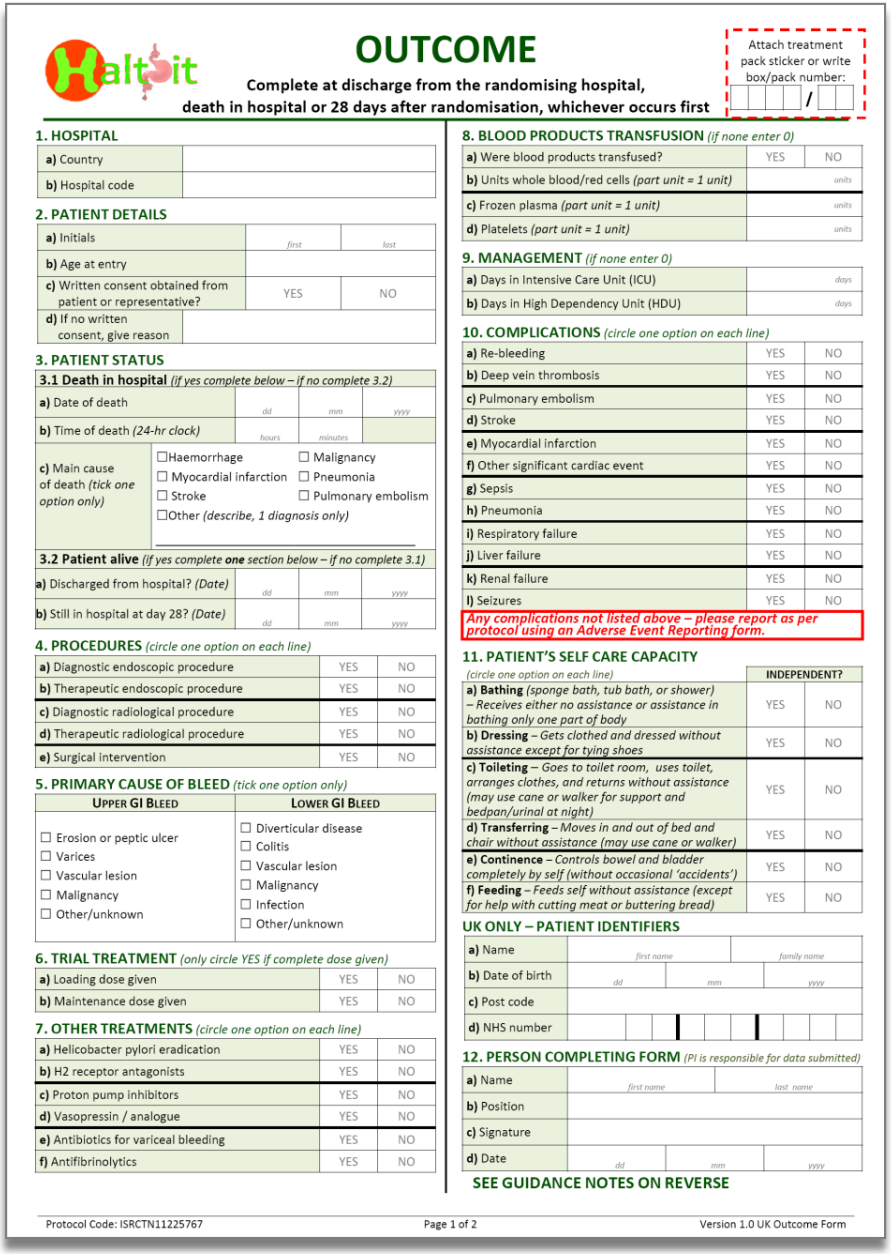
PLEASE SEND THESE DATA TO THE COORDINATING CENTRE **IMMEDIATELY** AFTER RANDOMISATION – **SEE GUIDANCE OVERLEAF**

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

Outcome form



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	☐ Diverticular disease
☐ Varices	☐ Colitis
☐ Vascular lesion	☐ Vascular lesion
☐ Malignancy	☐ Malignancy
☐ Other/unknown	☐ 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	YES	NO
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

UK ONLY – PATIENT IDENTIFIERS

a) Name	first name	family name	
b) Date of birth	dd	mm	yyyy
c) Post code			
d) NHS number			

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

SEE GUIDANCE NOTES ON REVERSE

Protocol Code: ISRCTN11225767 Page 1 of 2 Version 1.0 UK Outcome Form

- 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

Rationale for eligibility

- Adult with significant upper or lower GI bleeding
- **Uncertainty principle:** the responsible clinician is substantially uncertain as to whether or not to use TXA

If the clinician believes there is a clear indication for, or clear contraindication to, tranexamic acid use, the patient should not be randomised.

JOIN THE GLOBAL COLLABORATION OR REGISTER FOR THE TRIAL RESULTS

haltit.Lshtm.ac.uk

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UKCRC Registered Clinical Trials Units

Haltit
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