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

CLINICAL TRIAL PROTOCOL

[International Generic version]

Protocol Number: ISRCTN11225767

	NUMBER	DATE
FINAL VERSION	1.0	26/11/2012
AMENDMENT	1.1	26/08/2016
AMENDMENT	2.0	23/08/2017
AMENDMENT	3.0	29/01/2019

SUMMARY

FULL TITLE OF STUDY	Tranexamic acid for the treatment of gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial		
SHORT TITLE	**H**aemorrhage **AL**leviation with **T**ranexamic acid – **I**n**T**estinal system		
TRIAL ACRONYM	HALT-IT		
PROTOCOL NUMBER	ISRCTN11225767		
EUDRACT NUMBER	2012-003192-19	**CLINICAL TRIALS.GOV**	NCT01658124

BACKGROUND: Gastrointestinal (GI) bleeding is a common emergency that causes substantial mortality worldwide. The common causes of upper GI bleeding are peptic ulcer, oesophageal varices and erosive mucosal disease. Acute upper GI bleeding accounts for about 60,000 hospital admissions each year in the UK and causes the death of about 10% of these patients. Lower GI bleeding accounts for a further 15,000 admissions each year with a case fatality of about 15%. GI bleeding is also common in low and middle income countries, where patients are usually young and poor. The source of bleeding is often varices. Re-bleeding occurs in about 10% of patients with non-variceal bleeding and up to 25% of those with variceal bleeding. Mortality is four times higher in patients who re-bleed.

Fibrinolysis may play an important role in GI bleeding and re-bleeding, due to premature breakdown of blood clots at the bleeding site. Tranexamic acid (TXA) reduces clot breakdown by inhibiting the action of plasmin. A systematic review of the effect of TXA in surgical patients shows that it reduces the probability of blood transfusion by about a third (RR=0.62, 95% CI 0.58 to 0.65), with no evidence of any increase in risk of thromboembolic events. The CRASH-2 trial showed that early administration of TXA reduces deaths due to bleeding (RR=0.85, 95% CI 0.76 to 0.96), and all-cause mortality (RR=0.91, 95% CI 0.85 to 0.97) in trauma patients, without increasing thromboembolic events. A systematic review of clinical trials of TXA in upper GI bleeding shows a reduction in the risk of death with TXA (RR=0.61, 95% CI 0.42 to 0.89), but the quality of the trials was poor and the estimate is imprecise. All but one of the trials were conducted before the use of endoscopy and proton pump inhibitors and were too small to assess the effect of TXA on thromboembolic events. For these reasons, we believe that the effectiveness and safety of TXA in GI bleeding is uncertain and that a high quality randomised controlled trial is needed.

AIM: The HALT-IT trial will determine the effect of early administration of TXA on mortality, morbidity (re-bleeding, non-fatal vascular events), blood transfusion, surgical intervention and health status in patients with acute gastrointestinal bleeding.

PRIMARY OUTCOME: The primary outcome is death from haemorrhage within 5 days of randomisation (all-cause and cause-specific mortality will also be recorded). Cause specific mortality will be described as per section 3.1 of the outcome form (haemorrhage, myocardial infarction, stroke, pulmonary embolism, pneumonia, malignancy, other).

SECONDARY OUTCOMES:

a) Death from haemorrhage within 28 days of randomisation
b) Mortality: all-cause and cause-specific mortality within 28 days of randomisation
c) Re-bleeding
d) Need for endoscopy, surgery or radiological intervention
e) Blood product transfusion
f) Thromboembolic events (deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction)
g) Other complications (significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure, liver failure, seizures)
h) Patient's self care capacity using the Katz Index of Independence in Activities of Daily Living
i) Days spent in intensive care unit or high dependency unit

TRIAL DESIGN:

A pragmatic, randomised, double blind, placebo controlled trial among 12,000 patients with significant gastrointestinal bleeding.

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA: Adults with significant acute upper or lower gastrointestinal bleeding. The diagnosis of significant bleeding is clinical but may include patients with hypotension, tachycardia, or those likely to need transfusion, urgent endoscopy or surgery. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use tranexamic acid in a particular patient with GI bleeding. If the clinician believes there is a clear indication for, or clear contraindication to, tranexamic acid use, the patient should not be randomised. There are no pre-specified exclusion criteria.
TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: A loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation, followed by an intravenous infusion of 3 grams of TXA or placebo (sodium chloride 0.9%) over 24 hours.
SETTING: This trial is coordinated from the London School of Hygiene & Tropical Medicine Clinical Trials Unit (University of London) and conducted in hospitals worldwide.
DURATION OF TREATMENT AND PARTICIPATION: Eligible patients should be randomised as soon as possible. The loading dose will be given immediately after randomisation and the maintenance dose will be given immediately after the loading dose, over 24 hours. Participation will end at discharge from randomising hospital, death or at 28 days post randomisation, whichever occurs first.
CRITERIA FOR EVALUATION: All patients randomly allocated to tranexamic acid will be compared with those allocated to placebo, irrespective of whether they received the allocated treatment or not ('intention to treat' analysis).

CLINICAL PHASE	3
PLANNED TRIAL START	2 January 2013
PLANNED DATE OF LAST PATIENT ENROLMENT	31 May 2019

SUMMARY OF CHANGES BETWEEN VERSIONS 2.0 AND 3.0

Protocol Section	Description of change
SUMMARY	**PRIMARY OUTCOME AND SECONDARY OUTCOMES:** **Change from**: The primary outcome is death in hospital within 28 days of randomisation (cause-specific mortality will also be recorded). **To**: The primary outcome is death from haemorrhage within 5 days of randomisation (all-cause and cause-specific mortality will also be recorded). All-cause and cause-specific mortality within 28 days will be reported as secondary outcomes. **Addition of the following:** a) Death from haemorrhage within 28 days of randomisation b)Mortality: all-cause and cause-specific mortality within 28 days of randomisation d) Need for **endoscopy**, surgery or radiological intervention
2.3 NUMBER OF PATIENTS NEEDED	**Addition of the following:** **Additional information for justification to changes made in Version 3.0:** Although the sample size remains at 12,000 as per the above justification, sample size calculations were rerun based on the amended primary outcome of death from haemorrhage within 5 days of randomisation. Blinded data from the HALT-IT trial show that only around 40% of deaths are due to bleeding and occur within 5 days of randomisation. Based on these estimates, a baseline event rate of 4% haemorrhage death within 5 days might reasonably be expected. Assuming a cumulative incidence of death due to bleeding of 4%, a study with 12,000 patients will have 85% power (two sided alpha = 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4% to 3%.
2.11 MEASURES OF OUTCOME	**PRIMARY OUTCOME AND SECONDARY OUTCOMES:** **Change from:** The primary outcome is death in hospital within 28 days of randomisation (cause-specific mortality will also be recorded). **To:** The primary outcome is death from haemorrhage within 5 days of randomisation (all-cause and cause-specific mortality will also be recorded). All-cause and cause-specific mortality within 28 days will be reported as secondary outcomes. **Addition of the following:** a) Death from haemorrhage within 28 days of randomisation b)Mortality: all-cause and cause-specific mortality within 28 days of randomisation d) Need for **endoscopy**, surgery or radiological intervention

SUMMARY OF CHANGES BETWEEN VERSIONS 1.1 AND 2.0

Protocol Section	Description of change
SUMMARY	**PRIMARY OUTCOME** **Addition of the following:** Cause specific mortality will be described as per section 3.1 of the outcome form (haemorrhage, myocardial infarction, stroke, pulmonary embolism, pneumonia, malignancy, other). **SECONDARY OUTCOMES:** **Addition of the following:** a) Death from haemorrhage **TRIAL DESIGN:** Change of the number of patients needed from 8,000 to 12,000 patients. **PLANNED DATE OF LAST PATIENT ENROLMENT:** Change from 30 November 2017 to 31 May 2019.
2.1 OVERVIEW	Change from "About eight thousand adults" to "About twelve thousand adults".
2.8.3 ADMINISTRATION OF TREATMENT	**Addition of the following:** Where fluid restriction is needed the volume used to administer the maintenance dose can be reduced to 500 mL.
2.11 MEASURES OF OUTCOME	**PRIMARY OUTCOME** **Addition of the following:** Cause specific mortality will be described as per section 3.1 of the outcome form (haemorrhage, myocardial infarction, stroke, pulmonary embolism, pneumonia, malignancy, other). **SECONDARY OUTCOMES:** **Addition of the following:** a) Death from haemorrhage

SUMMARY OF CHANGES BETWEEN VERSIONS 1.0 AND 1.1

Protocol Section	Description of change
SUMMARY	**PLANNED DATE OF LAST PATIENT ENROLMENT:** Change from 30 November 2016 to 30 November 2017.

CONTENTS

1. INTRODUCTION

Acute gastrointestinal (GI) bleeding is a common emergency and an important cause of mortality and morbidity worldwide. Acute upper GI bleeding accounts for about 60,000 hospital admissions each year in the UK and has a case fatality of about 10%.[1, 2] Lower GI bleeding accounts for about 15,000 admissions each year with a case fatality of about 15%.[3] GI bleeding is also common in low and middle income countries, where patients are usually young and poor.

Common causes of acute upper GI bleeding in high income countries are ulcers (40%) and oesophageal varices (11%).[2] In low and middle income countries variceal bleeding is particularly common (45%), with peptic ulcers accounting for about 30% of cases. In sub-Saharan Africa, schistosomiasis is an important cause of portal hypertension, responsible for about 130,000 deaths from haematemesis each year.[4] Despite advances in the management of upper GI bleeding in the past two decades, mortality remains high. In a recent nationwide UK study, the case fatality for new presentations to hospital was 7%, rising to over 26% in patients already hospitalised for another condition.[2, 5]

A strong predictor of mortality in patients with upper GI bleeding is re-bleeding, which occurs in about 10% of non-variceal[5, 6] and 25% of variceal bleeding.[7, 8] A study in patients with bleeding peptic ulcers[9] found that more than half of the re-bleeds occurred in the 24 hours after initial treatment. Re-bleeding rates have not changed significantly over the past 15 years[2, 10, 11] and ongoing research should focus on improving this outcome.[10]

Leading causes of lower GI bleeding are diverticular disease, colitis and cancer.[12] Mortality from lower GI bleeding is less than 5% but increases to about 20% in patients who bleed during admission to hospital for other reasons.[13] Most cases occur in the elderly and many are associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs).[3, 14]

Additional information to support the rationale for this study in each country is available in Appendix 5 of this Protocol.

Tranexamic acid (TXA) is commonly given to patients either before or during surgery to reduce bleeding and the need for blood transfusion. A systematic review of randomised controlled trials of TXA in surgical patients[15] shows that it reduces the probability of receiving a blood transfusion by about a third (RR=0.62, 95% CI 0.58 to 0.65), with no evidence of an increase in risk of thromboembolic events.

TXA has been shown to reduce mortality in bleeding trauma patients. The CRASH-2 trial, which enrolled 20,211 patients from hospitals in 40 countries, shows that the administration of TXA within 8 hours of injury reduces deaths due to bleeding (RR=0.85, 95% CI 0.76 to 0.96), and all-cause mortality (RR=0.91, 95% CI 0.85 to 0.97) compared to placebo, with no apparent increase in thromboembolic events.[16] Among patients treated soon after injury, the reduction in mortality with TXA is even greater.[17] Cost-effectiveness analysis reveals that the administration of TXA to bleeding trauma patients is highly cost effective.[18] As a consequence of the CRASH-2 trial results, TXA has been incorporated into trauma treatment protocols worldwide and is included on the WHO List of Essential Medicines.[19]

The knowledge that TXA reduces blood loss in surgery and reduces mortality in traumatic bleeding raises the possibility that it might also be effective for GI bleeding. A systematic review of TXA in upper GI bleeding identified seven trials.[20] Although there was a statistically significant reduction in the risk of death (RR=0.61, 95% CI 0.42 to 0.89) and surgical intervention (RR=0.62, 95% CI 0.35 to 1.09) in patients receiving TXA, the quality of the trials was poor and the estimates are imprecise. Only one trial used adequate allocation concealment. All but one were conducted before the widespread use of therapeutic endoscopy and proton pump inhibitors. Furthermore, the trials are too small to assess the effect of TXA on thromboembolic events. For these reasons, the effectiveness and safety of TXA for GI bleeding is uncertain and it is not routinely used for treatment. In a UK audit in 2007, fewer than 1% of patients with upper GI bleeding were given TXA.[5] TXA is not referred to in two recent international consensus documents on the management of GI bleeding (the 2010 *International consensus recommendation on the management of patients with non-variceal upper GI bleeding*[21] and the 2011 *Asia-Pacific Working Group consensus on non-variceal upper GI bleeding*[22]), nor in the 2012 UK National Institute for Health and Clinical Excellence (NICE) guidelines for acute upper GI bleeding.[23]

1.1 NEED FOR A TRIAL

The HALT-IT trial will help to determine whether or not TXA should be used in the treatment of GI bleeding. If TXA reduces mortality in patients with GI bleeding, this would be of considerable significance worldwide. TXA might also reduce the need for transfusion. Blood is a scarce resource with a risk of transfusion transmitted infections.

The results will be disseminated in peer reviewed medical journals, conference presentations, and in an updated systematic review of treatments for GI bleeding. There is evidence that hospitals participating in multi-centre trials are more likely to implement the trial results.[24] For this reason, an international multi-centre trial like the HALT-IT trial could have a substantial impact on clinical practice. The large network of collaborating sites will help to ensure that the results are disseminated worldwide.

1.2 TRANEXAMIC ACID AND ITS EFFECT ON BLEEDING

In normal haemostasis, coagulation occurs rapidly at the site of a damaged blood vessel forming a stable fibrin blood clot. However, fibrinolytic enzymes in the blood can impair clot stability and worsen bleeding.[25] TXA inhibits fibrinolytic enzymes and can thus enhance the ability to form stable blood clots.

Fibrinolysis may play an important role in GI bleeding due to the premature breakdown of fibrin blood clots at the bleeding site.[26, 27] Studies have shown that many patients with acute upper GI bleeding have elevated levels of fibrin degradation products (a surrogate marker for fibrinolysis) and that this is associated with worse outcomes.[26, 27] Fibrinolysis may also increase the risk of re-bleeding.

TXA reduces blood loss and the need for transfusion when administered before and during surgery and increases survival in traumatic bleeding, especially when given soon after injury. Early administration in patients with acute GI bleeding could possibly reduce the duration and amount of bleeding at presentation and the risk of re-bleeding by stabilising blood clots at the bleeding site. This could reduce mortality and the need for blood transfusion.

1.3 POTENTIAL SIDE EFFECTS OF TRANEXAMIC ACID

The systematic review of TXA in surgery provides no evidence for any increase in the risk of thromboembolic events in patients given TXA.[15] There was no increase in the risk of thromboembolic events in patients treated with TXA in the CRASH-2 trial.[16, 17] Indeed, there were fewer vascular occlusive deaths with TXA (RR=0.69, 95% CI 0.44 to 1.07) and there was a statistically significant reduction in fatal and non-fatal myocardial infarction (RR=0.64, 95% CI 0.42 to 0.97). We do not know whether TXA increases or decreases the risk of thromboembolic events in patients with GI bleeding. The trials to date are too small to assess the effect of TXA on these outcomes.[20]

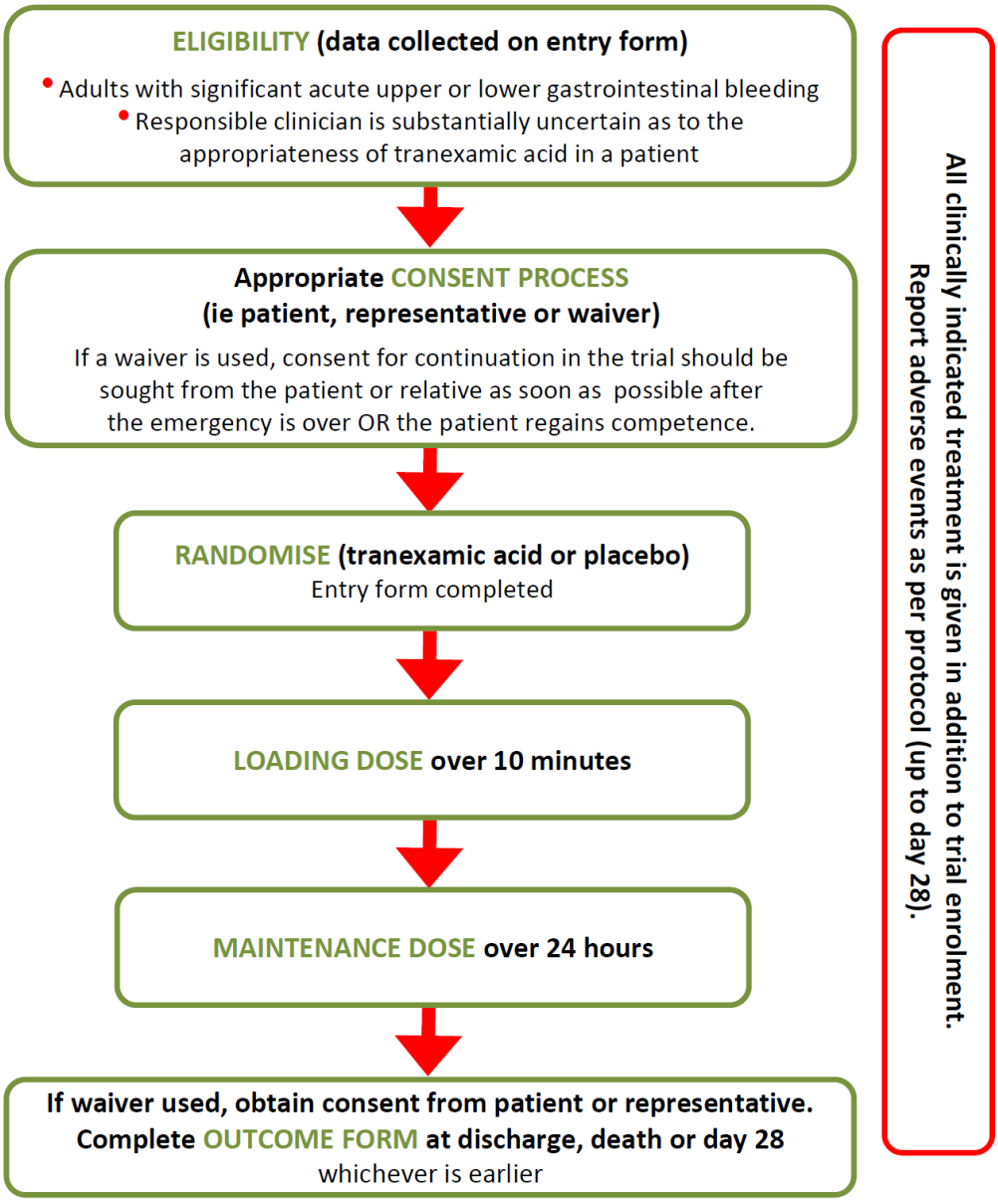
TXA is not a new drug. Adverse events are uncommon and usually manifest as nausea or diarrhoea, or occasionally as orthostatic reactions.[28] These symptoms are commonly associated with GI bleeding. There is some evidence from observational studies that high-dose TXA is associated with an increased risk of seizures in patients undergoing cardiac surgery.[29–32] The doses of TXA used in these studies (total doses from 7.5g up to 20g) are much higher than that proposed in the HALT-IT trial (4g). An association between TXA and seizures has not been confirmed in randomised trials.

1.4 OBJECTIVE

The HALT-IT trial will provide reliable evidence as to whether early administration of TXA reduces mortality and other clinical outcomes in patients with significant acute gastrointestinal bleeding.

2. TRIAL DESIGN

2.1 OVERVIEW



HALT-IT trial is a large, pragmatic, randomised, double blind, placebo controlled trial to quantify the effects of the early administration of TXA on death, blood transfusion and other relevant outcomes. About twelve thousand adults, who have significant upper or lower GI bleeding 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 practice. The eligibility criteria are based on the uncertainty principle, which is a well established approach to trial eligibility.[33] A patient can be enrolled if, and only if, the responsible clinician is substantially uncertain as to which trial treatment would be most appropriate for that particular patient. A patient should not be enrolled if the responsible clinician or the patient (or his/her representative) are for any medical or non-medical reasons reasonably certain that one of the two allocated treatments (TXA or placebo) would not be appropriate for this particular individual (in comparison with either no treatment or some other treatment that could be offered). Clinicians, patients and their representatives will be provided with information about the trial treatment to assist them in their judgement.

Randomisation: Patients eligible should be randomised as soon as possible, and the study treatment started immediately. 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 but a short Outcome form (Appendix 2) must be completed from the medical records 28 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 28 days after randomisation.

2.2 SETTINGS

The pragmatic nature of this trial will allow for the recruitment of patients from a wide variety of health care facilities. Participating hospitals will be selected worldwide. There is no limit to the maximum number of patients to be recruited at each site.

2.3 NUMBER OF PATIENTS NEEDED

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

Estimated event rate: Previous studies on GI bleeding suggest an overall mortality of 8–16%.[34] About 10% of patients with GI bleeding die in hospital.[2, 5] Based on these estimates, a baseline event rate of 10% mortality might reasonably be expected.

Sample size and size of treatment effect that should be detectable: Assuming a control group mortality rate of 10%, a study with 8,000 patients would have over 90% power (two sided alpha=5%) to detect a clinically important 25% reduction from 10% to 7.5% in mortality. Experience from the CRASH-1 and CRASH-2 clinical trials suggests that the anticipated rate of loss to follow-up (less than 1%) would not impact importantly on study power

Additional information for justification to changes made in Version 2.0
Summary of amendment: Accumulating evidence of the effect of TXA on traumatic bleeding (CRASH-2 trial)[1,2], and postpartum haemorrhage (The WOMAN trial)[3], show that TXA reduces deaths from haemorrhage with no apparent effect on any other cause of death. The reductions in bleeding deaths in trauma and obstetric patients provide good reason to anticipate that TXA may reduce bleeding deaths (but not other causes of death), in patients with gastrointestinal haemorrhage.

Effect of tranexamic acid on bleeding and non-bleeding related deaths:

Patient group	**Bleeding deaths**	**Non bleeding deaths**
Trauma (CRASH-2 trial)	RR=0.85 (95%CI 0.76–0.96, p=0.0035)	RR=0.94 (0.86, 1.02, p=0.13)
Obstetrics (WOMAN trial)	RR=0.81 (95%CI 0·65-0.99, p=0·045)	RR=1.10 (0.79, 1.54, p=0.57)

The primary outcome in the HALT-IT trial was originally all-cause mortality within 28 days of randomisation. This was based on the assumption that most deaths in the trial would be from bleeding. However, the accumulated (blinded) data shows that a substantial proportion of deaths are non-bleeding related (e.g. cancer, pneumonia, liver failure). As the effect of TXA is likely to be on death from haemorrhage, with the original sample size of 8,000 patients there was a risk that the trial might fail to detect a clinically relevant treatment benefit, leaving the therapeutic question unresolved. The sample size was therefore increased from 8,000 to 12,000 patients and death from haemorrhage was added as the main secondary outcome. The recruitment period was extended by 18 months. With the increase in the sample size, it was expected that the trial should have enough power to detect a reduction in death from haemorrhage and there would be a smaller chance of missing a clinically important reduction in all-cause mortality.

Rationale: Our original sample size estimate assumed a control group all-cause mortality risk of 10%. We estimated that a trial with 8,000 patients would have over 90% power (two sided alpha of 5%) to detect a 25% reduction (RR=0.75) in all-cause mortality. However, because the proportion of bleeding deaths is lower than expected, we might not find such a large (25%) reduction in all-cause mortality. The control group all-cause mortality risk will be about 10% by the time 12,000 patients are recruited. We expected about 60% of deaths to be due to bleeding. If tranexamic acid reduces bleeding deaths by 25% (RR=0.75), with no effect on non-bleeding deaths, the trial has over 80% power to detect a 15%

(RR=0.6×0.75 +0.4×1.0=0.85) reduction in all-cause mortality. In summary, increasing the sample size to 12,000 patients should provide adequate power to detect a plausible reduction in death from haemorrhage and all-cause mortality.

1. The CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet,* 2010. 376(9734): p. 23-32.
2. The CRASH-2 Collaborators The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet,* 2011. 377(9771): p. 1096-101, 1101 e1-2.
3. The WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet,* 2017. 389 (10084): p. 2105-2116.

Additional information for justification to changes made in Version 3.0: Although the sample size remains at 12,000 as per the above justification, sample size calculations were rerun based on the amended primary outcome of death from haemorrhage within 5 days of randomisation. Blinded data from the HALT-IT trial show that only around 40% of deaths are due to bleeding and occur within 5 days of randomisation. Based on these estimates, a baseline event rate of 4% haemorrhage death within 5 days might reasonably be expected. Assuming a cumulative incidence of death due to bleeding of 4%, a study with 12,000 patients will have 85% power (two sided alpha = 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4% to 3%.

2.4 RECRUITMENT OF COLLABORATING INVESTIGATORS

The trial will recruit hospitals worldwide and will continue to add sites to ensure the sample size is achieved. Suitable collaborating sites and investigators will be assessed on the number of potentially eligible patients and their ability to conduct the trial. In advance of the trial starting at a site, the Principal Investigator must agree to follow Good Clinical Practice Guidelines and all relevant regulations in their country. All relevant regulatory and ethics approvals must be in place. A hospital will not be considered suitable for participating in the HALT-IT trial if TXA is in routine use for the treatment of GI bleeding.

2.5 ELIGIBILITY

Inclusion criteria:
All adults with significant acute upper or lower GI bleeding:
- where the responsible clinician is substantially uncertain as to whether or not to use TXA
- when consent has been obtained according to approved procedures

The diagnosis of significant bleeding is clinical but may include patients with hypotension, tachycardia, or those likely to need transfusion, urgent endoscopy or surgery. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use TXA in a particular patient with GI bleeding.

Exclusion criteria:
- Patients for whom the responsible clinician considers there is a clear indication for TXA should not be randomised.
- Patients for whom the responsible clinician considers there is a clear contraindication for TXA should not be randomised (e.g. a known allergy to TXA).

The TXA summary of product characteristics[35] and an Investigator's Brochure will be provided to investigators to ensure they have adequate information when considering the risk-benefit ratio and the appropriateness of the trial for each patient.

2.6 CONSENT AND ETHICAL CONSIDERATIONS

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 blood loss. Because randomisation and administration of the trial treatment should be done as early as possible once significant GI bleeding is suspected, 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.

Prior information giving: Bearing in mind the clinical situation and their level of distress, the patient and, if present, the patient's relative will be provided with brief information about the trial. The responsible doctor will explain to the patient and relative that the patient will receive the usual emergency treatments for GI bleeding but that in addition to these, if they agree, the patient will be enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being conducted to see whether using a drug called tranexamic acid will help patients with GI bleeding. The patient/relative will be informed that the patient will be given an infusion into a vein over 24 hours of either tranexamic acid or a dummy medicine (a liquid which does not contain tranexamic acid). The doctor will explain that tranexamic acid has been shown to improve outcome in patients with other types of severe bleeding and that whilst we hope that it will also improve recovery after GI bleeding, at present we cannot be sure about this. A brief information leaflet will be provided (Appendix 3a). If the patient or relative objects to the inclusion of the patient in the trial, his/her views will be respected.

The process by which information will be given and consent obtained will depend on the need for urgent clinical intervention and the patient's physical, mental and emotional state. Factors which may impair the patient's decision making process including altered level of consciousness due to a degree of blood loss or co-morbidities (e.g. liver failure), will be taken into consideration. Also, the availability of a personal representative and his/her ability to make a decision on the patient's behalf will have to be taken into consideration. The approach that allows the patient to have the most input into the decision making process without endangering his/her life will be utilised.

a) The patient is fully competent: The patient will be approached at the time of diagnosis. The Information Sheet (Appendix 3c) will be provided, the study will be discussed with the patient and a written consent obtained (Appendix 3d). If the patient is unable to read or write, then the information sheet may be read to him/her and s/he 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 patient's mental capacity is impaired and either a personal or professional representative is available: Information should be given to the patient taking his/her level of mental impairment into consideration. Refusal by the patient should be respected and s/he should not be enrolled.

If a Personal Representative (PeR) who is knowledgeable about the patient's values and beliefs is available, the Information Sheet will be provided (Appendix 3c). Opportunity for questions will be given and written consent obtained (Appendix 3d). 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.

If a PeR is not available and the patient is unable to provide valid informed consent, then an independent doctor or other site staff allowed to fulfil this role (ideally the primary carer if 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 patient's presumed will.

c) The patient's mental capacity is impaired and neither a personal nor professional representative is available: Information should be given to the patient taking his/her level of mental impairment into consideration. Refusal by the patient should be respected and s/he should not be enrolled.

The investigator and ONE independent person (doctor or nurse) who is not participating in this trial may enrol the patient into the trial by certifying in writing in the patient's medical records that:

- the patient has significant gastrointestinal bleeding;
- the patient is unable to give consent as a result of his/her medical condition;
- it is not feasible to contact the patient's PeR/PrR to obtain consent; and
- neither the patient nor the patient's PeR/PrR nor any member of the family has informed the investigator of any objections to the patient being enrolled as a participant in this trial.

For patients enrolled under such an emergency consent procedure, the patient or his/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 statistician from Sealed Envelope Ltd (UK). The codes will be made available to a Good Manufacturing Practice (GMP) certified clinical trial supply company, which will prepare the treatment packs in accordance with the randomisation list. Eligibility will be determined from routinely collected clinical information and recorded on the trial Entry form. No trial-specific tests are required. Patients eligible for inclusion should be randomised as soon as possible to TXA or placebo by taking the next lowest consecutively numbered pack from a box of eight treatment packs. When all the treatment ampoules are confirmed as being intact, at this point the patient is considered randomised onto the trial and the trial treatment must be started immediately.

Once a patient has been randomised, the Entry form data will be sent to the Trial Coordinating Centre as soon as possible and the outcome of the patient should be obtained even if the trial treatment is interrupted or is not actually given.

2.8 TREATMENT

Tranexamic acid (4 grams) will be compared with matching placebo (sodium chloride 0.9%).

2.8.1 DOSE SELECTION

In randomised trials in cardiac 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 1–12 hours.[36] A loading dose of 10 mg/kg of TXA followed by an infusion of 1 mg/kg/hour has been shown to produce plasma concentrations sufficient to inhibit fibrinolysis *in vitro*.[37]

In the emergency situation, the administration of a fixed dose is more practicable since weighing patients is difficult. In the CRASH-2 trial, a fixed dose of 1 gram loading dose of TXA, followed by 1 gram maintenance dose over 8 hours was found to reduce mortality in bleeding trauma patients with no evidence of significant adverse effects.[16, 17]

In the HALT-IT trial, a fixed dosage of 1 gram loading dose of TXA followed by 3 grams infused over 24 hours has been selected. This dosage is within the range that has been shown to inhibit fibrinolysis.[37] It 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.[36, 37] The loading dose (1 gram) is the same used in the CRASH-2 trial.[16] A maintenance dose is provided, but over a longer duration (24 hours) than used in the CRASH-2 trial, to cover the period that is at greatest risk of re-bleeding.

2.8.2 DRUG MANUFACTURE, BLINDING AND SUPPLY OF TRIAL TREATMENT

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 UK's GMP regulations.

Placebo (sodium chloride 0.9%) will be manufactured to match the tranexamic acid by a GMP certified manufacturer.

Ampoules and packaging will be identical in appearance. The blinding process and first stage Qualified Person (QP) release will be done by the designated clinical trial supply company. 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.

The designated clinical trial supply company 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 the blinding process will be performed on a random sample of final QP released drug packs. High Performance Liquid Chromatography (HPLC) separation of known TXA 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 Trial 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. A separate Manual of Operating Procedures will detail the drug accountability system. The Investigator's Brochure will detail labelling of the trial treatment and other processes for assuring adherence to Good Manufacturing Practice.

2.8.3 ADMINISTRATION OF TRIAL TREATMENT

Each treatment pack will contain:

- 8 x 500 mg ampoules of tranexamic acid or placebo
- 2 x sterile 10 mL syringes and 21FG needles

TREATMENT	AMPOULES	DOSE (TXA OR PLACEBO)	ADMINISTRATION
Loading dose	2	1 gram	Added to 100 mL sodium chloride 0.9% and infused over 10 minutes.
Maintenance dose	6	3 grams	Added to 1,000 mL of any isotonic intravenous solution and infused at 125 mg/hr [42 mL/hr] for about 24 hours.
The trial treatment injections should not be mixed with blood for transfusion, or infusion solutions containing penicillin or mannitol.			

The loading dose of the trial treatment must be administered by intravenous infusion immediately after randomisation. The maintenance dose (by intravenous infusion) should commence as soon as the loading dose is completed. Where fluid restriction is needed the volume used to administer the maintenance dose can be reduced to 500 mL.

2.8.4 OTHER TREATMENTS FOR GASTROINTESTINAL BLEEDING

As the trial will be conducted worldwide, each participating site should follow its own clinical practice for the treatment of GI bleeding. 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 GI bleeding.

2.9 ADVERSE EVENTS

TXA is not a new drug and has a documented safety profile. Although the Summary of Product Characteristics suggests that rare cases of thromboembolic events and seizures might be associated with TXA administration, there is no evidence that the TXA treatment regimen used in this trial is associated with an increased risk of thromboembolic events or seizures.

Data on thromboembolic events (such as deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke), seizures, other significant cardiac event, respiratory, liver and renal failure will be collected as secondary outcomes up to day 28 after randomisation and will be presented 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; or
- results in persistent or significant disability/incapacity;
- 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 and life-threatening complications are pre-specified outcomes to be reported in this trial and also to the independent DMC. 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 patient 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 GI bleeding or expected complications of this condition should not be reported as adverse events.

In addition, if a patient is discharged from the randomising hospital before day 28 and is readmitted to hospital, requires medical care for any reason, or is known to have died, an adverse event reporting form should be completed irrespective of the cause.

If a Serious Adverse Event occurs, reporting advice can be obtained by calling the TCC Emergency Helpline and a written report must be 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 TXA develops after randomisation (e.g. the patient becomes anuric and the clinical team is concerned about acute renal failure and risk of TXA accumulation), 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 tranexamic acid 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 tranexamic acid 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 single page Outcome form (Appendix 2) will be completed 28 days after randomisation, at discharge from the randomising hospital, or at death (whichever occurs first).

Additional information for justification to changes made in Version 3.0
Summary of amendment: The primary outcome has been changed from death from all causes within 28 days of randomisation to death from haemorrhage within 5 days of randomisation.

Rationale: TXA is an antifibrinolytic drug that helps stop bleeding by inhibiting the breakdown of fibrin blood clots. Combined data from large randomized controlled trials using TXA in acute severe haemorrhage showed that TXA reduced deaths from haemorrhage with no apparent effect on other causes of death.[43] The original primary outcome in the HALT-IT trial (all-cause mortality within 28 days) was based on the assumption that most deaths in the trial would be from bleeding. However, an analysis of blinded data shows that over half (55%) of patients died from non-bleeding causes such as cancer, pneumonia and liver failure.

Because all-cause mortality is a composite of different causes of death, the treatment effect on all-cause mortality is a weighted average of the cause-specific effects. For example, assuming 45% of deaths are due to bleeding and TXA reduces these by 25% but has no effect on other causes of death, the treatment effect on all-cause mortality would be:

$$RR = (0.45 \times 0.75) + (0.55 \times 1.00) = 0.89$$

The inclusion of non-bleeding causes of death, unlikely to be affected by TXA, would dilute the treatment effect towards the null, reducing the power to detect an effect if one exists. Although the original sample size of 8,000 patients was increased to 12,000, if non-bleeding deaths are unaffected by TXA, even with 12,000 patients the trial will have low power to detect an effect on all-cause mortality. For example, a trial with a 10% event rate would have just 54% power

to detect an 11% reduction in all-cause mortality. In contrast, a trial with a 4% event rate would have 85% power to detect a 25% reduction in death from haemorrhage. By changing the primary outcome, the power of the trial is substantially increased.

Additionally, because the relative contributions of different causes of death vary within and between patient populations, all-cause mortality is not a generalisable outcome measure.

Finally, around 10% of patients with acute GI bleeding experience re-bleeding, which affects over 50% of those with variceal bleeding and is associated with increased mortality. These re-bleeding episodes can occur several days or weeks after the index bleed. Patients receive tranexamic acid (or placebo) for their index bleed but not for rebleeding episodes. TXA has a half-life of around 3 hours and so is unlikely to affect the risk of late deaths due to bleeding that occurs after it has been excreted. As such, we chose to restrict the primary outcome to early deaths from haemorrhage defined as those occurring within 5 days of randomisation.

In summary, changing the primary outcome to death from haemorrhage within 5 days of randomisation should provide adequate power to detect a plausible reduction in death due to bleeding.

Primary Outcome: The primary outcome is death from haemorrhage within 5 days of randomisation (all-cause and cause-specific mortality will also be recorded). Cause specific mortality will be described as per section 3.1 of the outcome form (haemorrhage, myocardial infarction, stroke, pulmonary embolism, pneumonia, malignancy, other).

Secondary outcomes:

a) Death from haemorrhage within 28 days of randomisation
b) Mortality: all-cause and cause-specific mortality within 28 days of randomisation
c) Re-bleeding
d) Need for endoscopy, surgery or radiological intervention
e) Blood product transfusion
f) Thromboembolic events (deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction)
g) Other complications (including other significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure, liver failure, seizures)
h) Functional status will be measured by the Katz Index of Independence in Activities of Daily Living[38] at discharge from the randomising hospital or in-hospital at 28 days after randomisation. The Index assesses adequacy of performance in six functions of bathing, dressing, toileting, transferring, continence and feeding. Patients are scored 'yes' or 'no' for independence in each of the functions (score of 6=full function, 4=moderate impairment, and ≤2=severe functional impairment)
i) Days spent in intensive care unit or high dependency unit

2.12 DATA COLLECTION

This trial will be coordinated from LSHTM and conducted in hospitals worldwide. 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 will be recorded on the Entry form before randomisation to assess eligibility and the form completed if patient randomised. The Outcome form should be completed at death, discharge from the randomising hospital, or 28 days after randomisation, whichever occurs first. This data should be collected from the patient's routine medical records as no special tests are required.

If the patient (or his/her PeR or PrR) withdraws a previously given informed consent or refuses to consent for continuation in the trial, or if the patient dies and no consent is available from either a PeR/PrR, his/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. The data will be used in accordance with local law and ethics committee approval.

The data will be treated in accordance with the UK Data Protection Act 1998. Access to the data will be restricted to authorised users and controlled and stored in accordance with the Act. All patient identifiable information will be stored at the TCC for a maximum of ten years after the trial ends. These data are for follow-up purposes only and will not be held in the clinical trial database and will not be included in any analyses or publications.

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 pragmatic, randomised placebo controlled trial. The intervention (tranexamic acid) has marketing authorisation in many countries and has been in clinical use for decades. The trial will collect data on adverse events which may be associated with this product and the condition under investigation, and these will be reviewed routinely by the independent DMC. The trial involves getting consent, giving the trial drug in the usual way and collecting brief information from the hospital notes. There are no extra tests or procedures. Apart from the trial drug, all other treatment will be as per usual practice. For these reasons, we believe that the risk of harm or injury (whether physical, psychological, social or economic) to trial participants is low. We will use central monitoring along with investigators' training and meetings, and extensive written guidance to make sure the trial is carried out properly. Statistically controlled sampling will be used to select data to be verified. We plan to carry out on-site monitoring for about 10% of the trial data.

Consent forms from trial sites will be monitored at the TCC but only where we have the written consent of the patients to do so.

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

Follow-up of the trial participants ends either at death, discharge, or 28 days post-randomisation, whichever occurs first. Adverse Event reporting will continue up to day 28.

The trial may be terminated early by the Trial Steering Committee (TSC). The Data Monitoring Committee (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 tranexamic acid with those allocated placebo, on an 'intention to treat' basis. Results will be presented as effect estimates with a measure of precision (95% confidence intervals). Subgroup analyses for the primary outcome will be based on time to treatment, source of bleeding (upper versus lower), suspected variceal bleeding and severity of bleeding. Interaction tests will be used to explore whether the effect of treatment (if any) differs across these subgroups. 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 HALT-IT 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.

Timothy Coats, Emergency Medicine University of Leicester Leicester, UK	Daniela Manno, Clinical Lecturer Clinical Trials Unit, LSHTM London, UK
Phil Edwards, Senior Lecturer Clinical Trials Unit, LSHTM London, UK	Ian Roberts, Chief Investigator LSHTM London, UK
Ian Gilmore, Consultant Gastroenterologist University of Liverpool Liverpool, UK	Haleema Shakur, Senior Lecturer Clinical Trials Unit, LSHTM London, UK
Vipul Jairath, SpR Gastroenterology/Hepatology Oxford University Hospitals NHS Trust Oxford, UK	Simon Stanworth, Consultant Haematologist John Radcliffe Hospital Oxford, UK
Katharine Ker, Lecturer Clinical Trials Unit, LSHTM London, UK	Andrew Veitch, Consultant Gastroenterologist New Cross Hospital Wolverhampton, UK

3.4 INDEPENDENT DATA MONITORING COMMITTEE (DMC)

The composition of the DMC is provided in Appendix 4.

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 TSC 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.[39] Membership includes expertise in the relevant field of study, statistics and research study design.

The DMC Charter includes, but is not limited to, defining:

- the schedule and format of the DMC meetings
- the format for presentation of data
- the method and timing of providing interim reports
- stopping rules

Standard Operating Procedures: The DMC is independent from the sponsor, ethics committees, regulatory agencies, investigators, steering committee membership, clinical care of the trial patients, and any other capacity related to trial operations. The 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[40, 41] 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 (TSC)

The composition of the TSC is provided in Appendix 4.

The role of the 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:

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

The TSC includes an experienced gastroenterologist, clinical trialists, chief investigator, clinical representative from a low and middle income country (LMIC), and a patient representative. Face to face meetings or teleconferences will be held at regular intervals determined by need, but no less than once a year. A TSC Charter, which will detail how it will conduct its business, will be agreed at the first meeting.

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 gastroenterology 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 PowerPoint presentations to assist with this);
- agree to comply with the final trial Protocol and any relevant amendments;
- ensure that all patients with gastrointestinal bleeding 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 data forms for five years after the end of the trial.

3.7 TRIAL MANAGEMENT GROUP AND TRIAL COORDINATING CENTRE RESPONSIBILITIES

The Trial Management Group (TMG) 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 of the Sponsor's responsibilities are carried out. The responsibilities include (but are 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 wall posters.

3.9 PUBLICATION AND DISSEMINATION OF RESULTS

The trial protocol and results will be published in peer-reviewed journals. All publications will follow the CONSORT statement.[42] 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 (haltit.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 depends entirely upon the collaboration of 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 HALT-IT trial is funded by the NIHR Health Technology Assessment programme. Funding for this trial covers trial materials, meetings and central organisational costs. 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
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GI	Gastrointestinal
HPLC	High Performance Liquid Chromatography
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
ICMJE	International Committee for Medical Journal Editors
kg	kilogram
LMIC	Low and Middle Income Country
LSHTM	London School of Hygiene & Tropical Medicine
mg	milligram
mL	milliLitre
PeR	Personal Representative
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	Trial Coordinating Centre
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic Acid
UK	United Kingdom
WHO	World Health Organization

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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 patients and relatives
b) Consent procedure overview
c) Information sheet for patients and representatives
d) Informed consent form

Appendix 4: Composition of the Data Monitoring Committee and the Trial Steering Committee

Appendix 5: Country specific rationale for study and other relevant protocol information

Appendix 1 – 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. Age						
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 require intervention (eg intravenous fluids)*			
14. Suspected current active bleeding? *(circle)*	**YES**	**NO**	*Clinical judgement after considering history, signs and symptoms*			
15. Major 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**

Entry form Version 1.0 dated 26 November 2012 Page 1 of 2 Protocol Code:ISRCTN11225767

DATA FORMS GUIDANCE

AFTER COMPLETING THIS PAPER FORM, YOU CAN:

- Enter these data directly into the trial database. For username and password, please contact **haltit.data@Lshtm.ac.uk**
- Send as a secure scanned document by email to **haltit.data@Lshtm.ac.uk** or upload a scanned copy online – see study file for details
- 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 AND WALL POSTERS

Appendix 2 – 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			
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*

Outcome Form International Version 2.0 dated 25 July 2018 Page 1 of 2 Protocol Code: ISRCTN11225767

ADDITIONAL RE-BLEEDING INFORMATION

Q.10 a ii) Date of re-bleed episodes cont. *(please report all ADDITIONAL episodes of re-bleeding that are NOT captured on page 1)*

EPISODE NUMBER	DATE		
4	dd	mm	yyyy
5	dd	mm	yyyy
6	dd	mm	yyyy
7	dd	mm	yyyy
8	dd	mm	yyyy
9	dd	mm	yyyy
10	dd	mm	yyyy
11	dd	mm	yyyy
12	dd	mm	yyyy
13	dd	mm	yyyy
14	dd	mm	yyyy
15	dd	mm	yyyy
16	dd	mm	yyyy
17	dd	mm	yyyy

DETAILED GUIDANCE ABOUT COMPLETING THIS FORM CAN BE FOUND IN YOUR INVESTIGATORS STUDY FILE

AFTER COMPLETING THIS PAPER FORM, YOU CAN:

- Enter these data directly into the trial database. For username and password, please contact **haltit.data@Lshtm.ac.uk**
- Send as a secure scanned document by email to **haltit.data@Lshtm.ac.uk** or upload a scanned copy – see study file for guidance
- Fax to **+44 20 7299 4663**

STORE THIS ORIGINAL FORM IN YOUR STUDY FILE

Appendix 3a – Brief information leaflet for patient and relatives

Haemorrhage ALleviation with Tranexamic Acid – InTestinal system (HALT-IT)

THE HALT-IT TRIAL
BRIEF INFORMATION ABOUT THE RESEARCH

Haemorrhage alleviation with tranexamic acid - Intestinal system

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

You (the patient) have bleeding from the gut that needs to be stopped quickly. All the usual treatments for the bleeding that we provide at this hospital will be given. As well as this, we are inviting you to take part in a study. This study will see if a treatment called *tranexamic acid* reduces gut bleeding. We hope that this treatment will lead to a better recovery. We know that the treatment helps people with other types of bleeding but we don't know yet if it works in gut bleeding.

In this study, half the patients will get the study treatment (*tranexamic acid*) and half a dummy treatment (a placebo). If you take part in this study, you (the patient) will receive the study treatment or placebo straight away. It will be given to you through a drip over 24 hours. We will also need to collect some information about your (the patient's) medical condition and send it to a central office in London.

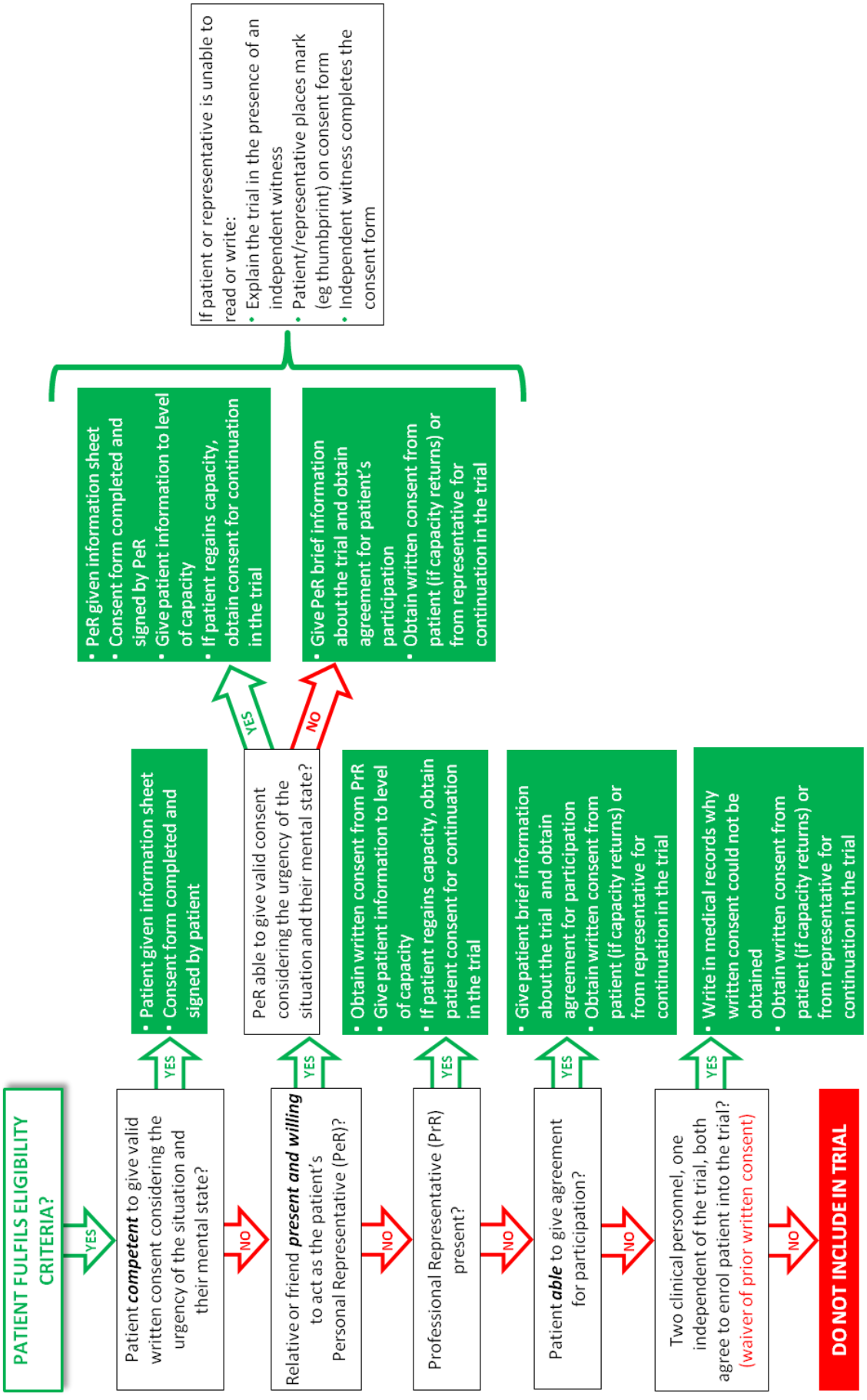
If you would like to know more about our study now, then we will tell you. But otherwise we will tell you more about it later. Are you willing for us to go ahead with the study treatment?

Yes, I am willing for you to go ahead.

_____	_____	_____
Name of Patient or representative	Date	Signature (thumbprint or other mark if unable to sign)

[This information can be presented verbally and does not need to be used verbatim. It can be adapted to each situation and is provided to be used only as a guide. A signed form is not mandatory and if signed, must not be viewed as a valid Informed Consent.]

Appendix 3b – Consent Procedure Overview



Appendix 3c – Information sheet for patient and representative

THE HALT-IT TRIAL
INFORMATION ABOUT THE RESEARCH

Title of Research: Tranexamic acid for the treatment of gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial
Trial site number:
Leaflet version: International v2.0; version date: 23/08/2017

This hospital is taking part in a study to find better treatments for gut bleeding

One of the following applies to you:

1) You are a patient with bleeding from your gut. We are inviting you to take part in this research study.
2) You are a patient who had bleeding from your gut. When you were very unwell you were included in this research study. We are now asking you to consider taking part in the rest of the study.
3) You are a representative of a patient who has bleeding from the gut. We are asking you to decide on the patient's behalf whether s/he can take part in this research study. You may wish to consider if you think that the patient would have agreed to take part if s/he had been well enough to decide.

What is this leaflet for?

Before you decide to take part in this study we would like you to know why it is being done and what it will involve.

One of our team will go through this leaflet with you and answer any questions you have. We think that this will take about 20 minutes.

You can talk to others about the study if you wish.

What is the study for?

We are looking to see if there is a better treatment for gut bleeding. We hope that the study treatment (a drug called tranexamic acid), which helps blood clotting, will reduce gut bleeding. But it is also possible that it could cause clots where they are not needed.

Tranexamic acid is not a new drug. It is already used to help people who are bleeding after an operation or an accident. We hope that this treatment will do more good than harm in patients who are bleeding from the gut but we don't yet know this for sure.

Why have I been asked to take part?

You (the patient) have bleeding from your gut that needs to be treated quickly. Your doctor thinks that you can join the study, but it is up to you to decide whether to take part or not.

If you do take part, you will be one of about 12,000 people with gut bleeding in this study from all over the world.

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
- he/she is not an adult

You (the patient) have been invited to take part in this study because none of the above conditions apply to you.

Do I have to take part?

No. It is up to you to decide to take part or not. If you don't want to take part, your doctor will still care for you and give you all the other treatments you need.

How does the study work?

We don't know if giving tranexamic acid as well as all the usual treatments for gut bleeding will be better or not. The best way to find out is to see how people who are given it do, compared to people who are not. To do this, the people taking part in the study will be put into one of two groups. One group will get the study treatment (tranexamic acid). The other group will get a dummy treatment (a placebo). Which group a person is put into is decided randomly and each person has an equal chance of being put into either group. The study treatment and the dummy treatment look the same, so you and your doctor will not know which group you are in.

What will happen to me if I take part?

You will get all the usual treatments to help your bleeding. You will also be given one of the study treatments (tranexamic acid or placebo). You will start this treatment straight away. It will be given to you through a drip over 24 hours. The study treatment is free. You will not need any extra tests or to spend longer in hospital because of the study.

We will give you this leaflet to keep and ask you to sign a consent form.

We would also like to send a letter to let your personal doctor know that you are taking part in the study.

What will happen afterwards?

We will want to know about your health after leaving hospital. Before you go home you will be given a card to take with you. If you see a doctor or nurse for an illness within a month of coming into hospital, you should show them the card.

Will I be hurt by taking part?

Other studies suggest that the study treatment (tranexamic acid) doesn't cause unwanted blood clots and there are no bad side effects with short term use, but we do not know if this will be the same for people with your condition. Your doctor will watch you and give you the best available care if there are any problems. They will also tell the people running the study.

Will I gain from taking part?

We do not know if this study will help you. But it will help doctors treat people who have gut bleeding in the future.

Can I change my mind about taking part?

Yes. If you change your mind about taking part, you just need to tell your doctor that you don't want to be in the study any more. You can do this at any time. Your doctor will still care for you and give you all the other treatments you need. We hope that you will still let us use the information about how you got on, but if you do not want us to use it please tell your doctor.

What information will be collected about me?

Details about your bleeding, the medicines you get and how you get on will be written down.

Staff at the main office in London may also want to collect a copy of your signed consent form. This will help them to ensure that the study is being carried out correctly.

Will my information be kept private?

All information collected about you will be kept private. People allowed to look at the information will be the doctors running the study, the staff at the main office in London and authorities who check that the study is being carried out properly.

Your doctor will send some details about you to the study team in London who will store it securely. Your personal details will be kept in a different safe place to the other study information and will be destroyed within five years of the end of the study.

The study results will be published in a medical journal so that other doctors can learn from them. Your personal information will not be included in the study report and there is no way that you can be identified from it.

The study data will be made available to researchers worldwide so that it can be used to improve medical knowledge and patient care. Your personal information will not be included and there is no way that you can be identified.

Who is in charge of this study?

The study is run by a team at the London School of Hygiene & Tropical Medicine at the University of London.

Who is paying for this study?

The study is paid for by the Government of United Kingdom. Your doctor is not being paid for including patients in this study. Only costs related to doing the trial will be provided.

Who has checked this study?

To look after your interests, this study has been carefully checked by an independent group of people called a Research Ethics Committee. They agreed that it is okay for us to ask people to take part.

Will I be able to find out what the study results are?

The study should end in the year 2020. If you would like to have a summary of the results of this study when it has ended, please let the doctor treating you know.

You can also visit the study's website to see the progress of the study (haltit.Lshtm.ac.uk).

Who can I talk to if I have any other questions or concerns?

You can talk to your doctors and nurses about the study. They will do their best to answer your questions. You can also speak to Dr [insert name] who is in charge of this study at your hospital. You can write to [him/her] at [address] or phone on [number].

If you remain unhappy you can make a formal complaint to the hospital director and/or the Ethics Committee which approved this trial at this hospital. Your doctor can give you details on how to do this.

What else do I need to know?

If something does go wrong and you are harmed during the study, and this is due to someone's negligence, then you may have grounds to seek compensation. 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 taking part in this study.

You are encouraged to ask any questions you wish, before, during or after the study. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the drug(s)/procedure(s) involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor.

Appendix 3d – Informed Consent Form

HALT-IT TRIAL CONSENT FORM

[HOSPITAL CONTACT DETAILS]

CONSENT FORM FOR PATIENT AND REPRESENTATIVE
THE HALT-IT TRIAL

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

Hospital code		Local Principal Investigator	
Patient hospital ID number		Randomisation number	BOX / PACK
Name of patient		If representative, relationship to patient	

Version 2.0 dated 23/08/2017

1. I have read and understood the information sheet (version number 2.0 dated 23 August 2017) and have had a chance to ask questions.
2. I understand that it is my choice to take part in this study. I am free to pull out at any time, without giving a reason and without my (the patient's) treatment or rights being affected.
3. I understand that parts of my (the patient's) medical notes may be looked at by people involved in the study. I allow them to see the notes.
4. I allow a copy of this form to be made available to the study staff in London for monitoring.
5. I allow my personal doctor to be told that I (the patient) am taking part in this study.
6. I give permission for the data collected about me in this trial (with my personal information removed) to be used by researchers worldwide.
7. I agree to me (the patient) taking part in the above study, the HALT-IT trial.

_____	_____	_____
Name of patient/representative	Date	Signature (thumbprint or other mark if unable to sign)
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____
Name of Principal Investigator	Date	Signature

The patient/representative is unable to sign. As a witness, I confirm that all the information about the trial was given and the patient/representative 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 patient's hospital records

Consent form International version 2.0 dated 23 August 2017 Protocol ISRCTN11225767

Appendix 4 – Composition of the DMC and the TSC

Composition of the Independent Data Monitoring Committee (DMC)

NAME	AFFILIATION	EXPERTISE
Professor Alan Barkun	McGill University, Canada	Clinical expert
Mr Tony Brady	Sealed Envelope Ltd, UK	Independent Statistician
Dr Philip Devereaux	McMaster University, Canada	Trials expert
Professor Richard Gray	Oxford University, UK	Statistician
Professor Suresh David	Pushpagiri Medical College Hospital, India	Clinical expert

Composition of the Trial Steering Committee (TSC)

NAME	AFFILIATION	EXPERTISE
Professor Christopher Hawkey	University of Nottingham, UK	Gastroenterologist and Chair of TSC
Dr Adefemi Afolabi	University of Ibadan, Nigeria	General Surgeon
Professor Jack Cuzick	University of London, UK	Statistician
Ms Barbara Farrell	University of Oxford, UK	Trials expert
Mr Ken Halligan	UK	Patient Representative
Professor David Henry	Bond University, Australia	Trials expert
Dr Chris Metcalfe	University of Bristol, UK	Statistician
Professor Ian Roberts	LSHTM, UK	Trials expert

APPENDIX 5 – country specific rationale for study and other relevant protocol information:

Public health relevance: ***[.....]***

Minimum age considered as adult for recruitment: ***[.....]***

Local organisation: ***[.....]***