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*Ian Roberts, Haleema Shakur-Still, Adefemi Afolabi, Adegboyega Akere, Monica Arribas, Emma Austin, Kiran Bal, Nuha Bazeer, Danielle Beaumont, Amy Brenner, Laura Carrington, Rizwana Chaudhri, Timothy Coats, Ian Gilmore, Kenneth Halligan, Irshad Hussain, Vipul Jairath, Kiran Javaid, Aasia Kayani, Ton Lisman, Raoul Mansukhani, Alec Miners, Muttiullah Mutti, Muhammad Arif Nadeem, Richard Pollok, Danielle Prowse, Jonathan Simmons, Simon Stanworth, Andrew Veitch and Jack Williams*





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# Abstract

## A high-dose 24-hour tranexamic acid infusion for the treatment of significant gastrointestinal bleeding: HALT-IT RCT

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**Background:** Tranexamic acid reduces blood loss in surgery and the risk of death in trauma patients. Meta-analyses of small trials suggest that tranexamic acid decreases the number of deaths from gastrointestinal bleeding, but these meta-analyses are prone to selection bias.

**Objective:** The trial provides reliable evidence of the effect of tranexamic acid on mortality, rebleeding and complications in significant acute gastrointestinal bleeding.

**Design:** A multicentre, randomised, placebo-controlled trial and economic analysis. Patients were assigned by selecting one treatment pack from a box of eight, which were identical apart from the pack number. Patients, caregivers and outcome assessors were masked to allocation. The main analyses were by intention to treat.

**Setting:** The setting was 164 hospitals in 15 countries, co-ordinated from the London School of Hygiene & Tropical Medicine.

**Participants:** Adults with significant upper or lower gastrointestinal bleeding ( $n = 12,009$ ) were eligible if the responsible clinician was substantially uncertain about whether or not to use tranexamic acid. The clinical diagnosis of significant bleeding implied a risk of bleeding to death, including hypotension, tachycardia or signs of shock, or urgent transfusion, endoscopy or surgery.

**Intervention:** Tranexamic acid (a 1-g loading dose over 10 minutes, then a 3-g maintenance dose over 24 hours) or matching placebo.

**Main outcome measures:** The primary outcome was death due to bleeding within 5 days of randomisation. Secondary outcomes were all-cause and cause-specific mortality; rebleeding; need for endoscopy, surgery or radiological intervention; blood product transfusion; complications; disability; and days spent in intensive care or a high-dependency unit.

**Results:** A total of 12,009 patients were allocated to receive tranexamic acid ( $n = 5994$ , 49.9%) or the matching placebo ( $n = 6015$ , 50.1%), of whom 11,952 (99.5%) received the first dose. Death due to bleeding within 5 days of randomisation occurred in 222 (3.7%) patients in the tranexamic acid group and in 226 (3.8%) patients in the placebo group (risk ratio 0.99, 95% confidence interval 0.82 to 1.18). Thromboembolic events occurred in 86 (1.4%) patients in the tranexamic acid group and 72 (1.2%) patients in the placebo group (risk ratio 1.20, 95% confidence interval 0.88 to 1.64). The risk of arterial thromboembolic events (myocardial infarction or stroke) was similar in both groups (0.7% in the tranexamic acid group vs. 0.8% in the placebo group; risk ratio 0.92, 95% confidence interval 0.60 to 1.39), but the risk of venous thromboembolic events (deep-vein thrombosis or pulmonary embolism) was higher in tranexamic acid-treated patients than in placebo-treated patients (0.8% vs. 0.4%; risk ratio 1.85, 95% confidence interval 1.15 to 2.98). Seizures occurred in 38 patients who received tranexamic acid and in 22 patients who received placebo (0.6% vs. 0.4%, respectively; risk ratio 1.73, 95% confidence interval 1.03 to 2.93). In the base-case economic analysis, tranexamic acid was not cost-effective and resulted in slightly poorer health outcomes than no tranexamic acid.

**Conclusions:** Tranexamic acid did not reduce death from gastrointestinal bleeding and, although inexpensive, it is not cost-effective in adults with acute gastrointestinal bleeding.

**Future work:** These results caution against a uniform approach to the management of patients with major haemorrhage and highlight the need for randomised trials targeted at specific pathophysiological processes.

**Limitations:** Although this is one of the largest randomised trials in gastrointestinal bleeding, we cannot rule out a modest increase or decrease in death due to bleeding with tranexamic acid.

**Trial registration:** Current Controlled Trials ISRCTN11225767, ClinicalTrials.gov NCT01658124 and EudraCT 2012-003192-19.

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## List of abbreviations

AGIB	acute gastrointestinal bleeding	MHRA	Medicines and Healthcare products Regulatory Agency
CEAC	cost-effectiveness acceptability curve	MREC	Multicentre Research Ethics Committee
CI	confidence interval	NICE	National Institute for Health and Care Excellence
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2	NIHR	National Institute for Health Research
CRASH-3	Clinical Randomisation of an Antifibrinolytic in Significant Head Injury 3	NSAID	non-steroidal anti-inflammatory drug
CTU	Clinical Trial Unit	PPI	patient and public involvement
DMC	Data Monitoring Committee	PSA	probabilistic sensitivity analysis
GI	gastrointestinal	QALY	quality-adjusted life-year
GMP	good manufacturing practice	QP	qualified person
HALT-IT	Haemorrhage ALleviation with Tranexamic acid – Intestinal system	RBC	red blood cell
HTA	Health Technology Assessment	RCT	randomised controlled trial
ICER	incremental cost-effectiveness ratio	RR	risk ratio
ICU	intensive care unit	SBP	systolic blood pressure
INMB	incremental net monetary benefit	SMR	standardised mortality ratio
LSHTM	London School of Hygiene & Tropical Medicine	TCC	Trial Co-ordinating Centre
LY	life-year	TRIGGER	Transfusion in Gastrointestinal Bleeding
		TXA	tranexamic acid
		WOMAN	World Maternal Antifibrinolytic



## Plain English summary

**A**cute gastrointestinal bleeding (bleeding from the gut) is a common emergency and an important cause of death and illness worldwide. In the UK, more than 65,000 people each year are admitted to hospital because of acute gastrointestinal bleeding; approximately 10% of them die within 30 days. Gastrointestinal bleeding is also common in low- and middle-income countries. The care of patients with gastrointestinal bleeding has improved in recent decades, but death rates remain high. Gastrointestinal bleeding is often caused by stomach ulcers, but also by liver damage owing to alcohol or hepatitis C infection. An effective and affordable treatment for gastrointestinal bleeding could save many lives and may reduce the need for blood transfusions, which is important because blood is a scarce resource in some health-care settings.

Tranexamic acid, also known as TXA, is a cheap drug that reduces bleeding in other conditions. It helps blood to clot, thereby decreasing bleeding. A trial in bleeding accident victims found that tranexamic acid reduced the chances of bleeding to death, without any increase in side effects. We wanted to find out if tranexamic acid safely improves outcomes in patients with gastrointestinal bleeding, particularly to prevent deaths.

To investigate this, the HALT-IT (Haemorrhage ALleviation with Tranexamic acid – Intestinal system) trial studied 12,009 patients with significant gastrointestinal bleeding in 164 hospitals across 15 countries. Half of the patients received tranexamic acid and the other half received a dummy drug, called a placebo. The treatments were assigned randomly and given in addition to all other treatments needed. Neither the patient nor the doctor knew which treatment a patient received.

The trial showed that tranexamic acid did not reduce deaths from gastrointestinal bleeding. Instead, tranexamic acid was linked to an increased risk of complications, including unwanted blood clots (such as deep-vein thrombosis) and seizures. The economic analysis indicated that giving tranexamic acid to patients with gastrointestinal bleeding does not represent value for money for the NHS.



# Scientific summary

## Background

Tranexamic acid reduces blood loss in surgery and death in trauma patients. Meta-analyses of small trials show that tranexamic acid may decrease the number of deaths from gastrointestinal bleeding. However, meta-analyses of small trials are prone to selection bias and have a low positive predictive value compared with results from large trials.

## Objectives

We assessed the effects of tranexamic acid on the occurrence of death, rebleeding and complications in acute gastrointestinal bleeding.

## Methods

In an international, multicentre, randomised, placebo-controlled trial, adults with significant upper or lower gastrointestinal bleeding were randomly assigned to receive tranexamic acid (1-g loading dose followed by a 3-g maintenance dose over 24 hours) or a matching placebo. Patients were assigned by selecting a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients, caregivers and those assessing outcomes were masked to allocation. The primary outcome was death due to bleeding within 5 days of randomisation. Secondary outcomes were cause-specific and all-cause mortality; rebleeding; surgical or radiological intervention; blood transfusion; thromboembolic events (deep-vein thrombosis, pulmonary embolism, stroke, myocardial infarction); seizures; and other complications.

## Results

Between July 2013 and June 2019, we randomly allocated 12,009 patients from 164 hospitals in 15 countries to receive tranexamic acid ( $n = 5994$ ; 49.9%) or matching placebo ( $n = 6015$ ; 50.1%), of whom 11,952 (99.5%) received the first dose of the allocated treatment.

## Primary outcome

Death due to bleeding within 5 days of randomisation occurred in 222 out of 5956 patients (4%) in the tranexamic acid group and in 226 out of 5981 patients (4%) in the placebo group (risk ratio 0.99, 95% confidence interval 0.82 to 1.18).

## Secondary outcomes

Fatal or non-fatal thromboembolic events occurred in 86 (1.4%) patients in the tranexamic acid group and 72 (1.2%) patients in the placebo group (risk ratio 1.20, 95% confidence interval 0.88 to 1.64). The risk of arterial thromboembolic events (myocardial infarction or stroke) was similar in tranexamic acid- and placebo-treated patients (0.7% vs. 0.8%; risk ratio 0.92, 95% confidence interval 0.60 to 1.39), but the risk of venous thromboembolic events (deep-vein thrombosis or pulmonary embolism) was

higher in tranexamic acid-treated patients than in placebo-treated patients (0.8% vs. 0.4%; risk ratio 1.85, 95% confidence interval 1.15 to 2.98). Seizures occurred in 38 patients who received tranexamic acid and in 22 patients who received placebo (0.6% vs. 0.4%; risk ratio 1.73, 95% confidence interval 1.03 to 2.93).

The effect of tranexamic acid on death due to bleeding within 5 days of randomisation did not appear to vary when stratified by country income, anticoagulant use or systolic blood pressure in an analysis that was not prespecified.

Death due to bleeding within 24 hours of randomisation occurred in 124 (2.1%) patients in the tranexamic acid group and in 120 (2.0%) patients in the placebo group (risk ratio 1.04, 95% confidence interval 0.81 to 1.33). Death due to bleeding within 28 days of randomisation occurred in 253 (4.2%) patients in the tranexamic acid group and in 262 (4.4%) patients in the placebo group (risk ratio 0.97, 95% confidence interval 0.82 to 1.15). Death from all causes within 28 days of randomisation occurred in 564 patients (9.5%) in the tranexamic acid group and in 548 patients (9.2%) in the placebo group (risk ratio 1.03, 95% confidence interval 0.92 to 1.16).

The proportion of patients with rebleeding was similar in both groups at 24 hours, 5 days and 28 days after randomisation.

The proportion of patients who had surgery, radiological intervention and blood product transfusion was also similar in both groups.

The results from the economic analysis suggest that the costs and outcomes of treating people with acute gastrointestinal bleeding with and without tranexamic acid are very similar, with no tranexamic acid being more likely to be the most cost-effective option.

## Conclusion

In this trial, tranexamic acid did not reduce death from gastrointestinal bleeding but was associated with an increased risk of venous thromboembolic events and seizures. Therefore, although it is inexpensive, tranexamic acid does not represent value for money in adults with acute gastrointestinal bleeding.

## Implications for practice

Many emergency physicians and surgeons believe that tranexamic acid improves outcomes in patients with acute severe gastrointestinal bleeding. The promotion of 'major haemorrhage protocols' in UK hospitals encourages the notion that all bleeding is fundamentally the same and can be treated in a similar way. Furthermore, the Cochrane systematic review and meta-analysis of previous trials of tranexamic acid in gastrointestinal bleeding shows a large reduction in mortality with tranexamic acid (pooled risk ratio 0.61, 95% confidence interval 0.42 to 0.89;  $p = 0.01$ ) (Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2012;1:CD006640).

The results from the HALT-IT (Haemorrhage ALleviation with Tranexamic acid – Intestinal system) trial caution against a 'one size fits all' approach to the management of patients with major haemorrhage, and highlight the need for randomised trials targeted at specific pathophysiological processes. Based on the HALT-IT trial results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial.

Because gastrointestinal bleeding is a licensed indication for tranexamic acid, our results could have regulatory implications.



## Recommendations for future research

Although we cannot rule out a modest increase or decrease in death due to bleeding with tranexamic acid, we can rule out the large mortality reduction suggested by the Cochrane systematic review and meta-analysis of previous small trials (Gluud, *et al.* 2012). In this respect, the HALT-IT trial highlights the dangers of overinterpreting results from systematic reviews of small trials.

The large discrepancy between the results of the Cochrane review (Gluud, *et al.* 2012) and the results of the HALT-IT trial should encourage a reconsideration of the role of systematic reviews of small trials in informing health care and health research. In most cases, the results of such reviews should be considered hypothesis generating, requiring confirmation in adequately powered randomised trials.

Because tranexamic acid reduces bleeding deaths in patients with traumatic and post-partum haemorrhage, individual patient data meta-analyses should assess the strength of the evidence that the effectiveness and safety of tranexamic acid varies by the site and cause of bleeding. Basic research could also inform this question by examining the role of fibrinolysis in patients with gastrointestinal bleeding and whether or not this varies depending on the aetiology of the bleeding.

A large proportion of patients in this trial had liver disease (40%), so future research could also assess the effect of tranexamic acid on bleeding from peptic ulcers in patients without liver disease.

## Trial registration

This trial is registered as ISRCTN11225767, ClinicalTrials.gov NCT01658124 and EudraCT 2012-003192-19.

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# Chapter 1 Introduction

Some of the text in this chapter is reproduced with permission from Roberts *et al.*,<sup>1</sup> Brenner *et al.*,<sup>2</sup> and the HALT-IT (Haemorrhage ALleviation with Tranexamic acid – Intestinal system) Trial Collaborators.<sup>3</sup> These are Open Access articles distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon these works, for commercial use, provided the original works are properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The text below includes minor additions and formatting changes to the original text.

Acute gastrointestinal bleeding (AGIB) is a common emergency and an important cause of death worldwide.<sup>4</sup> Bleeding can occur from the upper or lower gastrointestinal (GI) tract, but upper GI bleeding is more common. Symptoms of GI bleeding include haematemesis and coffee ground vomitus, melaena and the passage of fresh red blood in the stool, and clinical signs of shock, such as hypotension and tachycardia. Despite evidence suggesting improvements in survival in recent decades, the case fatality rate is about 10% for upper GI bleeding and 3% for lower GI bleeding.<sup>5,6</sup> However, mortality in patients with lower GI bleeding increases to about 20% in patients who are admitted to hospital for other reasons and have a GI bleed.<sup>7</sup> Most cases occur in the elderly and many are associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs).<sup>8,9</sup>

## Prevalence of gastrointestinal bleeding

The incidence of GI bleeding varies widely between countries, depending on the population prevalence of risk factors, with a reported incidence of upper GI bleeding of 50–140 per 100,000 people across the USA, Europe and Scandinavia.<sup>10–18</sup> In the UK, acute upper GI bleeding accounts for about 60,000 hospital admissions each year and causes the death of about 10% of these patients.<sup>5,10</sup> Lower GI bleeding accounts for a further 15,000 UK 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.

## Causes of gastrointestinal bleeding

The leading causes of upper GI bleeding are peptic ulcer, oesophageal varices and erosive mucosal disease. Peptic ulcer disease and erosions due to *Helicobacter pylori* infection and NSAID use are common causes of GI bleeding worldwide.<sup>4,5,10,15,19–24</sup> Leading causes of lower GI bleeding are diverticular disease, colitis and cancer.<sup>25</sup> Common causes of acute upper GI bleeding in high-income countries are ulcers (40%) and oesophageal varices (11%).<sup>5</sup> Although gastro-oesophageal varices due to liver cirrhosis are an increasingly common cause of bleeding in the West, they are also a major cause of bleeding in parts of South America, Asia, Africa and the Middle East, where there is high prevalence of hepatitis or schistosomiasis.<sup>26–33</sup> 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.<sup>34</sup> Despite advances in the management of upper GI bleeding in the past two decades, mortality remains high. In a nationwide UK study, the case fatality for new presentations to hospital was 7%, rising to > 26% in patients already hospitalised for another condition.<sup>5,35</sup> In addition to cause of bleeding, other factors associated with mortality include older age, signs of shock, severe bleeding, active bleeding, rebleeding and extent of comorbid disease.<sup>4,36–39</sup>

## Rebleeding

Some patients with GI bleeding initially stop bleeding and have a brief period of haemodynamic stability before starting to bleed again. This phenomenon, known as rebleeding, is common and can affect between 5% and 40% of patients with acute GI bleeding. Rebleeding is a strong predictor of mortality in patients with GI bleeding and is associated with a four-fold increased risk of death.<sup>5,6,36,37,40</sup> The risk of rebleeding is highest in the days immediately after the index bleed and declines rapidly with time.<sup>41-43</sup> A study in patients with bleeding peptic ulcers<sup>44</sup> found that more than half of the rebleeds occurred in the 24 hours after initial treatment. Rebleeding rates have not changed significantly over the past 15 years,<sup>5,45,46</sup> and ongoing research should focus on improving this outcome.<sup>45</sup>

## Existing treatment options for gastrointestinal bleeding

Patients with acute severe GI bleeding usually present with haematemesis or melaena. Patients are often haemodynamically unstable and in need of urgent resuscitation. Acute management of GI bleeding includes blood product transfusion, medical or endoscopic therapy and surgery.

For patients with massive acute upper GI bleeding, the National Institute for Health and Care Excellence (NICE) guidelines recommend transfusing patients with blood, platelets and clotting factors in line with local protocols for managing massive bleeding.<sup>47</sup> Patients with severe acute upper GI bleeding are usually referred for endoscopy immediately after resuscitation. For the endoscopic treatment of non-variceal upper GI bleeding, one of the following is recommended: a mechanical method (e.g. clips) with or without adrenaline, thermal coagulation with adrenaline, or fibrin or thrombin with adrenaline.<sup>47</sup> If endoscopy in such patients also reveals stigmata of recent haemorrhage, then proton pump inhibitors are recommended.<sup>47</sup> Interventional radiology is used in unstable patients who rebleed after endoscopic treatment and these patients are urgently referred for surgery if interventional radiology is not immediately available. Terlipressin is recommended for patients with suspected variceal bleeding at presentation. For oesophageal varices, band ligation is often used, and transjugular intrahepatic portosystemic shunts may be considered if the bleeding is not controlled by band ligation.<sup>47</sup> For upper GI bleeding from gastric varices, the NICE guidelines recommend endoscopic injection of *N*-butyl-2-cyanoacrylate and then, if that fails to control the bleeding, transjugular intrahepatic portosystemic shunts.<sup>47</sup>

For patients with lower GI bleeding, the most common intervention is red blood cell (RBC) transfusion.<sup>48</sup> Flexible sigmoidoscopy and colonoscopy can be used to provide endoscopic treatment, although this is not commonly used in the UK.<sup>6</sup> Radiological investigations are used in > 25% of cases.<sup>6</sup> If extravasation of contrast is shown on computed tomography angiography, formal, invasive angiography with the option of mesenteric embolisation can be undertaken, although, in practice, embolisation is used in < 1% of all cases.<sup>49</sup>

## Tranexamic acid and gastrointestinal 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 through the process of clot breakdown, known as fibrinolysis.<sup>50</sup> Fibrinolysis may play an important role in GI bleeding and rebleeding because blood clots at the bleeding site may break down prematurely,<sup>51,52</sup> which may worsen the bleeding. Tranexamic acid (TXA) reduces bleeding by inhibiting fibrinolysis through the inhibition of fibrin degradation by plasmin. It can, therefore, enhance the ability to form stable blood clots.

Tranexamic acid is commonly given to patients either before or during surgery to reduce bleeding and the need for blood transfusion. It has been shown to decrease bleeding and the need for blood transfusion in surgery and to reduce death due to bleeding in patients with traumatic and post-partum haemorrhage.<sup>53-55</sup>

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.

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.<sup>51,52</sup> Fibrinolysis may also increase the risk of rebleeding. 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 rebleeding by stabilising blood clots at the bleeding site. This could reduce mortality and the need for blood transfusion.

## Existing research on tranexamic acid

Tranexamic acid is commonly given to surgical patients to reduce bleeding and the need for blood transfusion. A systematic review of the effect of TXA in surgical patients showed that it reduces the probability of blood transfusion by about one-third [risk ratio (RR) 0.62, 95% confidence interval (CI) 0.58 to 0.65], with no evidence of any increase in risk of thromboembolic events.<sup>53</sup>

Tranexamic acid decreases surgical bleeding and reduces death due to bleeding in patients with traumatic and post-partum haemorrhage.<sup>54-57</sup> The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2)<sup>54</sup> 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. Among patients treated soon after injury, the reduction in mortality with TXA is even greater.<sup>58</sup> The Clinical Randomisation of an Antifibrinolytic in Significant Head Injury 3 (CRASH-3)<sup>57</sup> trial showed that early TXA treatment reduces head injury deaths. Cost-effectiveness analysis reveals that the administration of TXA to bleeding trauma patients is highly cost-effective.<sup>59</sup> Based on these results, TXA was included in guidelines for the pre-hospital care of trauma patients.

A systematic review and meta-analysis<sup>60</sup> of TXA in patients with upper GI bleeding found a significant reduction in all-cause mortality with TXA (RR 0.60, 95% CI 0.42 to 0.87;  $p = 0.007$ ) and a non-significant reduction in rebleeding (RR 0.72, 95% CI 0.50 to 1.03). However, the quality of the included trials was poor and, therefore, this estimate is imprecise. Moreover, the included trials were too small to assess the effect of TXA on thromboembolic events. Therefore, the effectiveness and safety of TXA in GI bleeding remains uncertain.<sup>60</sup>

## Rationale for trial

A meta-analysis<sup>60</sup> of clinical trials on TXA in patients with upper GI bleeding found a significant reduction in all-cause mortality with TXA (RR 0.60, 95% CI 0.42 to 0.87;  $p = 0.007$ ). However, 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. The HALT-IT trial aims to provide reliable evidence about the effects of TXA on death and thromboembolic events in acute GI bleeding.<sup>1</sup> If TXA reduces mortality in patients with GI bleeding, this would be of considerable significance worldwide.



## Chapter 2 Methods

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### Trial design

The HALT-IT trial was a large, international, pragmatic, randomised, double-blind, placebo-controlled trial to quantify the effects of TXA (Cyklokapron® injection, Pfizer, Inc., New York, NY, USA) on mortality and morbidity in adults with significant acute upper or lower GI bleeding.<sup>1</sup> The trial protocol was peer reviewed and published in BioMed Central's *Trials* as an open access article in 2014.<sup>1</sup> [See the trial protocol at the National Institute for Health Research (NIHR) Journals Library web page; [www.journalslibrary.nihr.ac.uk/programmes/hta/110104/#/documentation](http://www.journalslibrary.nihr.ac.uk/programmes/hta/110104/#/documentation); accessed October 2021.]

The HALT-IT trial was the fourth international, multicentre, randomised, placebo-controlled trial in significant haemorrhagic conditions conducted by the London School of Hygiene & Tropical Medicine (LSHTM) Trial Co-ordinating Centre (TCC). CRASH-2<sup>54</sup> examined the effects of early administration of a short course of TXA in trauma patients. The trial recruited 20,211 patients from 274 hospitals in 40 countries. The World Maternal Antifibrinolytic (WOMAN)<sup>55</sup> trial assessed the effects of early administration of TXA on death, hysterectomy and other relevant outcomes in women with post-partum haemorrhage. The WOMAN<sup>55</sup> trial recruited 20,060 women from 193 hospitals in 21 countries. CRASH-3<sup>57</sup> investigated the effects of TXA on death and disability in patients with traumatic brain injury and recruited 12,737 patients from 175 hospitals in 29 countries.

The HALT-IT trial recruited patients from 164 hospitals in 15 countries. Suitable collaborating sites and investigators were assessed on the number of potentially eligible patients and their ability to conduct the trial. In advance of the trial starting at a site, all potential principal investigators had to agree to follow good clinical practice guidelines and all relevant regulations in their country. All relevant regulatory and ethics approvals were in place before the trial started at a site. See *Appendix 1* for a list of the trial collaborators by country.

Various treatments are used for GI bleeding and, as the trial was conducted worldwide, each participating site was instructed to follow its own clinical guidelines for the treatment of patients with GI bleeding. No clinically indicated treatment needed to be withheld for the trial. TXA or placebo was provided as a treatment in addition to the usual management of GI haemorrhage.

### Approvals

The Medical Research and Ethics Committee and Health Research Authority reviewed the HALT-IT trial protocol and supporting documents and gave a favourable opinion on 13 March 2013 (Research Ethics Committee reference 13/EE/0038). The Medicines and Healthcare products Regulatory Agency (MHRA) granted authorisation for the HALT-IT trial on 12 February 2013 (reference 17072/0008/001-0001). A favourable ethics opinion was received from the Observational/Interventions Research Ethics Committee at LSHTM on 19 December 2012 (reference 6328). Protocol amendments and their approval dates are listed in *Amendments to the trial*.

All relevant approvals were also obtained from national and local research ethics committees and national regulatory authorities, where applicable, in all participating non-UK countries.

### Participants (inclusion and exclusion)

All adults with significant acute upper or lower GI bleeding were eligible for the trial. The diagnosis of significant bleeding was clinical, but significant implies a risk of bleeding to death, and patients with significant bleeding may include those with hypotension, tachycardia or signs of shock, as well as those needing urgent transfusion, endoscopy or surgery. Patients were randomised once consent had been obtained in accordance with the approved procedures.

The fundamental eligibility criterion was the responsible clinician's 'uncertainty' as to whether or not to use TXA in a particular patient with GI bleeding. The eligibility criteria were based on the uncertainty principle, which is a well-established approach to trial eligibility.<sup>61</sup> A patient could be enrolled if, and only if, the responsible clinician was substantially uncertain as to which trial treatment would be the most appropriate for that particular patient. A patient was not to be enrolled if the responsible clinician or the patient (or his/her representative) were 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). In other words, patients in whom the responsible clinician considered there to be a clear indication for TXA (e.g. traumatic haemorrhage) or contraindication to TXA (e.g. history of convulsions, thromboembolic disease) were excluded.

The pragmatic design allowed us to find out how effective the treatment actually is in routine practice. Clinicians, patients and their representatives were provided with information about the trial treatment to assist them in their judgement. The TXA summary of product characteristics<sup>62</sup> and an investigator's brochure were provided to investigators to ensure that they had adequate information when considering the risk-benefit ratio and the appropriateness of the trial for each patient.

### Consent

Significant acute GI bleeding is an emergency, and the priority is to provide appropriate emergency care. Eligible patients have a life-threatening condition. Their physical, mental and emotional state may be affected by their blood loss. This may impair their decision-making and affect their ability to give prior informed consent to participate in the trial. Because randomisation and administration of the trial treatment should be undertaken as early as possible once significant GI bleeding is suspected, the consent process in this situation required careful consideration, bearing in mind the applicable regulatory requirements, adherence to the International Council for Harmonisation – Good Clinical Practice<sup>63</sup> and the requirements in the Declaration of Helsinki.<sup>64</sup> As acknowledged in the Declaration of Helsinki, patients who are incapable of giving consent are an exception to the general rule of informed consent in clinical trials.<sup>64</sup>

In the HALT-IT trial, bearing in mind the clinical situation and the patient's level of distress, the patient and, if present, the patient's relative were provided with brief information about the trial (see the brief information sheet in *Appendix 2*). If the patient was fully competent, written consent was sought. If the patient's capacity was impaired and a personal or professional representative was available, consent was sought from the patient's representative. If the patient or their representative objected to the inclusion of the patient in the trial, their views were respected and the patient was not enrolled.



If neither was able to provide informed consent, the need for consent was waived. This process involved the investigator and one independent person who was not participating in the trial enrolling the patient. They were required to confirm that the patient had significant GI bleeding and was unable to give consent because of their condition, that it was not feasible to contact a representative for the patient to obtain consent, and that they were not aware of any objections to the patient participating in the trial. The patient, or their representative, was then informed about the trial and asked for consent for ongoing data collection as soon as possible afterwards. If the patient or their representative declined consent, participation stopped.

The approach that allowed the patient to have the most input into the decision-making process without endangering their life was utilised. If the person giving consent was unable to read or write, the information sheet was read to them and they then marked the consent form with either a cross or a thumbprint. In this event, a witness not associated with the trial was required to provide a full signature confirming the mark.

All requirements of local and national ethics committees were adhered to (see *Appendix 3* for an overview of the consent procedure).

## Randomisation and blinding

Patient eligibility was determined from routinely collected clinical information and recorded on the trial entry form (see *Appendix 4*). No trial-specific tests were required. Sites were advised to randomise eligible patients as soon as possible. Following confirmation of eligibility, patients were randomly allocated to receive TXA or matching placebo (sodium chloride 0.9%) by intravenous injection in the case of the loading dose and by intravenous infusion in the case of the maintenance dose. Block randomisation was used but randomisation was not stratified. Randomisation codes were generated and secured by an independent statistician from Sealed Envelope Ltd (London, UK). The codes were then given to Sharp Clinical Services, UK (Crickhowell, UK), a good manufacturing practice (GMP)-certified clinical trial service provider, to make the treatment packs in accordance with the randomisation list.

After baseline information was collected on the entry form, patients were randomised by taking the next lowest consecutively numbered pack from a box of eight treatment packs. At the point when all of the treatment ampoules were confirmed as being intact, the patient was considered to be randomised to the trial. The trial treatment was then started immediately. Once a patient was randomised, the entry form data were sent to the TCC as soon as possible. This was carried out by trial team members entering the data into a secure online database.

Both participants and study staff (site investigators and TCC staff) were masked to treatment allocation. An emergency unblinding service was available for use in the rare situations when the clinician believed that clinical management depended on the knowledge of whether the patient had received TXA or placebo.

Pfizer Manufacturing (Sandwich, UK) (marketing authorisation number PL 00057/0952) manufactured the TXA (cyclokapron injection) and Torbay and South Devon NHS Foundation Trust [manufacturing authorisation number (investigational medicinal product) 13079] manufactured the sodium chloride 0.9% placebo. The ampoules and packaging were identical in appearance.

Sharp Clinical Services, UK (Crickhowell, UK) [manufacturing authorisation number (investigational medicinal product) 10284], was responsible for masking, manufacturing the study drug treatment packs, which contained either the active drug TXA or placebo and the first-stage qualified person (QP) release. This involved removing the original manufacturer's label and replacing it with the clinical trial label and treatment pack number. Apart from the randomisation number, the pack label text was

identical for TXA and placebo. Sharp Clinical Services, UK, was also responsible for maintaining the product specification file until final database lock and unblinding of the trial data.

The coding of the blinded ampoules was checked by testing random samples of final QP-released drug packs from each batch with high-performance liquid chromatography to determine the contents. The tested samples were unblinded to assure accuracy of blinding.

### Trial intervention

Eligible patients were randomised to TXA or placebo as soon as possible and the treatment was started immediately. Patients received a loading dose of 1 g of TXA or placebo (sodium chloride 0.9%), which was added to a 100-ml infusion bag of 0.9% sodium chloride and infused by slow intravenous injection over 10 minutes. This was followed by a maintenance dose of 3 g of TXA or placebo added to 1 litre of any isotonic intravenous solution and infused at 125 mg/hour for 24 hours. The maintenance dose was started as soon as the loading dose was completed. Where fluid restriction was required, the volume used to administer the maintenance dose could be reduced to 500 ml.

Every patient was assigned a uniquely numbered treatment pack, each of which contained eight ampoules of TXA 500 mg or placebo, one 100-ml bag of 0.9% sodium chloride (to use with the loading dose), two sterile 10-ml syringes and needles, stickers with the trial details and randomisation number (for attaching to infusion bags, forms and the medical records), and instructions. The lowest-numbered treatment pack was taken from a box of eight packs. We separately provided information for patients and representatives, consent forms and data collection forms. The stickers, instructions, leaflets and forms were in local languages.

The TCC was responsible for ensuring that all relevant approvals were available at the TCC before release of the trial treatment to a site. A separate manual of operating procedures detailed the drug accountability system. The investigator's brochure and investigational medicinal product dossier provided detail about the labelling of the trial treatment and other processes for ensuring adherence to GMP.

### Dose selection

Tranexamic acid has been used to reduce bleeding in elective surgery for many years. In randomised trials in cardiac surgery, TXA dose regimens vary widely. Loading doses range from 2.5 to 100 mg/kg and maintenance doses range from 0.25 to 4 mg/kg/hour, which are given over periods of 1–12 hours.<sup>65</sup> 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*.<sup>66</sup> In emergency situations, the administration of a fixed dose is more practicable, given that weighing patients is difficult. In the CRASH-2 trial, a fixed dose of a 1-g loading dose of TXA followed by a 1-g maintenance dose over 8 hours was found to reduce mortality in bleeding trauma patients, with no evidence of significant adverse effects.<sup>54,58</sup> In the HALT-IT trial, a fixed dosage of a 1-g loading dose of TXA followed by 3 g infused over 24 hours was selected. This dosage is within the range that has been shown to inhibit fibrinolysis.<sup>66</sup> It was efficacious for larger patients (> 100 kg) but was also safe for smaller patients (< 50 kg), given that the estimated dose per kilogram that the patients in the latter group would receive has been applied in other trials without significant adverse effects.<sup>65,66</sup> The loading dose (1 g) is the same as was used in the CRASH-2<sup>54</sup> and CRASH-3<sup>57</sup> trials. A maintenance dose is provided but over a longer duration (24 hours) than in the CRASH-2<sup>54</sup> and CRASH-3<sup>57</sup> trials to cover the period when the patient is at greatest risk of rebleeding.

## Sites

We recruited patients with significant acute upper or lower GI bleeding from 164 hospitals in 15 countries. We enrolled the first patient on 4 July 2013 and the last patient on 21 June 2019. We stopped recruiting when the planned sample size was reached. A total of 12,009 patients were enrolled worldwide. See *Appendix 5* for the total number of randomised patients by geographical region.

## Data collection

Data were collected at each site by local investigators and transmitted to the TCC. Only data outlined on the entry, outcome and adverse event forms were collected for this trial.

To allow for variation in available technology for data transfer, a variety of methods were used. Data were collected by the investigator on paper case report forms and transmitted to the TCC by fax or e-mail, or by entering the data directly into the trial database. The data were used in accordance with local laws and ethics committee approval.

### Baseline data

The trial entry form (see *Appendix 4*) was used to collect the following baseline characteristics: age, biological sex, time from onset of GI bleeding symptoms to randomisation, suspected location of bleeding, clinical symptoms (e.g. haematemesis and melaena), suspected variceal bleeding, systolic blood pressure (SBP), heart rate, signs of shock, suspected active bleeding, major comorbidities, anticoagulation therapy and type of admission. Relevant data were recorded on the entry form to assess the patient's eligibility before randomisation and the form was completed if the patient was randomised.

### Outcome data

The trial protocol required the outcome form (see *Appendix 6*) to be completed at death, discharge from the randomising hospital or 28 days after randomisation, whichever occurred first. These data were collected from the patients' routine medical records because no special tests were required. Any adverse events that became known to the investigator were reported up to 28 days after randomisation. Once patients were randomised, outcome data were collected even if the treatment was interrupted or was not actually given. Specific patient-orientated outcomes were assessed.

Initially, the collection of patient-identifiable information, including a patient's name, date of birth, NHS number and postcode, was planned to allow trial staff based at LSHTM to follow up the patients' status at 12 months after randomisation. Follow-up was planned by linking this personal information to Hospital Episode Statistics through the Trusted Data Linkage Service of the NHS Information Centre for England and to the Patient Episode Database for Wales through the Secure Anonymised Information Linkage Databank.

In July 2018, the outcome form was modified to allow the collection of the date or dates on which the patients experienced rebleeding.

## Monitoring

The trial was assessed as low risk, because TXA is widely used; the trial collected adverse event data, which were then reviewed routinely by the independent Data Monitoring Committee (DMC), and all treatment apart from the study drug was given as per usual practice. Therefore, central trial monitoring and central statistical monitoring were used in conjunction with investigators' training and meetings,

and extensive written guidance, to make sure that the trial was carried out properly. Trial investigators and their institutions provided direct access to the source data for trial-related monitoring, audits and regulatory inspections. Monitoring was carried out in accordance with the sponsor's standard operating procedure and the trial protocol. Formal inspections were carried out by the relevant regulatory agencies including the UK MHRA, Irish Health Products Regulatory Authority and Nigeria's National Agency for Food and Drug Administration and Control. The adherence to allocation sequence was monitored throughout the trial and any out-of-sequence pack use was automatically flagged in the trial database and the investigators were retrained.

The progress of the HALT-IT trial, including recruitment, data quality, outcomes and safety data, was reviewed by an independent DMC. Four interim analyses were conducted by the DMC in total.

## Outcome measures

### Primary outcome

The primary outcome was death due to bleeding within 5 days of randomisation. The primary end point was originally death due to bleeding within 28 days of randomisation, but the protocol was changed in March 2019. Cause of death was assigned by local principal investigators, who provided a narrative of the events leading to death. These were reviewed by the chief investigator (blind to treatment allocation) and queried if more information was needed to confirm whether death was due to bleeding or another cause.

### Secondary outcome

Secondary outcomes were death due to bleeding within 24 hours and within 28 days of randomisation, all-cause and cause-specific mortality at 28 days, rebleeding within 24 hours, within 5 days and within 28 days of randomisation, surgery or radiological intervention, blood product transfusion, thromboembolic events (i.e. deep-vein thrombosis, pulmonary embolism, stroke and myocardial infarction), seizures, other complications (including other significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure and liver failure), days in an intensive care unit (ICU), and functional status.

Death due to bleeding within 28 days was changed to a secondary outcome in March 2019. The diagnosis of rebleeding was made by the clinician based on established criteria. A diagnosis of thromboembolic events was made using strict definitions and diagnostic criteria, including a clinical assessment, diagnostic imaging, biomarker tests and post-mortem examination. Seizures were diagnosed by clinical assessment. Functional status was measured with the Katz Index of Independence in Activities of Daily Living either at hospital discharge or in hospital at 28 days.

## Adverse events

Tranexamic acid is not a new drug and has a well-documented safety profile. Although the *Summary of Product Characteristics*<sup>62</sup> 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.

Nevertheless, data on thromboembolic events (e.g. deep-vein thrombosis, pulmonary embolism, myocardial infarction and stroke), seizures, other significant cardiac event, and respiratory, liver and renal failure were collected as secondary outcomes up to day 28 after randomisation and were presented to the independent DMC for unblinded review.

## Amendments to the trial

Various amendments were made to the HALT-IT trial throughout the time that it was being conducted. The main amendments and the rationale for them are summarised below.

### ***Substantial amendment to the protocol from version 1.0 to version 1.1 (UK), August 2014***

The UK protocol was amended to clarify that clinicians in participating hospitals would at all times retain the freedom to act in the patient's best interest, and that each participating site should follow its own clinical practice for the treatment of GI bleeding. Centres in which TXA is in routine use (including those where it is either specifically mandated or recommended for GI bleeding in a massive haemorrhage treatment protocol) were excluded from taking part in the trial. This amendment included monitoring the use of open-label TXA for the treatment of GI bleeding at collaborating sites and the procedure to be followed at sites where this is common.

#### **Rationale**

These changes were made in line with the recommendations of the Research Ethics Committee. The Data Access Advisory Group, Health and Social Care Information Centre also requested an amendment to the information sheet and consent form to allow data on patient status in England and Wales to be shared with us at 1 year.

This amendment was approved by the Multicentre Research Ethics Committee (MREC) on 12 August 2014 and by the MHRA on 21 August 2014.

### ***Non-substantial amendment to the protocol from UK version 1.1 to version 1.2 and international protocol version 1.0 to version 1.1, October 2016***

The protocol was updated to version 1.2 to extend the planned date of last patient enrolment by 1 year, from 30 November 2016 to 30 November 2017.

#### **Rationale**

A delay in the issue of the funding contract had led to recruitment starting late. The recruitment extension was necessary to ensure that the target number of patients were recruited.

### ***Substantial amendment to increase the number of patients from the UK and European Economic Area, February 2017***

A substantial amendment was submitted to increase the UK sample size from 4000 to 5000 patients, and to increase the European Economic Area sample size from 5000 to 6000 patients. The total international sample size remained as 8000 patients. The protocol was not updated as a result of this amendment.

#### **Rationale**

When the original trial application was submitted, there were no reliable data on which to base recruitment in the UK. We, therefore, originally planned for a more conservative number. However, recruitment in the UK was much higher than anticipated.

This amendment was approved by the MREC on 27 February 2017.

### ***Substantial amendment to the protocol from version 1.2 (UK) and version 1.1 (international) to version 2.0, November 2017***

This amendment increased the sample size from 8000 to 12,000 patients and added death from haemorrhage as the main secondary outcome. The recruitment period was also extended by 18 months from 30 November 2017 to 31 May 2019.

## Rationale

Accumulating evidence of the effect of TXA on traumatic bleeding (CRASH-2 trial<sup>54</sup>) and post-partum haemorrhage (the WOMAN trial<sup>55</sup>) showed 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 provided good reason to anticipate that TXA may reduce bleeding deaths (but not other causes of death) in patients with GI haemorrhage. The primary outcome in the HALT-IT trial was 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 showed that a substantial proportion of deaths are not bleeding related (e.g. cancer, pneumonia and liver failure). Given that the effect of TXA was likely to be on death from haemorrhage, with the original sample size of 8000 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 8000 to 12,000 patients and death from haemorrhage was added as the main secondary outcome. The recruitment period was also extended by 18 months. The increase in the sample size meant 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. This amendment was given a favourable opinion by the MREC on 23 October 2017 and was approved by the MHRA on 14 November 2017.

### *Substantial amendment to the protocol from version 2.0 to version 2.1 (UK), May 2018*

An amendment to the UK protocol was made to provide clarification on the definition of 'significant bleeding', stating that 'the diagnosis of significant bleeding is clinical but significant implies a risk of bleeding to death and may include patients with hypotension, tachycardia, signs of shock, or those needing urgent transfusion, endoscopy or surgery'.

## Rationale

This amendment was submitted following the recommendation of MHRA. This amendment was given a favourable opinion by the MREC on 1 May 2018 and was approved by the MHRA on 25 May 2018.

### *Substantial amendment to the outcome form from version 1.0 to version 2.0, September 2018*

This amendment was submitted to retrospectively collect the date when patients experienced rebleeding. The outcome form was modified to allow the collection of the date when any rebleeding took place. Rebleeding was a secondary outcome of the HALT-IT trial, and if patients experienced rebleeds this was captured in the outcome form as a complication. The outcome form was completed 28 days after randomisation, at discharge from the randomising hospital or at death, whichever occurred first.

## Rationale

In addition to reducing the duration and amount of bleeding, early administration of TXA could reduce the risk of rebleeding. However, a patient may experience a rebleed long after having received the trial treatment, and this would be recorded if it occurred up to 28 days post randomisation. In some cases, even if a patient received TXA, this may have little or no biological effect if the rebleed occurred outside the TXA therapeutic window. The amendment was given a favourable opinion by the MREC on 24 August 2018 and was approved by the MHRA on 9 September 2018.

### *Substantial amendment to the protocol from version 2.1 (UK) and version 2.0 (international) to version 3.0, November 2018*

The decision to refine the primary outcome was made by the Trial Steering Committee in November 2018. The primary outcome was changed from death from all causes within 28 days of randomisation to death from haemorrhage within 5 days of randomisation. Death from haemorrhage within 28 days of randomisation, all-cause and cause-specific mortality within 28 days of randomisation and need for endoscopy were added as secondary outcomes. The recruitment period was extended by 4 months from 31 May 2019 to 30 September 2019.

## Rationale

Tranexamic acid is an antifibrinolytic drug that helps to stop bleeding by inhibiting the breakdown of fibrin blood clots. Combined data from large randomised controlled trials (RCTs) using TXA in acute severe haemorrhage have shown that TXA reduces deaths from haemorrhage with no apparent effect on other causes of death. 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 due to 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 that 45% of deaths are due to bleeding and that TXA reduces deaths by 25% but has no effect on other causes of death, the treatment effect on all-cause mortality would be:

$$RR = (0.45 \times 0.75) + (0.55 \times 1.00) = 0.89. \quad (1)$$

The inclusion of non-bleeding causes of death, which are 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 8000 patients was increased to 12,000, if non-bleeding deaths are unaffected by TXA, even with 12,000 patients, the trial would 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. By 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 was substantially increased. In addition, 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 rebleeding, which affects > 50% of those with variceal bleeding and is associated with increased mortality. These rebleeding episodes can occur several days or weeks after the index bleed. Patients receive TXA (or placebo) for their index bleed but not for rebleeding episodes. TXA has a half-life of around 3 hours and, therefore, is unlikely to affect the risk of late death due to bleeding that occurs after it has been excreted. Therefore, 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 have provided adequate power to detect a plausible reduction in death due to bleeding.

This amendment received a favourable opinion from the MREC on 10 April 2019 and MHRA approval on 25 April 2019.

## Sample size

The original sample size estimate assumed a control group all-cause mortality risk of 10%. It was, therefore, originally estimated that a trial with 8000 patients would have > 90% power (two-sided alpha of 5%) to detect a 25% reduction (RR 0.75) in all-cause mortality. The sample size calculation was initially based on all-cause mortality as the primary outcome because we expected that most deaths would be due to bleeding.<sup>1</sup> However, while the trial was under way, we observed that over half of all deaths were due to non-bleeding causes. Accumulating evidence from other large trials of TXA found no apparent effect on non-bleeding deaths.<sup>67</sup> The sample size was, therefore, increased to 12,000 patients to provide adequate power to detect a plausible reduction in death from haemorrhage and all-cause mortality. The trial was then estimated to have > 80% power to detect a 15% (RR 0.85) reduction in all-cause mortality. In 2019, the primary outcome was changed to death due to bleeding within 5 days of randomisation. Based on the amended primary outcome, and assuming a risk of death due to bleeding of 4%, a study with 12,000 patients would have about 85% power (two-sided alpha = 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4% to 3%.

## Statistical methods and analysis plan

The statistical analysis plan was published before unblinding.<sup>2</sup> The plan gave our reasons for amending the primary outcome measure and for increasing the sample size. The main analyses compared those patients allocated to TXA with those allocated to placebo on a modified intention-to-treat basis, excluding patients who received neither dose of the allocated treatment. Effect estimates (RRs) were calculated with a measure of precision (95% CIs). The safety of participants was overseen by an independent DMC, which reviewed four unblinded interim analyses.

### Subgroup analysis

Four subgroup analyses were planned to examine the effects of TXA on the primary outcome stratified by the following baseline characteristics: time to treatment ( $\leq 3$  vs.  $> 3$  hours), site of bleeding (upper vs. lower GI), cause of bleeding (suspected variceal bleeding and/or comorbid liver disease vs. other or unknown causes) and clinical Rockall score. We fitted an interaction term between treatment group and each of the subgroup factors in a Poisson regression model. We used a test for interaction to explore whether or not the treatment effect (if any) varied across the subgroups. Time to treatment was analysed as both a categorical and a continuous variable. Post hoc subgroup analyses were conducted to examine the effects of TXA on the primary outcome stratified by World Bank classification of country income level (high vs. low or middle income), anticoagulant use and SBP.

## Economic evaluation methods

An economic analysis was conducted to evaluate the cost-effectiveness of the current standard of care for people with AGIB with and without the administration of TXA. The evaluated TXA regimen mirrored that used in the HALT-IT trial. The analysis followed the NICE technology appraisal guidelines for conducting economic evaluations.<sup>68</sup> The evaluation used a decision model to combine the clinical results from the HALT-IT trial with evidence from other sources to estimate costs and outcomes over a lifetime horizon for the two treatment options. The analysis adopts a UK NHS cost perspective and expresses health outcomes in terms of life-years (LYs) and quality-adjusted life-years (QALYs). Full details of the methods and results are provided in *Chapter 5*.

## Patient and public involvement

Patient and public involvement (PPI) that was previously conducted by the TCC team was used to inform the HALT-IT trial procedures and to achieve the following objectives:

- to gain lay perspectives on PPI involvement in the design and management of emergency care clinical trials
- to identify an appropriate consent procedure for entering critically ill trauma patients into emergency clinical trials that could be used for the HALT-IT trial
- to ensure that patient-facing documents for the trial were appropriate and clear
- to provide a lay perspective on the management of the trial and interpretation of the results.

We included PPI groups' input into different stages of the trial; this included people who suffered severe haemorrhage. Formative research and research with a PPI group had previously been carried out to guide the PPI activities for our programme of emergency care research. The outcome of much of this PPI engagement was used to inform the HALT-IT trial procedures. This is summarised below.



### ***Formative research method***

A qualitative study was conducted to elicit views on how best to involve patients and the public in the design, conduct and reporting of clinical trials involving people in emergency situations, gathering perspectives on which areas of the research programme they believed that public contribution would be most appropriate. Approaches to designing a consent process to enter patients into emergency clinical trials were also explored.

Specifically for the HALT-IT trial, two focus group discussions were carried out involving a group of older men belonging to a social club and a group of older women who were involved in a continuing education project and crafts-based activities.

The sessions included a PowerPoint® (Microsoft Corporation, Redmond, WA, USA) presentation detailing why clinical trials are conducted in emergency medicine, how they are conducted and the key principles, including issues of consent, randomisation and the use of placebos. This was followed by three exercises using group work and discussion techniques.

Two key areas of inquiry emerged from these discussions: public involvement in the design and management of clinical trials and decisions about entering patients into clinical trials in an emergency.

### ***Formative research outcome: involvement in clinical trial design and management***

Participants were highly supportive of clinical medical research, seeing it as essential for the progress of medical science. They also had a sense that the public should be consulted in principle. However, they struggled to identify how they might usefully contribute to the design and management of clinical trials in practice, seeing this as the province of highly skilled and qualified experts. Although there were individuals who could envisage a role for themselves with appropriate information and preparation, it was important to acknowledge that others felt that they had neither the inclination nor the aptitude to become involved, trusting the expertise and competence of clinical researchers. Participants did have strong opinions in one area, namely that decision-making about the outcomes of clinical research should not be confined to treatment efficacy or safety but must take account of quality-of-life issues, which they considered patients and the public to be well placed to comment on.

### ***Formative research outcome: consent process for involving patients in clinical trials in an emergency***

Initially, a minority opposed entering patients into trials without their consent, but these views tended to be modified as participants considered the comments of others about the incapacitation of patients, the time-critical nature of emergency medicine and the necessity of clinical trials for medical progress.

Overall, among both groups there was a very high regard for the medical profession and a strong faith in the skills and competence of medics, as well as a belief that clinicians would always act in the best interest of the patient. This was reflected in a sense that clinicians should be allowed to exercise their clinical judgement without undue burden to seek consent from next of kin when patients could not consent for themselves. However, moderating this perspective for some was a belief in the principle that, where practicable, next of kin should be consulted; others argued that this might place a heavy burden of responsibility on families and that the clinician's greater expertise may in fact render better decisions.

Interestingly, when the participants were asked what they would want for themselves, all the participants expressed a desire for the clinician (or their own family) to enter them into the trial.

## **Patient and public involvement for the HALT-IT trial**

Drafts of the brief information sheet, full information sheet and consent form were reviewed by PPI representatives.

## METHODS

A PPI representative who had experience of severe gastrointestinal haemorrhage provided a lay perspective on the management of the trial as part of the Trial Steering Committee. They also provided a lay perspective on the trial results and dissemination as part of the Writing Committee for the trial.

### ***Outcome of patient and public involvement***

Patient and public involvement contributed to the success of the trial. The consent process that was developed with PPI groups was used in all countries that took part in the trial, and was accepted by all ethics committees and regulatory agencies, with only local modifications needed.

## Chapter 3 Baseline results

The first patient was enrolled on 4 July 2013 and the last patient was enrolled on 21 June 2019. Recruitment ended when the planned sample size of 12,000 patients had been reached. When the decision to refine the primary outcome was made in November 2018, we had recruited 10,190 patients. This decision was made blind to the accumulating trial data.

A total of 12,009 patients were enrolled and randomly assigned to received either TXA ( $n = 5994$ , 49.9%) or matching placebo ( $n = 6015$ , 50.1%), of whom 11,952 (99.5%) received the first dose of the allocated treatment (Figure 1). A total of 29 patients (11 in the TXA group and 18 in the placebo group) withdrew consent after randomisation, but, of those, 12 (five in the TXA group and seven in the placebo group) agreed to provide outcome data or had outcome data collected as part of adverse event reporting. We obtained primary outcome data for all but three patients in the TXA group. There were 14 protocol violations (seven in the TXA group and seven in the placebo group). Eleven patients did not meet the inclusion criteria [10 received TXA prior to randomisation (six in the TXA group and four in the placebo group) and one patient in the placebo group was aged < 16 years] and there were three consent protocol violations (one in the TXA group and two in the placebo group). A total of 28 patients were unmasked to treatment [17 because the hospital team wanted to administer TXA, six because of adverse events, three because of clinical concerns and two as part of post-mortem investigations (13 in the TXA group and 15 in the placebo group)]. Fifty-two patients received neither dose of the allocated trial treatment (29 patients in the TXA group and 23 patients in the placebo group). A total of 223 patients received antifibrinolytic drugs as part of their clinical care, outside the trial protocol (105 patients in the TXA group and 118 patients in the placebo group). Baseline characteristics were similar in both groups (Table 1).

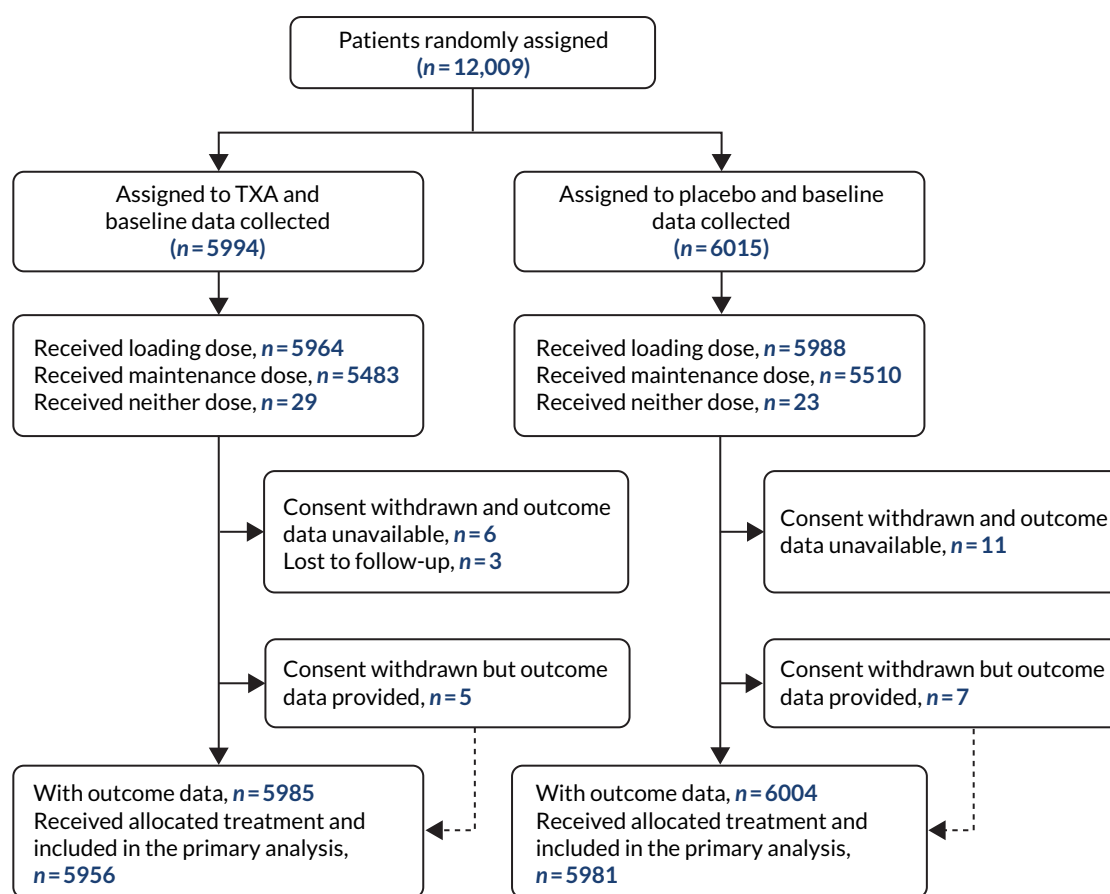


FIGURE 1 Trial profile.

## BASELINE RESULTS

TABLE 1 Baseline characteristics of participants prior to randomisation

Baseline characteristic	Treatment group, n (%)	
	TXA (N = 5994)	Placebo (N = 6015)
Age at randomisation (years)		
Mean (SD)	58.1 (17.0)	58.1 (17.0)
< 40	791 (13)	779 (13)
40–59	2356 (39)	2333 (39)
60–79	2078 (35)	2130 (35)
≥ 80	769 (13)	773 (13)
Sex		
Female	2142 (36)	2124 (35)
Male	3852 (64)	3891 (65)
Time from onset to randomisation (hours)		
Mean (SD)	21.4 (36.4)	22.5 (37.8)
≤ 3	960 (16)	975 (16)
> 3 to ≤ 8	1607 (27)	1551 (26)
> 8	3427 (57)	3488 (58)
Missing	0	1 (< 1)
Suspected location of bleeding		
Lower GI tract	674 (11)	654 (11)
Upper GI tract	5320 (89)	5361 (89)
Haematemesis		
Yes	4285 (72)	4240 (71)
No	1709 (29)	1775 (30)
Melaena or fresh blood per rectum		
Yes	4573 (76)	4626 (77)
No	1421 (24)	1389 (23)
Suspected variceal bleeding		
Yes	2694 (45)	2739 (46)
No	3300 (55)	3276 (54)
Suspected active bleeding		
Yes	5247 (88)	5226 (87)
No	747 (12)	789 (13)
SBP (mmHg)		
≥ 90	5222 (87)	5216 (87)
76–89	577 (10)	577 (10)
≤ 75	181 (3)	201 (3)
Missing	14 (< 1)	21 (< 1)

TABLE 1 Baseline characteristics of participants prior to randomisation (continued)

Baseline characteristic	Treatment group, n (%)	
	TXA (N = 5994)	Placebo (N = 6015)
Heart rate (beats per minute)		
< 77	812 (14)	756 (13)
77–91	1546 (26)	1644 (27)
92–107	1760 (29)	1720 (29)
> 107	1864 (31)	1885 (31)
Missing	12 (< 1)	10 (< 1)
Signs of shock		
Yes	2574 (43)	2648 (44)
No	3420 (57)	3367 (56)
Rockall score		
1–2	1419 (24)	1395 (23)
3–4	2306 (38)	2332 (39)
5–7	2269 (38)	2288 (38)
Taking anticoagulants		
Yes	528 (9)	500 (8)
No	5422 (90)	5466 (91)
Unknown	44 (1)	49 (1)
Emergency admission		
Yes	5673 (95)	5687 (94)
No	321 (5)	328 (6)
Major comorbidities		
Cardiovascular	1108 (18)	1132 (19)
Respiratory	337 (6)	324 (5)
Liver	2432 (41)	2532 (42)
Renal	325 (5)	310 (5)
Malignancy	417 (7)	382 (6)
Other	999 (17)	968 (16)
Any comorbidity	4308 (72)	4329 (72)

SD, standard deviation.



## Chapter 4 Outcome and results

Outcome data were available for 11,989 randomised patients (5985 patients allocated to the TXA group and 6004 patients allocated to the placebo group). A total of 11,952 (99.5%) patients received the loading dose of the allocated treatment and 10,993 (91.5%) received the 24-hour maintenance dose.

### Primary outcome

Figure 2 shows the number of deaths and cause of death by days since randomisation. There were 1121 deaths in total. The median time to death was 55 hours after randomisation (interquartile range 18.2–161.8 hours).

Death due to bleeding within 5 days of randomisation (Table 2) occurred in 222 patients (3.7%) in the TXA group and in 226 patients (3.8%) in the placebo group (RR 0.99, 95% CI 0.82 to 1.18). Similar results were obtained after adjusting for baseline covariates (RR 0.98, 95% CI 0.82 to 1.17) and in a per-protocol

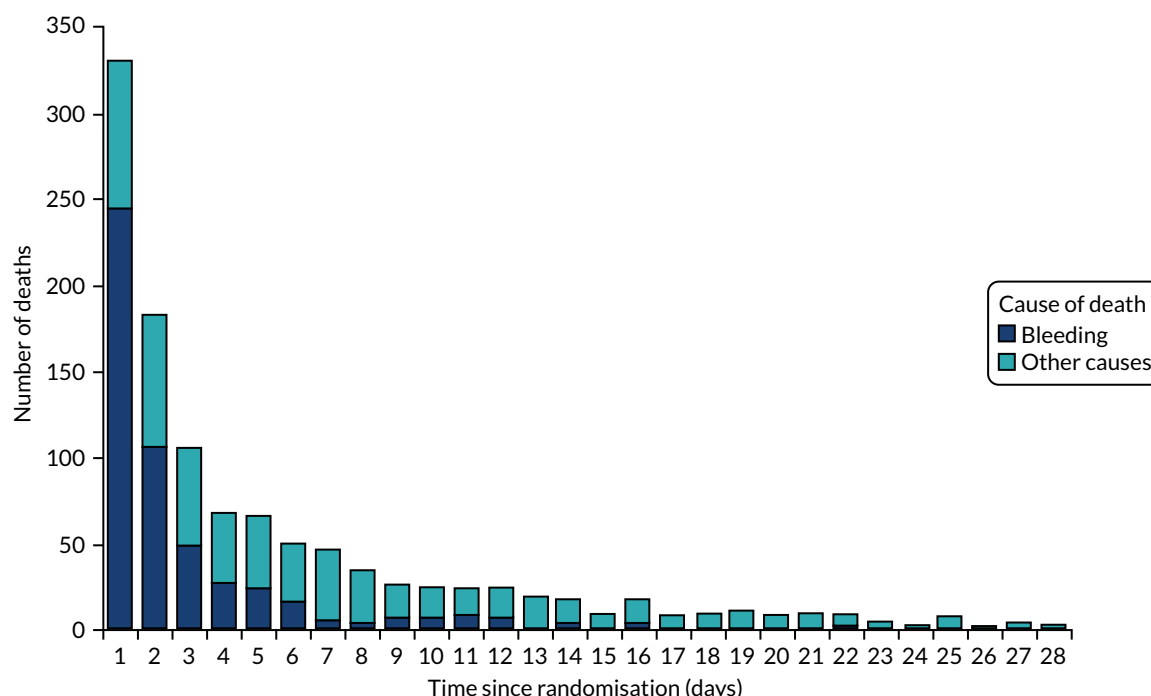


FIGURE 2 Mortality by days from randomisation.

TABLE 2 Effect of TXA on death due to bleeding and rebleeding

	Treatment group, n (%)		RR (95% CI)
	TXA (N = 5956)	Placebo (N = 5981)	
Death due to bleeding within 24 hours	124 (2.1)	120 (2.0)	1.04 (0.81 to 1.33)
Death due to bleeding within 5 days	222 (3.7)	226 (3.8)	0.99 (0.82 to 1.18)
Death due to bleeding within 28 days	253 (4.2)	262 (4.4)	0.97 (0.82 to 1.15)
Rebleeding within 24 hours <sup>a</sup>	41 (0.7)	41 (0.7)	1.00 (0.65 to 1.55)
Rebleeding within 5 days <sup>a</sup>	287 (4.8)	315 (5.3)	0.91 (0.78 to 1.07)
Rebleeding within 28 days <sup>a</sup>	410 (6.8)	448 (7.5)	0.92 (0.81 to 1.05)

<sup>a</sup> Excludes 13 patients missing data on rebleed status or rebleed date. Death or rebleeding in hospital during follow-up.

analysis (RR 0.94, 95% CI 0.71 to 1.23). When the 223 patients who received open-label antifibrinolytics were removed from the analysis, the results were similar (RR 0.97, 95% CI 0.81 to 1.17) (Table 3).

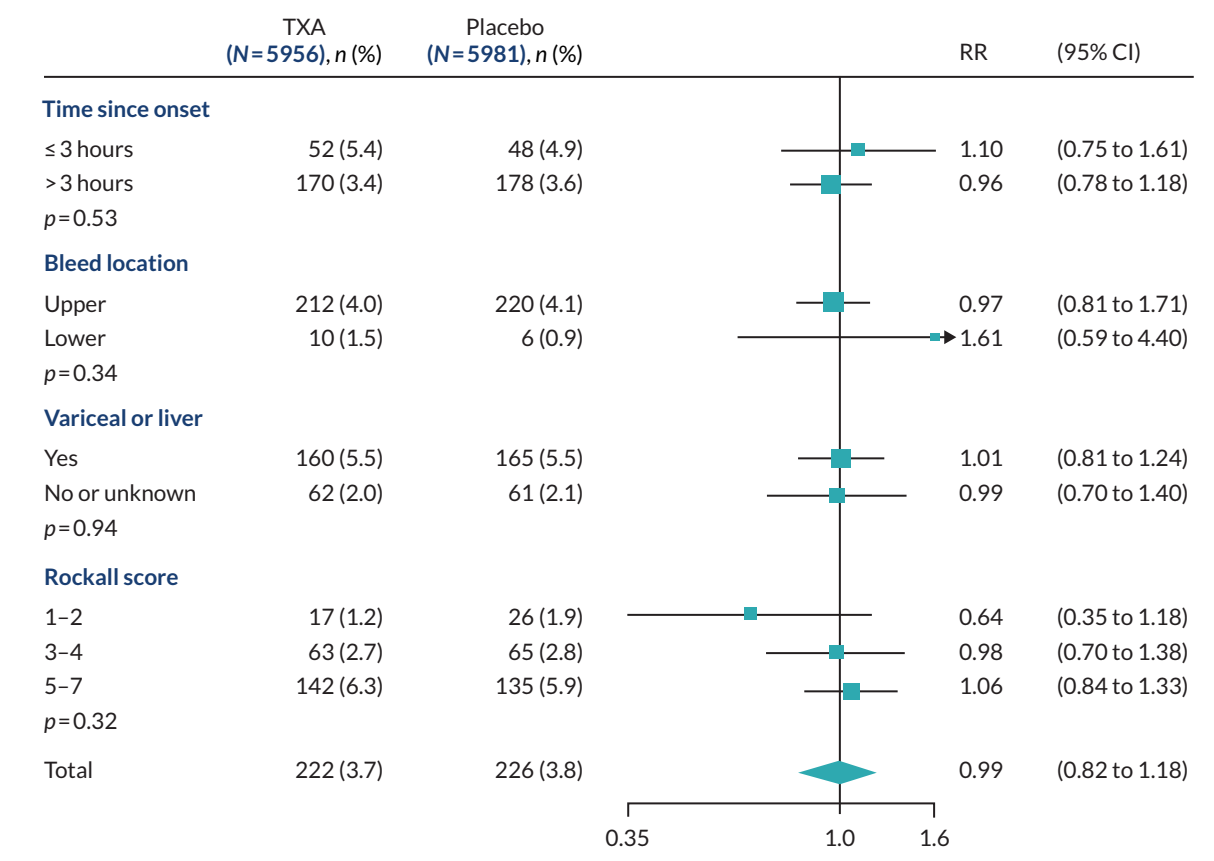
### Subgroup analysis

We examined the effect of TXA on death due to bleeding within 5 days of randomisation in prespecified subgroup analyses stratified by time to treatment (heterogeneity  $p = 0.53$ ), location of bleeding ( $p = 0.34$ ), cause of bleeding ( $p = 0.94$ ) and clinical Rockall score ( $p = 0.32$ ), but recorded no evidence of heterogeneity for these factors (Figure 3). When time since bleeding onset was modelled as a continuous variable, there was no evidence of an interaction (heterogeneity  $p = 0.53$ ).

We examined the effect of TXA on death due to bleeding within 5 days of randomisation, stratified by the World Bank’s classification of country income level (high vs. low or middle income), anticoagulant use and SBP. These exploratory analyses were not prespecified. The RRs did not appear to vary by country income, anticoagulant use or SBP.

**TABLE 3** Patients’ risk of death within 5 days of randomisation to treatment with TXA or placebo, excluding patients who received off-label antifibrinolytics, vasopressin or proton pump inhibitors

	Treatment group, n/N (%)		RR (95% CI)
	TXA	Placebo	
No antifibrinolytics	214/5854 (3.66)	220/5867 (3.75)	0.97 (0.81 to 1.17)
No vasopressin	76/3608 (2.11)	77/3554 (2.17)	0.97 (0.71 to 1.33)
No proton pump inhibitor	23/647 (3.55)	20/588 (3.4)	1.05 (0.58 to 1.88)



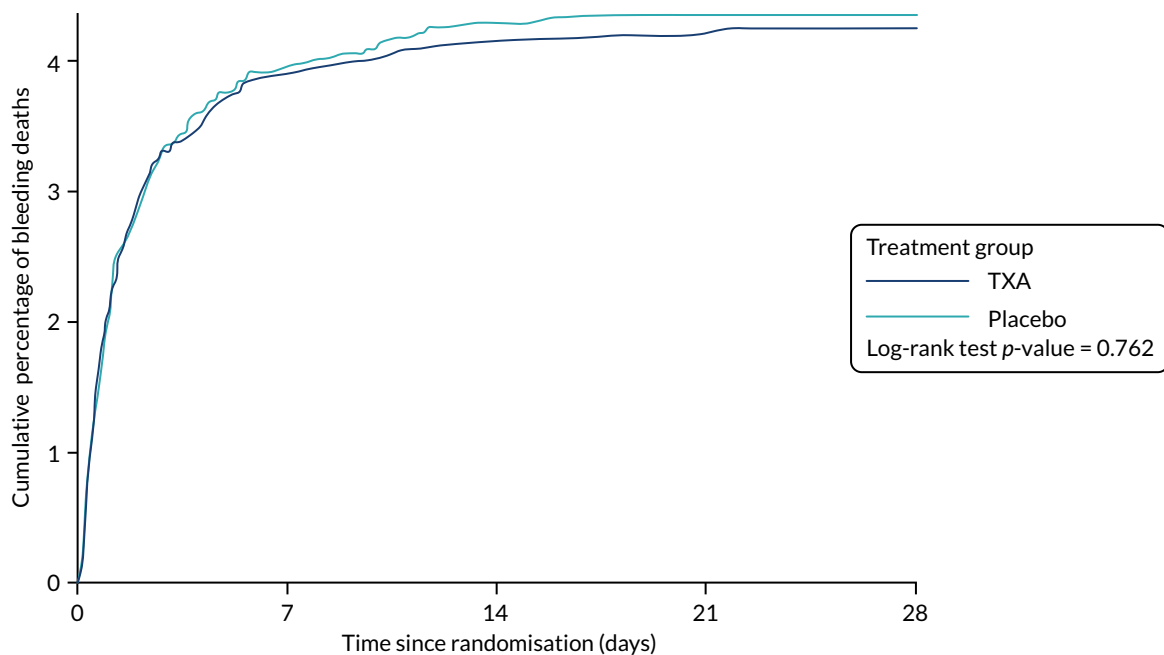
**FIGURE 3** Effect of TXA on death due to bleeding within 5 days. Analysis stratified by time since bleeding onset, suspected bleed location, suspected variceal bleeding or comorbid liver disease, and Rockall score.



## Secondary outcome

Death due to bleeding within 24 hours of randomisation occurred in 124 (2.1%) patients in the TXA group and 120 (2.0%) patients in the placebo group. Death due to bleeding within 28 days of randomisation occurred in 253 (4.2%) patients in the TXA group and 262 (4.4%) patients in the placebo group (RR 1.04, 95% CI 0.81 to 1.33) (Figure 4). Death due to bleeding within 28 days of randomisation occurred in 253 (4.2%) patients in the TXA group and 262 (4.4%) patients in the placebo group (0.97, 95% CI 0.82 to 1.15). Death from all causes within 28 days of randomisation (Table 4) occurred in 564 patients (9.5%) in the TXA group and in 548 patients (9.2%) in the placebo group (RR 1.03, 95% CI 0.92 to 1.16).

The proportion of patients with rebleeding was similar in both groups at 24 hours, 5 days and 28 days after randomisation (see Table 2). The proportion of patients who had surgery, radiological intervention and blood product transfusion was also similar in both groups (Table 5).



Number at risk					
TXA	5956	5723	5708	5705	5703
Placebo	5981	5744	5724	5720	5720

FIGURE 4 Cumulative incidence plot of death due to bleeding. Hazard ratio 0.97, 95% CI 0.82 to 1.16.

TABLE 4 Effect of TXA on all-cause mortality

Cause of death	Treatment group, n (%)		RR (95% CI)
	TXA (N = 5956)	Placebo (N = 5981)	
Bleeding	253 (4.2)	262 (4.4)	0.97 (0.82 to 1.15)
Thromboembolic event	26 (0.4)	17 (0.3)	1.54 (0.83 to 2.83)
Organ failure	109 (1.8)	114 (1.9)	0.96 (0.74 to 1.25)
Pneumonia	57 (1.0)	42 (0.7)	1.36 (0.92 to 2.03)
Sepsis	33 (0.6)	49 (0.8)	0.68 (0.44 to 1.05)
Malignancy	65 (1.1)	40 (0.7)	1.63 (1.10 to 2.42)
Other	21 (0.4)	24 (0.4)	0.88 (0.49 to 1.58)
All cause	564 (9.5)	548 (9.2)	1.03 (0.92 to 1.16)

Death in hospital during follow-up.

TABLE 5 Effect of TXA on the need for surgical, endoscopic and radiological interventions or blood product transfusion

	Treatment group		Effect size (95% CI)
	TXA	Placebo	
Interventions, n/N (%)			
Diagnostic endoscopy	4781/5953 (80.3)	4729/5978 (79.1)	1.02 (1.00 to 1.03) <sup>a</sup>
Therapeutic endoscopy	2542/5952 (42.7)	2658/5978 (44.5)	0.96 (0.92 to 1.00) <sup>a</sup>
Diagnostic radiological procedure	1704/5953 (28.6)	1744/5978 (29.2)	0.98 (0.93 to 1.04) <sup>a</sup>
Therapeutic radiological procedure	74/5953 (1.2)	89/5978 (1.5)	0.83 (0.61 to 1.13) <sup>a</sup>
Surgical intervention	146/5953 (2.5)	158/5978 (2.6)	0.93 (0.74 to 1.16) <sup>a</sup>
Any surgical, endoscopic or radiological intervention	5216/5956 (87.6)	5236/5981 (87.5)	1.00 (0.99 to 1.01) <sup>a</sup>
Any transfusion	4076/5951 (68.5)	4129/5978 (69.1)	0.99 (0.97 to 1.02) <sup>a</sup>
Whole blood or red cells	3984/4076 (97.7)	4018/4129 (97.3)	1.00 (1.00 to 1.01) <sup>a</sup>
Frozen plasma	910/4076 (22.3)	993/4129 (24.0)	0.93 (0.86 to 1.00) <sup>a</sup>
Any platelets	219/4076 (5.4)	255/4129 (6.2)	0.87 (0.73 to 1.04) <sup>a</sup>
Blood product transfusions, mean (SD)			
Units of whole blood or red cells	2.8 (2.4)	2.9 (2.7)	-0.06 (0.05 to -0.18) <sup>b</sup>
Units of frozen plasma	0.9 (2.4)	1.0 (2.6)	-0.05 (-0.01 to -0.23) <sup>b</sup>
Units of any platelets	0.2 (0.9)	0.2 (1.0)	-0.02 (0.02 to -0.06) <sup>b</sup>

a Data are in the form RR (95% CI).

b Data are in the form difference in means (95% CI).

The mean number of days spent in intensive care was similar in both groups (*Table 6*). The mean score on the Katz Index of Independence in Activities of Daily Living was also similar in both groups (see *Table 6*).

## Adverse events

The risk of fatal or non-fatal thromboembolic events and arterial thromboembolic events (myocardial infarction or stroke) was similar in the TXA group and the placebo group (see *Table 6*). The risk of venous thromboembolic events (deep-vein thrombosis or pulmonary embolus) was higher in the TXA group than in the placebo group (see *Table 6*), and similar risk was observed after excluding patients who did not receive the maintenance dose (42 events with TXA compared with 20 events with placebo) (RR 2.11, 95% CI 1.24 to 3.59). In an exploratory subgroup analysis, the risk of venous thromboembolic events was higher in patients with suspected variceal bleeding or liver disease (14 vs. 2 events; RR 7.26, 95% CI 1.65 to 31.90) than in patients with other causes of bleeding (34 vs. 24 events; RR 1.38, 95% CI 0.82 to 2.32;  $p = 0.035$  for heterogeneity). The risk of renal, hepatic and respiratory failure, cardiac events, sepsis and pneumonia was similar in TXA- and placebo-treated patients (see *Table 6*). Seizures occurred in 38 patients in the TXA group and in 22 patients in the placebo group (0.6% vs. 0.4%; RR 1.73, 95% CI 1.03 to 2.93) (see *Table 6*); after excluding patients who did not receive the maintenance dose the corresponding numbers were 33, compared with 17 events (RR 1.95, 95% CI 1.09 to 3.50). See *Appendix 7* for a list of all adverse events.

Analyses that are specified in the statistical analysis plan, but not reported above, will be reported in separate publications.

TABLE 6 Complications and self-care capacity in study groups

	Treatment group		Effect size (95% CI)
	TXA	Placebo	
Complications, n/N (%)			
Any thromboembolic event	86/5952 (1.4)	72/5977 (1.2)	1.20 (0.88 to 1.64) <sup>a</sup>
Venous events (deep-vein thrombosis, pulmonary embolism)	48/5952 (0.8)	26/5977 (0.4)	1.85 (1.15 to 2.98) <sup>a</sup>
Deep-vein thrombosis	23/5952 (0.4)	12/5977 (0.2)	1.92 (0.96 to 3.86) <sup>a</sup>
Pulmonary embolism	28/5952 (0.5)	16/5977 (0.3)	1.76 (0.95 to 3.24) <sup>a</sup>
Arterial events (myocardial infarction, stroke)	42/5952 (0.7)	46/5977 (0.8)	0.92 (0.60 to 1.39) <sup>a</sup>
Myocardial infarction	24/5952 (0.4)	28/5977 (0.5)	0.86 (0.50 to 1.48) <sup>a</sup>
Stroke	19/5952 (0.3)	18/5977 (0.3)	1.06 (0.56 to 2.02) <sup>a</sup>
Renal failure	142/5951 (2.4)	157/5978 (2.6)	0.91 (0.73 to 1.14) <sup>a</sup>
Liver failure	196/5952 (3.3)	184/5977 (3.1)	1.07 (0.88 to 1.30) <sup>a</sup>
Respiratory failure	105/5952 (1.8)	131/5978 (2.2)	0.81 (0.62 to 1.04) <sup>a</sup>
Cardiac event	100/5952 (1.7)	89/5977 (1.5)	1.13 (0.85 to 1.50) <sup>a</sup>
Sepsis	210/5952 (3.5)	216/5977 (3.6)	0.98 (0.81 to 1.18) <sup>a</sup>
Pneumonia	193/5952 (3.2)	174/5978 (2.9)	1.11 (0.91 to 1.36) <sup>a</sup>
Seizure	38/5952 (0.6)	22/5977 (0.4)	1.73 (1.03 to 2.93) <sup>a</sup>
Self-care capacity, mean (SD)			
Days in ICU	0.4 (1.8)	0.4 (2.0)	-0.06 (0.01 to -0.13) <sup>b</sup>
Katz score	5.5 (1.5)	5.5 (1.4)	-0.03 (0.02 to -0.09) <sup>b</sup>

a Data are in the form RR (95% CI).

b Data are in the form difference in means (95% CI).

**Note**

Thromboembolic events and complications are not mutually exclusive.



## Chapter 5 Economic evaluation results

The HALT-IT trial did not demonstrate that TXA significantly reduces key outcome measures, such as death due to bleeding within 5 days of randomisation (RR 0.99, 95% CI 0.82 to 1.18) or all-cause mortality (RR 1.03, 95% CI 0.92 to 1.16), when administered to people with AGIB. This means by default that, even if it is relatively inexpensive, TXA is unlikely to represent value for money in this indication. However, we have proceeded with the economic evaluation on the basis that it is important to assess the level of uncertainty around the cost-effectiveness of TXA based on the data available.

### Methods

#### Decision problem

The analysis evaluates the cost-effectiveness of the current standard of care for people with AGIB with and without the administration of TXA. The evaluated TXA regimen mirrors that used in the HALT-IT trial, specifically a TXA loading dose (1 g) added to a 100-ml infusion bag of 0.9% sodium chloride, infused by slow intravenous injection over 10 minutes, and a TXA maintenance dose (3 g) added to 1 litre of an isotonic intravenous solution, infused over 24 hours.

We followed the NICE technology appraisal guidelines for conducting economic evaluations.<sup>68</sup> The evaluation uses a decision model to combine the clinical results from the HALT-IT trial with evidence from other sources to estimate costs and outcomes over a lifetime horizon for the two treatment options. The analysis adopts a UK NHS cost perspective and expresses health outcomes in terms of LYs and QALYs. Costs are reported in 2017/18 Great British pounds. All future costs and QALYs have been discounted at an annual rate of 3.5%.

#### Decision model

We have based our analysis on an existing Markov model of TXA following AGIB to estimate its cost-effectiveness in the AGIB setting.<sup>69</sup> The model consists of two health states, alive and dead, as shown in Figure 5. People with AGIB enter the model in the alive health state. People in the no-TXA group progress to the dead health state over the initial 28-day period (the HALT-IT trial period) using daily data taken directly from the trial on all-cause deaths from the placebo group of the HALT-IT trial; this includes data for all UK and non-UK participants. For the remaining 337 days of the first year, the daily probability of death in the no-TXA group was estimated using UK general population age-related mortality statistics,<sup>70</sup> adjusted using a standardised mortality ratio (SMR) to reflect the long-term risk of excess death associated with surviving an AGIB episode.<sup>71</sup> In the base case, this SMR is applied for the entire time horizon. After this initial 1-year period, the model cycles yearly, applying the same probability function of death adjusted for the yearly rather than the daily cycle period. In line with the HALT-IT trial, the mean age of people entering the model was assumed to be 58.1 years.

The SMR associated with the risk of death following an AGIB episode compared with that of the general population was derived from a study by Crooks *et al.*,<sup>71</sup> in which longitudinal data from the UK's Hospital Episodes Statistics data set, the General Practice Research Database and the Office for National Statistics death register between 1997 and 2010 were linked to define a cohort of people with non-variceal bleeds. Controls were matched at the start of the study by age, sex, practice and year.



FIGURE 5 Markov model structure showing both health states in the model.

Given that the study showed that the risk of death was highest in the first year following an AGIB episode, separate SMRs were derived for year 1 (SMR 5.21, 95% CI 4.25 to 6.38) and year 2 onwards (SMR 1.74, 95% CI 1.42 to 2.13). In the deterministic sensitivity analysis, excess mortality was excluded after 1 year.

### **Treatment effect**

The base-case cycle probabilities of death in the TXA group were calculated in exactly the same manner as in the placebo group, but a relative treatment effect was also applied using a RR of all-cause death of 1.03 (95% CI 0.92 to 1.16); this RR is based on all trial participants and is not UK specific given that the subgroup analysis did not reveal any differences in treatment effect by country income level. Note that the HALT-IT trial results for the primary outcome measure, death due to bleeding within 5 days from randomisation, were similar in both treatment groups (RR 0.99, 95% CI 0.82 to 1.18), although the mean estimate slightly favoured TXA. However, given that the risks of venous thromboembolic events (deep-vein thrombosis or pulmonary embolus) and death from malignancy (RR 1.63, 95% CI 1.10 to 2.42) were higher in the TXA group than in the placebo group (RR 1.85, 95% CI 1.15 to 2.98), the RR of all-cause mortality was used as the estimate of effect, as it reflects the overall observed relative impact of TXA treatment on survival.

### **Utilities**

Utility data were not collected as part of the HALT-IT trial; therefore, values were sourced from the existing literature. Only one directly relevant study could be identified: the relatively recent TRIGGER (Transfusion in Gastrointestinal Bleeding) RCT.<sup>72</sup> This trial evaluated the feasibility and safety of a restrictive compared with liberal RBC transfusion policy for adults admitted to UK hospitals with AGIB. Between August 2012 and March 2013, almost 950 people were randomised. Similar to the HALT-IT trial, the trial time horizon was 28 days. Of note, the EuroQol-5 Dimensions, three-level version, questionnaire<sup>73</sup> was administered in the study, and the utility values have been reported in a separate publication.<sup>74</sup>

We have taken a relatively simple approach to applying the utility values within the model base case, although this approach mirrors that used in a previous economic evaluation of TXA.<sup>69</sup> Specifically, individuals who died within the first 28 days were all assigned a utility of 0 over the entirety of this 28-day period. Campbell *et al.*<sup>74</sup> report a mean utility value of 0.735 (95% CI 0.70 to 0.77) for AGIB survivors on day 28 in the TRIGGER trial. In the base-case analysis, this value was applied to all participants in both treatment groups, who were alive at day 28, both during the initial 28-day period and at all times thereafter until death. Note that functional status was measured in the HALT-IT trial using the Katz Index of Independence in Activities of Daily Living<sup>75</sup> either at hospital discharge or in hospital at day 28; the scores in both groups were similar. An age adjustment was also applied to the utility value in each cycle using the decrements reported by Kind *et al.*,<sup>76</sup> so that overall utility declined with age. In a sensitivity analysis, the utility value of 0.735 after 1 year was replaced with age-adjusted population values, also reported by Kind *et al.*,<sup>76</sup> whereby the utility values after the first year increased in line with the utility values of the UK's general population. The latter approach mimics survivors of AGIB returning to 'full health' after 1 year; however, given the high prevalence of comorbidities in this population, which are themselves risk factors for an AGIB episode, it is unclear whether or not this is a realistic scenario.

### **Costs**

#### **Tranexamic acid treatment**

The resources associated with providing TXA treatment were derived from the HALT-IT trial and by making a number of assumptions. The total TXA dose (4 g) included the loading and maintenance dose, for which the total cost was derived from the *British National Formulary*<sup>77</sup> (£12 per patient). The cost of the equipment for treatment was assumed to include a needle (£0.04), syringe (£0.06), sodium chloride infusion bag (£0.55) and isotonic intravenous solution (£3.77). To account for the administration time

of TXA, hourly staff costs were calculated from the Personal Social Services Research Unit costs for 2018.<sup>78</sup> The model assumed that a band 5 nurse would take 21 minutes to administer TXA (£12.95), following the treatment administration and expert guidance used within the economic evaluations of the CRASH<sup>59,69</sup> and WOMAN trials.<sup>79</sup> This led to a total TXA treatment and administration cost of £29.37 per person (Table 7).

### Inpatient stay costs during the initial 28 days

Information from the HALT-IT trial was used to derive the costs of inpatient stays during this period. The total mean length of stay recorded by people receiving TXA was 5.83 days, and by those receiving placebo it was 5.80 days (Table 8). In both treatment groups, 0.4 of these days were spent in the ICU. These lengths of stay were multiplied by NHS reference costs for 2017/18<sup>80</sup> for non-elective stays to derive mean hospital costs of £2292 per person for TXA and £2284 per person for no TXA.

### Procedures

While in hospital during the 28-day trial period, participants underwent a number of procedures, including endoscopies, surgery and radiological interventions (see Table 8). The cost of these procedures by treatment group was calculated using information from the HALT-IT trial, multiplying the probability that of each procedure being required by the NHS reference cost for 2017/18.<sup>80</sup> The mean per-person procedural cost was £2216 in the TXA group and £2260 in the placebo group.

### Transfusions

While in hospital during the initial 28 days, some participants received transfusions of blood/RBCs, fresh-frozen plasma and platelets (see Table 8). Information from the HALT-IT trial on the frequency and the mean number of units for each transfusion type were combined with unit costs from the *NHS Blood and Transplant Price List*<sup>81</sup> to generate overall costs. The mean per-person transfusion cost was £234 in the TXA group and £245 in the placebo group.

TABLE 7 Base-case model input parameters and their source

Parameter	Value	95% CIs	Distribution	Source
Age at model start (years)	58.1	-	-	HALT-IT
SMR year 1	5.21	4.25 to 6.38	Log-normal	Crooks <i>et al.</i> <sup>71</sup>
SMR year 2	1.74	1.42 to 2.13	Log-normal	Crooks <i>et al.</i> <sup>71</sup>
RR of all-cause mortality	1.03	0.92 to 1.16	Log-normal	HALT-IT
28-day probability of death <sup>a</sup>	0.092	0.084 to 0.099	Beta	HALT-IT
Utility AGIB survivor	0.735	0.70 to 0.77	Beta	Campbell <i>et al.</i> <sup>74</sup>
Utility decrements by age (years)				Kind <i>et al.</i> <sup>76</sup>
55–64	0	-	-	
65–74	0.02	-	-	
≥ 75	0.07	-	-	
Utility UK general population	By age	-	-	Kind <i>et al.</i> <sup>76</sup>
All-cause mortality	By age	-	-	ONS <sup>70</sup>
Discount rate costs	3.5%	-	-	NICE <sup>68</sup>
Discount rate QALYs	3.5%	-	-	NICE <sup>68</sup>

ONS, Office for National Statistics.

a The 28-day risk of death in the placebo group was sampled from a beta-distribution during the probabilistic sensitivity analysis, based on the proportion of deaths during the trial period (548/5981). The deaths occurring on each day, as a proportion of the overall 28-day risk, remained the same during sampling.

TABLE 8 Base-case cost parameters and their source

Parameter	Value	Standard error or proportion	Distribution	Source
TXA administration	£29.37	-	-	<i>British National Formulary</i> , <sup>77</sup> assumptions
<b>Inpatient stays to day 28</b>				
<i>Total length of stay (days)</i>				
TXA	5.83	1.46	Gamma	HALT-IT
No TXA	5.80	1.47	Gamma	HALT-IT
<i>Days in ICU</i>				
TXA	0.4	0.46	Gamma	HALT-IT
No TXA	0.4	0.51	Gamma	HALT-IT
Unit cost per day in non-ICU	£313	-	-	NHS reference costs <sup>80</sup>
Unit cost per day in ICU	£1479	-	-	NHS reference costs <sup>80</sup>
<b>Procedures to day 28</b>				
<i>Probability endoscopy: diagnostic</i>				
TXA	0.8	4781/5953	Beta	HALT-IT
No TXA	0.79	4729/5978	Beta	HALT-IT
Unit cost	£617	-	-	NHS reference costs <sup>80</sup>
<i>Probability endoscopy therapeutic</i>				
TXA	0.43	2542/5953	Beta	HALT-IT
No TXA	0.44	2658/5978	Beta	HALT-IT
Unit cost	£721	-	-	NHS reference costs <sup>80</sup>
<i>Probability surgical intervention</i>				
TXA	0.02	146/5953	Beta	HALT-IT
No TXA	0.03	158/5978	Beta	HALT-IT
Unit cost	£1065	-	-	NHS reference costs <sup>80</sup>
<i>Probability radiological diagnostic</i>				
TXA	0.29	1704/5953	Beta	HALT-IT
No TXA	0.29	1744/5978	Beta	HALT-IT
Unit cost	£4625	-	-	NHS reference costs <sup>80</sup>
<i>Probability radiological therapeutic</i>				
TXA	0.01	74/5953	Beta	HALT-IT
No TXA	0.01	89/5978	Beta	HALT-IT
Unit cost	£4625	-	-	NHS reference costs <sup>80</sup>
<b>Transfusions</b>				
<i>Probability blood or red cells</i>				
TXA	0.67	3984/5951	Beta	HALT-IT
No TXA	0.67	4018/5978	Beta	HALT-IT
<i>Mean units of blood or red cells</i>				
TXA	2.80	0.61	Gamma	HALT-IT
No TXA	2.90	0.69	Gamma	HALT-IT
Unit cost	£122	-	-	<i>NHS Blood and Transplant Price List</i> <sup>81</sup>



TABLE 8 Base-case cost parameters and their source (continued)

Parameter	Value	Standard error or proportion	Distribution	Source
<i>Probability fresh-frozen plasma</i>				
TXA	0.15	910/5951	Beta	HALT-IT
No TXA	0.16	993/5978	Beta	HALT-IT
<i>Mean units of fresh-frozen plasma</i>				
TXA	0.90	0.61	Gamma	HALT-IT
No TXA	1.0	0.66	Gamma	HALT-IT
Unit cost	£28	-	-	NHS Blood and Transplant Price List <sup>81</sup>
<i>Probability platelets</i>				
TXA	0.04	219/5951	Beta	HALT-IT
No TXA	0.04	255/5978	Beta	HALT-IT
<i>Mean units of platelets</i>				
TXA	0.20	0.23	Gamma	HALT-IT
No TXA	0.20	0.26	Gamma	HALT-IT
Unit cost	£178	-	-	NHS Blood and Transplant Price List <sup>81</sup>
<i>Post-discharge costs</i>				
Year 1	£3989	£1995 <sup>a</sup>	Gamma	Ramagopalan <i>et al.</i> <sup>82</sup>
Year 2	£1816	£908 <sup>a</sup>	Gamma	Ramagopalan <i>et al.</i> <sup>82</sup>
Year 3	£1777	£889 <sup>a</sup>	Gamma	Ramagopalan <i>et al.</i> <sup>82</sup>

a Standard errors were assumed to be 50% of the mean value in the base-case analysis.

### Post-discharge costs

The HALT-IT and TRIGGER trials observed participants for a maximum of 28 days; therefore, longer-term care costs were sourced from the literature. A specific study related to AGIB could not be identified. However, a recent UK study by Ramagopalan *et al.*<sup>82</sup> estimated the costs of GI bleeding among people with non-valvular atrial fibrillation by comparing the costs in people who were and those who were not experiencing a bleed, and used a difference-in-difference approach to calculate the costs attributable to a GI bleed (cases,  $n = 7753$ ; controls,  $n = 7753$ ). The controls were matched to cases on a 1 : 1 basis using a propensity scoring approach and nearest neighbour matching with replacement. Information on resource use was derived from the Clinical Practice Research Data link and Hospital Episode Statistics, and included information on primary care, procedures, prescriptions, inpatient stays and outpatient visits. A matching study used a variety of sources to estimate unit costs in this study, including the 2017/18 NHS reference costs.<sup>80</sup>

The study allows the annual costs of caring for people with a bleed to be calculated for 3 years after the date of the bleeding event (see Table 8). In the absence of other information, the reported year 3 costs were inputted to the model for year 4 onwards, although they were assumed to be one-third of the original amount. The standard errors that the costing study reports could not be easily incorporated into our analysis (the statistical approach used allowed costs to be negative) and, therefore, were assumed to be 50% of the mean value in all instances, which is considered to reflect a relatively large degree of uncertainty in the mean estimates. The importance of these assumptions was assessed in the sensitivity analysis.

### Subgroup analysis

The HALT-IT trial protocol<sup>2</sup> specifies subgroup analyses to examine the effects of TXA on death due to bleeding within 5 days of randomisation based on time to treatment ( $\leq 3$  vs.  $> 3$  hours), site of bleeding (upper vs. lower GI), cause of bleeding (suspected variceal bleeding or comorbid liver disease vs. other or unknown causes) and clinical Rockall score. Post hoc subgroup analyses stratified by World Bank classification of country income level (high vs. low or middle income), anticoagulant use and SBP were also undertaken. However, no evidence of heterogeneity was recorded. For this reason, we do not report any cost-effectiveness results for different AGIB subgroups.

### Sensitivity analysis

Various one-way deterministic sensitivity analyses were undertaken to assess the robustness of the results to alternative assumptions. A probabilistic sensitivity analysis (PSA) was also undertaken using 10,000 Monte Carlo simulations; the parameter distributions are specified in *Tables 7 and 8*. Risk ratios were specified as log-normal distributions, utilities and other proportions as beta-distributions and costs as gamma-distributions. Parameters that were excluded from the PSA are not assigned a distribution type in the tables.

We report the results as incremental cost-effectiveness ratios (ICERs), incremental net monetary benefits (INMBs), cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). A threshold of willingness to pay for an additional QALY of £20,000–30,000 was used to determine cost-effectiveness, in line with the NICE technology appraisal recommendations.<sup>68</sup>

## Results

The base-case results are shown in *Table 9*. In both the deterministic and the probabilistic analyses TXA was associated with marginally smaller gains in LYs and QALYs, and lower costs, than treatment without TXA. For example, the deterministic QALYs and costs associated with TXA and no TXA were 8.58 and 8.61, and £16,706 and £16,764, respectively. The associated ICERs are £1413 per LY gained and £1981 per QALY gained if no TXA is used instead of TXA (i.e. at NICE-recommended threshold willingness-to-pay values, no TXA is the preferred option). The deterministic and mean probabilistic results are almost identical (see *Table 9*).

The lower mean health outcomes for TXA are driven by the fact that the mean RR for all-cause mortality (i.e. the relative treatment effect inputted to the model) slightly favours the no-TXA treatment group (RR 1.03). The higher incremental costs associated with no TXA are largely driven by the fact that people who did not receive TXA live for marginally longer than those who received TXA; thus, patients who are not treated with TXA incur slightly higher post-discharge costs and marginally higher intervention and transfusion costs than those who are treated with TXA, and these costs more than outweigh the additional cost of TXA administration.

TABLE 9 Base-case probabilistic results

Analysis	Costs (£)	LYs	QALYs	ICER LYs (£)	ICER QALYs (£)
<b>Deterministic</b>					
No TXA	16,764	12.08	8.61	1413	1981
TXA	16,706	12.04	8.58	–	–
<b>Probabilistic (PSA)</b>					
No TXA	16,895	12.21	8.70	1419	1988
TXA	16,840	12.17	8.67	–	–

Various deterministic one-way sensitivity analyses are shown *Table 10*. In all but one instance the results show that the base-case ICER was very robust to alternative model parameter and structural assumptions. The exception is when the RR of all-cause mortality is reduced to 0.92 (the lower bound of the 95% CI). In this instance, TXA produces marginally better health outcomes at slightly higher costs than no TXA, producing an ICER of £1144 per QALY gained if TXA is used instead of no TXA. Note that, even when the cost of TXA and its administration was set to £0 instead of the base-case value of £29.37, the ICER per QALY gained remained under £3000, favouring no TXA.

The base-case cost-effectiveness plane and CEAC for the probabilistic costs and QALYs are shown in *Figures 6 and 7*, respectively. The cost-effectiveness plane shows that the simulations are clustered around the origin and distributed relatively evenly across all four cost-effectiveness quadrants. This is because the point estimate for the RR of all-cause mortality is only slightly above 1, and is included within its CI (RR 1.03, 95% CI 0.92 to 1.16); therefore, there is little to choose between the two treatment options in terms of outcomes. The same is also true of the relatively low cost of TXA administration (£29.37 per person), meaning that the majority of the costs incurred are the hospital costs (hospital stay, interventions and transfusions) and post-discharge costs. The CEAC summarises the cost-effectiveness plane and shows that at any willingness to pay for an additional QALY above £2000, no TXA is likely to be the more cost-effective option. For example, at the NICE-specified willingness-to-pay threshold levels of £20,000 and £30,000 per additional QALY, TXA has a 34% and 33% probability of being the most cost-effective option, respectively. Note that the base-case CEAC

TABLE 10 Deterministic one-way sensitivity analysis results

Parameter	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER LYs (£)	ICER QALYs (£)	INMB (QALY) (£)
Base case	-58	-0.04	-0.03	1413	1981	-524
Excess mortality excluded after first year	-62	-0.05	-0.03	1306	1843	-611
Monitoring costs (full monitoring costs for year 4 onwards)	-96	-0.04	-0.03	2357	3304	-486
Monitoring costs not included beyond 3 years	-38	-0.04	-0.03	941	1319	-544
0% discount rate	-70	-0.06	-0.04	1162	1646	-783
6% discount rate	-52	-0.03	-0.02	1609	2243	-412
Utility: general population utility after first year	-58	-0.04	-0.03	1413	1826	-574
Monitoring costs: inpatient costs excluded in year 1	-49	-0.04	-0.03	1204	1688	-533
TXA all-cause mortality RR (0.92)	79	0.10	0.07	816 <sup>a</sup>	1144 <sup>a</sup>	1310
TXA all-cause mortality RR (1.16)	-210	-0.19	-0.14	1080	1514	-2568
Total TXA administration at £0	-87	-0.04	-0.03	2133	2990	-600

<sup>a</sup> In this scenario, the ICERs flip, meaning that they favour TXA treatment (hence the positive INMBs). INMBs are calculated using a £20,000 willingness to pay for an additional LY/QALY threshold. Negative costs, LYs and QALYs indicate that TXA is less costly and less effective than no TXA.

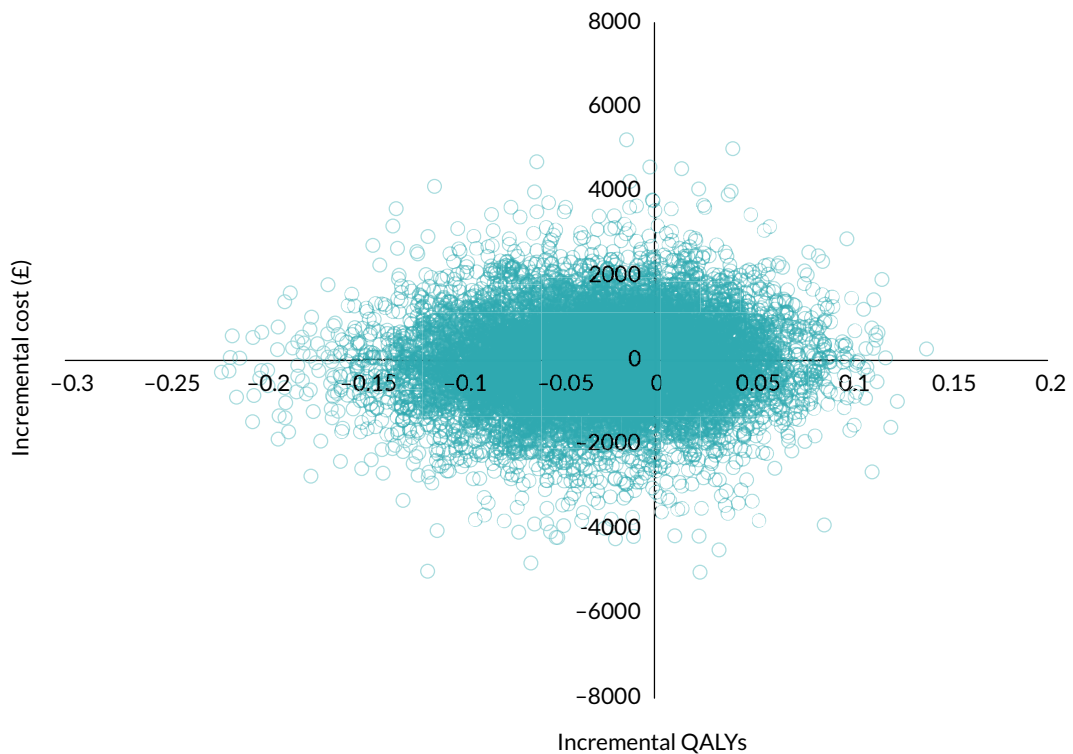


FIGURE 6 Base-case cost-effectiveness plane. The north-east quadrant contains 15% of simulations, the south-west quadrant 37%, the south-east quadrant 14% and the north-west quadrant 34%.

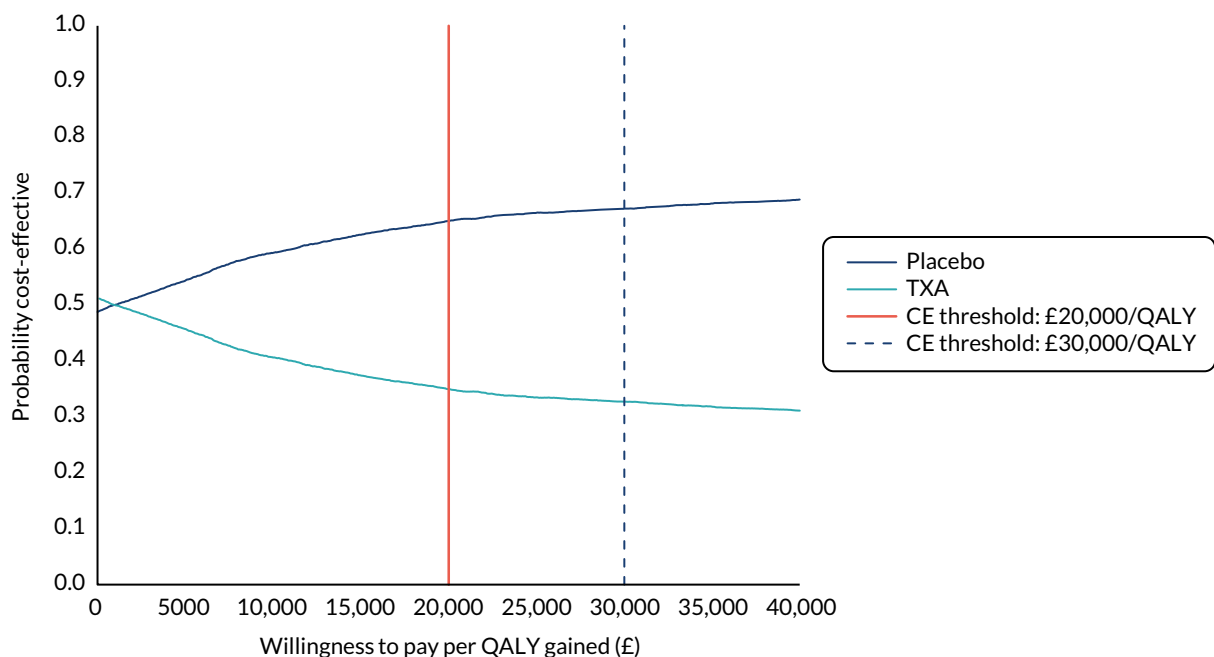


FIGURE 7 Base-case CEAC. The north-east quadrant contains 27% of simulations, the south-west quadrant 25%, the south-east quadrant 24% and the north-west quadrant 24%.

does not indicate that there is a 0% probability that TXA is the most cost-effective treatment option, irrespective of the willingness-to-pay value. The lowest that this value can reduce to is 15% because TXA treatment produced more QALYs at lower cost in this proportion of simulations (i.e. it was the 'dominant' treatment option in this proportion of simulations). Re-running the PSA assuming the standard error of the post-discharge costs to be 20%, instead of 50%, of their mean value had a negligible impact on the probability of TXA being cost-effective.

To demonstrate the sensitivity of the results to alternative parameter values for the RR for all-cause mortality, the PSA was re-run assuming a RR of 1.00 (95% CI 0.88 to 1.10). These values are somewhat arbitrary/hypothetical, but include a point estimate that does not favour either treatment, with a wide CI that still includes a value of 1. Irrespective of the threshold willingness-to-pay level, the probability of TXA being the most cost-effective option is approximately 50% (Figure 8), demonstrating its low administration cost.

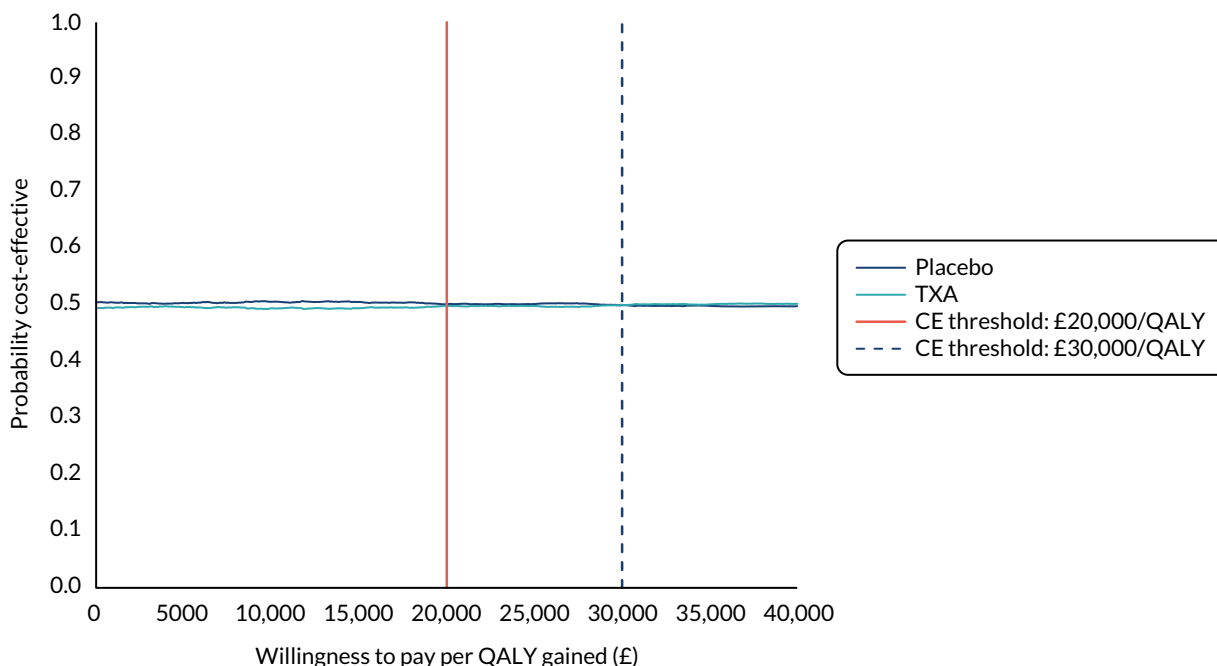


FIGURE 8 Cost-effectiveness acceptability curve assuming a hypothetical RR of all-cause mortality of 1.00 (95% CI 0.88 to 1.10).



## Chapter 6 Discussion

In this trial, TXA did not reduce death from GI bleeding but was associated with an increased risk of venous thromboembolic events and seizures. The proportion of patients experiencing rebleeding was similar in the TXA and placebo groups.

Administration of TXA within 3 hours of bleeding onset reduces death due to bleeding in patients with trauma or post-partum haemorrhage without increasing the risk of thromboembolic events. In these bleeding scenarios, the timing of onset is easy to determine: most patients present early and there are well-documented changes in fibrinolysis that provide a biological rationale for TXA treatment.<sup>83,84</sup> However, in the case of GI bleeding it is difficult to determine the time of bleeding onset, presentation is often delayed (> 80% of patients present > 3 hours after bleeding onset) and the contribution of increased fibrinolysis to bleeding is less clear.

Almost half of the patients included in our trial had suspected variceal bleeding due to liver disease, and because these patients have a greater risk of death they accounted for nearly three-quarters of deaths. Recent research shows that acutely ill patients with cirrhosis have a mixed fibrinolytic phenotype.<sup>85</sup> Some have increased fibrinolysis but others have profound hypofibrinolysis. The prevalence of hypofibrinolysis appears to be greatest in the most critically ill patients. Using the same clot lysis assay, reduced fibrinolysis has been shown to be associated with a small increased risk of venous thrombosis.<sup>86</sup> In our trial, the increased risk of venous thromboembolic events with TXA appeared to be more marked in patients with liver disease, although this was an exploratory subgroup analysis and there was no strong evidence of heterogeneity. Nevertheless, reduced fibrinolysis in patients with liver disease might explain the lack of any reduction in bleeding deaths with TXA and the increased risk of venous thromboembolic events.

The dose of TXA used in this trial was higher and the duration of treatment was longer (4 g over 24 hours) than that in randomised trials of TXA in trauma<sup>54,57</sup> (2 g over 8 hours) or post-partum haemorrhage<sup>55</sup> (1-g bolus with a repeat 1-g dose if bleeding continued), which did not record any increase in adverse events with TXA. Patients with GI bleeding often rebleed after initial haemostasis, particularly within the first 24 hours. Because TXA has a short half-life, we used a longer treatment duration to cover this high-risk period. Furthermore, previous trials in GI bleeding that appeared to show a large mortality reduction with TXA used a high dose and a longer duration of treatment than trials in trauma and post-partum haemorrhage.<sup>87</sup> The longer duration of TXA treatment in this trial may explain the increased risk of venous thromboembolic events, and the higher dose may explain the increased risk of seizures.<sup>88</sup>

In summary, we found no evidence that TXA decreases the risk of death in patients with GI bleeding. Our results caution against a uniform approach to the management of patients with major haemorrhage and highlight the need for randomised trials targeted at specific pathophysiological processes. Given that GI bleeding is a licensed indication for TXA, our results may have regulatory implications.

### Strengths and limitations

Our trial had several strengths but also some limitations. The randomisation method ensured that participating clinicians had no foreknowledge of the treatment allocation and the placebo control ensured that the outcome assessment was blind to treatment group. The inclusion criteria were clinical, reflecting the full range of GI bleeding presentations that doctors face in day-to-day practice. Baseline prognostic factors were well balanced and almost all randomly assigned patients were followed up. The primary outcome was death due to bleeding within 5 days of randomisation. Our scientific reasons for prespecifying death due to bleeding as the primary outcome in the statistical analysis plan are presented in detail elsewhere.<sup>67</sup> Although some misclassification of cause of death is possible, the

assessment was blind to the treatment group. However, as there was no evidence of a treatment effect for the prespecified primary end point (death due to bleeding at 5 days) or for death from any cause at 28 days, the choice of end point does not influence the interpretation of the results. Misclassification might also have affected our subgroup analyses because at the time of recruitment the site and cause of bleeding could not be known with certainty. Our use of the pre-endoscopy Rockall score may have misclassified the baseline risk.<sup>89</sup> To minimise the risk of false positives, we used strict criteria to diagnose thromboembolic events, including a positive result on imaging (e.g. ultrasound) or at post-mortem examination. Although this may have led to some under-reporting because the diagnostic tests have high specificity, the RR estimates should be unbiased. Although some patients received antifibrinolytics outside the protocol, the treatment effect was the same when these patients were excluded. Although this is one of the largest randomised trials in GI bleeding, we cannot rule out a modest increase or decrease in death due to bleeding with TXA. However, we can rule out the large mortality reduction suggested by the Cochrane systematic review and meta-analysis of previous small trials.<sup>87</sup>

## Cost-effectiveness

The results of the analysis suggest that the costs and outcomes of treating people with AGIB with and without TXA, as enrolled and treated in the HALT-IT trial, are very similar. However, the base-case probabilistic analysis showed that the probability that TXA is the most cost-effective option is 34% and 33% at thresholds of willingness to pay for an additional QALY of £20,000 and £30,000, respectively. This means that, on balance, no TXA is more likely to be the most cost-effective option. The deterministic sensitivity analyses confirmed the robustness of this finding. These results are in line with our prior expectations given the additional, albeit modest cost (£29.37), of providing TXA and the knowledge that it was not associated with a statistically significant reduction in all-cause mortality (RR 1.03, 95% CI 0.92 to 1.16), as reported by the HALT-IT trial.

As with all decision models, our analysis includes a number of parameter and structural assumptions. For example, assumptions were made regarding the longer-term costs of caring for people who recover from an initial episode of AGIB, and the utility values were sourced from outside the HALT-IT study and were assumed to be equal for both treatment groups. Moreover, unlike previous economic evaluations of TXA, we estimated the impact of treatment based on a RR of all-cause mortality rather than death due to bleeding, given that TXA was associated with a higher risk of death due to thromboembolic events and malignancies. However, only the scenarios that included a point RR of all-cause mortality favouring TXA over no TXA resulted in TXA being considered the most cost-effective option. We therefore do not believe that any of the assumptions that have been made, or the use of alternative measure of treatment effect, are of particular importance in terms of affecting the overall conclusions regarding cost-effectiveness.

To the best of our knowledge, no other cost-effectiveness analyses of TXA for people with AGIB have been reported. However, economic evaluations based on the series of CRASH RCTs<sup>57</sup> and the WOMAN RCT<sup>55</sup> concluded that TXA is highly cost-effective in other indications, specifically following trauma injury<sup>69</sup> and post-partum haemorrhage.<sup>79</sup> The dose of TXA used in the HALT-IT trial is higher than that used in the previous studies. However, the increased cost of treatment is negligible and does not explain the clearly different cost-effectiveness results. The basic reason for the difference is that the HALT-IT trial did not provide any evidence to support a statistically significant improvement in health outcomes from using TXA, whereas evidence of benefit was much stronger in the other indications. However, 80% of participants in the HALT-IT trial received treatment > 3 hours after the suspected onset of bleeding. This is important because there is reason to believe from the RCTs of TXA in trauma and post-partum haemorrhage that earlier treatment is associated with improved outcomes. Our cost-effectiveness results reflect the timing of treatment as given in the HALT-IT trial, meaning that we cannot rule out the possibility of TXA being the most cost-effective option if treatment is more promptly administered.



## Findings in context

### *Evidence before this study*

Before this study, a Cochrane systematic review and meta-analysis<sup>87</sup> of randomised trials of TXA for upper GI bleeding included seven trials with a total of 1654 patients. There was a large reduction in mortality with TXA (pooled RR 0.61, 95% CI 0.42 to 0.89;  $p = 0.01$ ).<sup>87</sup> However, given the small size of the included trials and the potential for selection and other biases, we considered this evidence to be hypothesis-generating, requiring confirmation in larger trials. Furthermore, there was substantial uncertainty about the risk of thromboembolic events with TXA (pooled RR 1.86, 95% CI 0.66 to 5.24).

### *Added value of this study*

The HALT-IT trial included 12,009 patients from 164 hospitals in 15 countries. Adult patients with significant upper or lower GI bleeding were randomly assigned to receive TXA (a 1-g loading dose followed by a 3-g maintenance dose over 24 hours) or matching placebo. TXA did not reduce death from GI bleeding (RR 0.99, 95% CI 0.82 to 1.18) but was associated with an increased risk of venous thromboembolic events (RR 1.85, 95% CI 1.15 to 2.98) and seizures (RR 1.73, 95% CI 1.03 to 2.93).

### *Implications of all the available evidence*

The most recent update of the Cochrane review included eight small randomised trials with 1701 participants and showed a reduction in mortality with TXA (RR 0.60, 95% CI 0.42 to 0.87). Although we cannot entirely rule out a modest increase or decrease in death due to bleeding with TXA, we can rule out the large mortality reduction suggested by the Cochrane review.<sup>60</sup> Furthermore, TXA appears to increase the risk of venous thromboembolic events in patients with GI bleeding. On the basis of our results, TXA should not be used for the treatment of GI bleeding outside the context of a randomised trial. Our results highlight the unreliability of meta-analyses of small trials.

## Implications for practice in the NHS

Many emergency physicians and surgeons believe that TXA improves outcomes in patients with acute severe GI bleeding. Emergency physicians and surgeons are familiar with TXA, which is widely used in trauma and elective surgery based on compelling evidence from large, high-quality, randomised trials. The promotion of 'major haemorrhage protocols' in UK hospitals encourages the notion that all bleeding is fundamentally the same and can be treated in a similar way. Furthermore, the Cochrane systematic review and meta-analysis<sup>87</sup> of previous trials of TXA in GI bleeding shows a large reduction in mortality with TXA (pooled RR 0.61, 95% CI 0.42 to 0.89;  $p = 0.01$ ). Despite the small size of the included trials, the potential for selection and other biases and the lack of data on adverse effects suggest that these results should be seen as hypothesis-generating rather than confirmatory; these methodological caveats can be lost on a doctor struggling to control a life-threatening GI bleed. Indeed, even the methodologically sophisticated NIHR Health Technology Assessment (HTA) Commissioning Board questioned the need for the HALT-IT trial given the evidence from the Cochrane review.

'The Board expressed significant concerns about the need of this trial in the light of current evidence for benefit for TXA in GI bleeding and other conditions. Therefore, the applicants should argue the case for this trial very thoroughly in their full application.' (NIHR, 2011, personal communication).

The results of the HALT-IT trial showed that TXA did not reduce death from GI bleeding but was associated with an increased risk of venous thromboembolic events and seizures. The proportion of patients with rebleeding was similar in the TXA and placebo groups. These results caution against a 'one size fits all' approach to the management of patients with major haemorrhage and highlight the need for randomised trials targeted at specific pathophysiological processes. In traumatic bleeding, the timing of bleeding onset is easy to determine: most patients present early and there are well-documented changes in fibrinolysis that provide a biological rationale for TXA treatment. However, in the case of GI

bleeding, it is difficult to determine the time of bleeding onset, presentation is often delayed (> 80% of patients present more than 3 hours after bleeding onset) and the contribution of increased fibrinolysis to bleeding is less clear. Based on the HALT-IT trial results, TXA should not be used for the treatment of GI bleeding outside the context of a randomised trial.

## Implications for research in the NHS

Although we cannot rule out a modest increase or decrease in the risk of death due to bleeding with TXA, we can rule out the large mortality reduction suggested by the Cochrane systematic review and meta-analysis<sup>87</sup> of previous small trials. In this respect, the HALT-IT trial highlights the dangers of overinterpreting results from systematic reviews of small trials. Although the review authors emphasised the methodological weakness of the included trials, pointing out the 'limitations in their internal and external validity', the large, statistically significant reduction in all-cause mortality is hard to ignore and has had a considerable impact on research on this topic. As previously stated, the HTA Board questioned the need for a trial given the systematic review evidence. The large mortality reduction also made it harder to justify a large randomised trial. The investigators sent the trial protocol to *The Lancet* for peer review. *The Lancet* reviewers' main concern was that the HALT-IT trial was unnecessarily large. The possibility that systematic reviews of small trials could cause research waste by encouraging underpowered trials was raised by the chief investigator in 2015:<sup>90</sup>

*Systematic reviews of small trials increase waste by advertising to the scientific community inflated, often significant treatment effects that become smaller or absent when large, high-quality trials are done. Effect estimates from systematic reviews often inform sample size calculations. However, because most reviews provide exaggerated estimates of treatment effects due to inclusion of small, poor-quality trials, new trials will be underpowered to detect modest but potentially important effects.*

*Reproduced with permission from Roberts and Ker<sup>90</sup> © Elsevier 2015*

Although it is hard to quantify the impact of the Cochrane review on clinical equipoise on this topic, open-label use of TXA was a recurrent problem in the UK and led to the closure of recruitment to the HALT-IT trial at many UK hospitals. Had it not been for brisk recruitment in the non-UK hospitals, the HALT-IT trial may not have achieved its recruitment target. The large discrepancy between the results of the Cochrane review and the results of the HALT-IT trial should encourage a reconsideration of the role of systematic reviews of small trials in informing health care and health research. Most meta-analyses are dominated by small trials. The median number of trials in Cochrane reviews is six, and the median number of patients per trial is approximately 80.<sup>91</sup> In most cases, the results of such reviews should be considered hypothesis-generating, requiring confirmation in adequately powered randomised trials.

Despite that, with 12,000 patients, the HALT-IT trial is, to the best of our knowledge, the largest randomised trial of TXA in GI bleeding, we cannot rule out a modest treatment benefit. Because there is strong evidence that TXA reduces bleeding deaths in patients with traumatic and post-partum haemorrhage, individual patient data meta-analyses should assess the strength of the evidence that the effectiveness and safety of TXA vary by the site and cause of bleeding. Basic research could also inform this question by examining the role of fibrinolysis in patients with GI bleeding and whether or not this varies depending on the aetiology of the bleeding.

## Chapter 7 Dissemination

A dissemination plan (see *Appendix 8*) was written to guide the dissemination of the study results. This document outlined the background to the trial, objectives of the dissemination strategy and planned specific outputs of dissemination.

### Objectives

A key objective of the dissemination plan was to inform the trial collaborators of the HALT-IT trial results and to help them to disseminate the results in their countries. The successful completion of the trial was entirely dependent on the work of collaborators in the participating hospitals. Hence, the results of the trial were reported first to trial collaborators.

Developing dissemination tools that collaborators could use for national and international audiences helped to achieve this. The various dissemination documents were uploaded onto the trial website to allow collaborators to download these resources and use them locally. Further dissemination tools for collaborating investigators were created to help them raise awareness of the trial results.

Dissemination of the results to all trial participants, particularly those who asked to be informed of the trial results, was also a vital objective. A lay summary of the results was sent to sites to communicate the results to their participants directly, and wider dissemination to participants took place via the media and the trial website (URL: <https://haltit.lshtm.ac.uk/>). The dissemination plan also aimed to make the results accessible to the public by using social media [including Twitter (Twitter, Inc., San Francisco, CA, USA; [www.twitter.com](http://www.twitter.com)), Facebook (Facebook, Inc., Menlo Park, CA, USA; [www.facebook.com](http://www.facebook.com)) and WhatsApp (Facebook, Inc.; [www.whatsapp.com](http://www.whatsapp.com)), the trial website (<https://haltit.lshtm.ac.uk/>), the LSHTM Clinical Trial Unit (CTU) website (<https://ctu.lshtm.ac.uk/>) and by broadcasting the results in The Resus Room podcast.

In terms of the scientific and medical community, the objective was to disseminate the results as widely as possible through publication of the results in a peer-reviewed medical journal, through conference presentations, by sharing the link to the publication in all applicable trial registers and by posting the dissemination materials on the HALT-IT website, on the LSHTM CTU website and on social media. Following completion of all prespecified analyses, another key dissemination objective was to share individual de-identified patient data, including data dictionary via the LSHTM CTU data-sharing platform, The Free Bank of Injury and Emergency Research Data (freeBIRD) at <https://freebird.lshtm.ac.uk>. The purpose of this was to allow maximum utilisation of the data to improve patient care and advance medical knowledge.

### Outputs

- The trial results were published in *The Lancet* on 20 June 2020.<sup>3</sup>
- All trial collaborators, regardless of whether or not their site recruited participants, were sent a copy of the publication in *The Lancet*, a PowerPoint presentation containing the trial results and the social media dissemination pack, enabling them to disseminate the trial results in their own hospitals and countries.
- Links to *The Lancet* publication were made available in all applicable trial registers, the HALT-IT trial website and the LSHTM CTU website.
- A PowerPoint presentation of the results was made available for use by doctors and other health-care professionals.

- The results were disseminated to patients via social media (LSHTM CTU Twitter account @CTU\_LSHTM and the LSHTM CTU Facebook page) and the trial website (URL: [haltit.lshtm.ac.uk](http://haltit.lshtm.ac.uk)).
- A lay summary of the results was provided to sites to be shared with trial participants.
- A social media dissemination pack was created for dissemination of the trial results and other dissemination tools on social media.
- The trial website was upgraded to ensure that trial-related dissemination materials could be downloaded by investigators and others and used for dissemination.
- A podcast with the breakdown of the trial results and an interview with Professor Ian Roberts was recorded with The Resus Room (@TheResusRoom).
- The trial protocol, statistical analysis plan and trial publication are all freely available online.
- Following completion of all prespecified analyses, totally anonymised trial data will be shared via the LSHTM CTU data-sharing platform at [freebird.lshtm.ac.uk](http://freebird.lshtm.ac.uk). This will allow for maximum utilisation of the data to improve patient care and advance medical knowledge.

### **The impact of COVID-19**

It is important to note that the trial results were published during the COVID-19 pandemic, and this limited the impact of our dissemination plan. As a result of the pandemic, both printed and broadcast media were, justifiably, almost entirely focused on COVID-19 and, therefore, there was no room for reporting non-COVID-related research. Unfortunately, this resulted in less coverage than was expected in the general media and we were unable to use the media to reach a wider audience with these important results.

## Chapter 8 Reflections and concluding remarks

The HALT-IT trial was one of the largest clinical trials in GI bleeding ever conducted. It found no evidence that TXA reduces deaths from stomach bleeding, but there was evidence that TXA may increase the risk of thromboembolic events (deep-vein thrombosis or pulmonary embolism). There were also more seizures with TXA and rebleeding was similar in both groups.

In 2010, the CRASH-2 trial,<sup>54</sup> a large multicentre randomised trial of TXA in trauma patients, found that this inexpensive, generic drug reduces the number of deaths by one-sixth. Following these results, the team at LSHTM CTU wondered whether or not TXA could have a similar effect in GI bleeding. The Cochrane review found a surprisingly large (40%) reduction in gastric bleeding deaths; however, this review was based on the results of a number of smaller trials. To determine whether or not TXA cuts gastric bleeding deaths, a large trial was needed, and the LSHTM CTU team began work on the HALT-IT trial.

Initially, NIHR questioned the need for a trial because of the Cochrane review. Even during the trial, many UK doctors would recruit bleeding patients, randomly allocate them to TXA or placebo but, if they continued bleeding, would give them TXA regardless. As a result, many UK hospitals were closed to recruitment owing to lack of clinical equipoise; without strong recruitment from non-UK hospitals, particularly in Pakistan, we would have failed to reach our recruitment target. The discrepancy between the results of the Cochrane review and the results of the HALT-IT trial is alarming, but not unusual. It should prompt a reconsideration of the role of systematic reviews in informing UK health care.

The funders originally requested a 1-year follow-up on the patients randomised in the UK; however, the follow-up period for these patients was 28 days. The LSHTM CTU team requested access to 1-year follow-up data from the NHS Health and Social Care Information Centre (now NHS Digital). After the protocol was finalised in 2014, the NHS Health and Social Care Information Centre requested changes in the patient information sheet and consent form as a condition of sharing its data. This allowed the data to be released in 2015. However, in 2016 the policy changed again, and data-sharing was refused.

These results also demonstrate that TXA should not be used for the treatment of GI bleeding outside the context of a randomised trial, and caution against the use of generic 'major haemorrhage protocols' in the UK. Although it is often assumed that a treatment that works in one bleeding situation, such as traumatic bleeding or post-partum haemorrhage, will probably work in another, these results highlight the need for clinical trials that target specific causes of bleeding. Patients with GI bleeding may respond differently to those with traumatic and post-partum bleeding. In particular, patients with underlying liver disease may be more prone to side effects from unwanted clotting. GI bleeding is currently a licensed indication for TXA and, therefore, our results could have regulatory implications.



# Acknowledgements

All authors made substantial contributions to the conception and design, or acquisition of data, analysis and interpretation of data, all were involved in the drafting of the manuscript or revising it critically for important intellectual content, and all authors approved the final version to be published.

## Role of funding source

The HALT-IT trial was funded by the NIHR HTA programme. The funders of the trial had no role in study design, data collection, data analysis, data interpretation, or report writing. The corresponding author and Writing Committee members had full access to all the study data and had final responsibility for the decision to submit for publication.

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**Monica Arribas** (<https://orcid.org/0000-0002-1405-9391>) (Trial Manager/Research Assistant) was involved in the design, conduct and reporting phases.

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**Laura Carrington** (<https://orcid.org/0000-0002-8322-2092>) (Assistant Trial Administrator) was involved in the conduct phase.

**Rizwana Chaudhri** (<https://orcid.org/0000-0002-5428-3988>) (Dean and Professor of Obstetrics and Gynaecology) was involved in the conduct and reporting phases.

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## Publications

Manno D, Ker K, Roberts I. How effective is tranexamic acid for acute gastrointestinal bleeding? *BMJ* 2014;**348**:g1421.

Brenner A, Afolabi A, Ahmad SM, Arribas M, Chaudhri R, Coats T, *et al.* Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2019;**20**:467.

Roberts I, Shakur-Still H, Afolabi A, Akere A, Arribas M, Brenner A, *et al.* Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet* 2020;**395**:1927–36.

### Related publications

The HALT-IT trial protocol is available here: <https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-450>.

The Statistical Analysis Plan for the HALT-IT trial is available here: <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3561-7>.

The HALT-IT trial results publication is available here: [www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30848-5/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30848-5/fulltext).

## Data-sharing statement

Individual de-identified patient data, including data dictionary, will be made available via our data-sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website, indefinitely (URL: <http://freebird.lshhtm.ac.uk>). This will allow for maximum utilisation of the data to improve patient care and advance medical knowledge. Requests for access to the data should be addressed to the corresponding author or through the data-sharing portal.

## Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here <https://understandingpatientdata.org.uk/data-citation>.



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# Appendix 1 HALT-IT trial organisation

## Trial Steering Committee

Christopher Hawkey (chairperson), Adefemi Afolabi, Jack Cuzick, Kenneth Halligan (patient representative), David Henry, Chris Metcalfe and Ian Roberts.

## Data Monitoring and Ethics Committee

Richard Gray (chairperson), Alan Barkun, Suresh David, Philip Devereaux and Tony Brady (independent statistician).

## Protocol Committee

Ian Roberts, Haleema Shakur-Still, Timothy Coats, Phil Edwards, Ian Gilmore, Vipul Jairath, Katharine Ker, Daniela Manno, Simon Stanworth and Andrew Veitch.

## Trial Co-ordinating Centre Team

### *Clinical Trials Unit*

Monica Arribas (trial manager/research assistant), Emma Austin (assistant trial manager), Kiran Bal (assistant trial manager), Eni Balogun (trial manager), Collette Barrow (trial administrator), Danielle Beaumont (senior trial manager/research fellow), Myriam Benyahia (CTU administrator), Amy Brenner (research fellow), Imogen Brooks (trial assistant 2016–18), Madeleine Cargill (data assistant), Laura Carrington (trial administrator), Phil Edwards (statistician 2012–16), Lauren Frimley (trial manager/research assistant), Amber Geer (assistant data manager), Daniel Gilbert (data assistant 2012–13), Catherine Gilliam (trial administrator), Julio Gil Onandia (clerical assistant), Nayia Golfi (trial manager 2013–15), Daniel Hetherington (trial assistant 2012–15), Courtenay Howe (CTU administrator 2015–17), Carolyn Hughes (data assistant 2016–17), David I'anson (assistant trial manager 2016–17), Rob Jackson (data manager 2012–15), Miland Joshi (statistician 2016–17), Sneha Kansagra (assistant trial manager 2016–18), Taemi Kawahara (senior trial manager 2012–15), Katharine Ker (lecturer), Sergey Kostrov (systems officer 2015–19), Daniela Manno (clinical lecturer 2012–15), Raoul Mansukhani (medical statistician 2019–20), Hakim Miah (IT systems manager 2013–19), Bernard Ndungu (assistant trial manager 2016–17), Kelly Needham (statistician 2018–20), Aroudra Outtandy (trial assistant 2013–15), Daniel Pearson (data assistant 2018–19), Tracey Pepple (acting senior data manager 2014–19), Danielle Prowse (assistant data manager), Nigel Quashi (data manager 2013–16), Anna Quinn (data assistant 2013–15), Maria Ramos (senior project administrator 2012–15), Laura Ranopa (trial assistant 2015–20), Mia Reid (clerical assistant 2016–18), Ian Roberts (chief investigator/CTU co-director), Chris Roukas (trial administrator 2013–15), Haleema Shakur-Still (project director/CTU co-director), Chelci Squires (trial assistant 2014–16), Jemma Tanner (clinical trials associate 2013–16), Andrew Thayne (data assistant) and Ruhama Uddin (trial assistant 2018–19).

### *Rawalpindi Medical University Pakistan National Co-ordinating Centre Team*

Rizwana Chaudhri (co-ordinating centre director), Muttiullah Mutti (clinical lead), Kiran Javaid (assistant research co-ordinator) and Aasia Kayani (research co-ordinator).

### ***Nigeria Co-ordinating Team, University College Hospital Ibadan***

Bukola Fawole (co-ordinating centre director), Folasade Adenike Bello (co-ordinating centre director), Oladapo Olayemi (co-ordinating centre director), Adefemi Afolabi (national principal investigator), Olujide Okunade (assistant trial co-ordinator) and Olusade Adetayo (assistant trial co-ordinator).

### ***National Co-ordinators***

Rizwana Chaudhri (Pakistan), Muttiullah Mutti (Pakistan), Adefemi Afolabi (Nigeria), Folasade Adenike Bello (Nigeria), Bukola Fawole (Nigeria), Oladapo Olayemi (Nigeria), Hussein Khamis (Egypt), Mohammad Shukri Bin Jahit (Malaysia), Tamar Gogichaishvili (Georgia), Radu Bogdan Mateescu (Romania), Ajay Adhikaree (Nepal), Abdelmounem Eltayeib Abdo (Sudan), Mohammad Zaher (Saudi Arabia), Conor Deasy (Ireland), Joaquin Alvarez Gregori (Spain), Bobby Welsh (Papua New Guinea) and Luke Lawton (Australia).

## **HALT-IT Trial Collaborators by country**

### ***UK (n = 4751)***

#### **Royal Stoke University Hospital (n = 303)**

Raghavendra Kamath, Adrian Barry, Racquel Carpio, Kay Finney and Holly Maguire.

#### **Queen's Medical Centre Campus Nottingham (n = 208)**

Martin James, Frank Coffey, Chris Gough, Lisa Sawers and Aye-Aye Thi.

#### **Royal Berkshire Hospital (n = 191)**

Jonathan Simmons, Claire Burnett, Nicola Jacques and Victoria Murray.

#### **St George's Hospital (n = 173)**

Richard Pollok, Heather Jarman, Christine Lambe and Sarah Rounding.

#### **Blackpool Victoria Hospital (n = 166)**

Simon Tucker, Romaih Al-Idari, Samuel Guest and Emma Stoddard.

#### **Queen Elizabeth Hospital Birmingham (n = 150)**

David Yeo, Colin Bergin, Elaine Hardy and Joanne Thunder.

#### **University Hospital Coventry (n = 128)**

Paul Jhalli, Edward Hartley, Catherine Jarvis and Carly Swann.

#### **Royal Infirmary of Edinburgh (n = 125)**

Matthew Reed, Bernadette Gallagher, Julia Grahamslaw and Rachel O'Brien.

#### **Royal London Hospital (n = 125)**

Timothy Harris, Geoffrey Bellhouse, Olivia Boulton and Imogen Skene.

#### **Glasgow Royal Infirmary (n = 120)**

Adrian Stanley, Janet Johnstone, Donogh Maguire and Susan Thornton.

#### **University College London Hospital (n = 113)**

Matthew Banks, Georgia Bercades, Daniel Marks and Jung Ryu.

**Whipps Cross University Hospital (n = 108)**

Timothy Harris, Claire Dowty, Jason Pott and Imogen Skene.

**John Radcliffe Hospital (n = 107)**

James East, Adam Bailey, Sally Beer and Sian Davies.

**Royal Devon & Exeter Hospital (n = 97)**

Andrew Appelboom, Daisy Mackle and Jennifer Small.

**Queen Alexandra Hospital Portsmouth (n = 88)**

Christiane Vorwerk, Rachel Atkins and Isobel Bradbury.

**Leicester Royal Infirmary (n = 84)**

Timothy Coats, Catriona Bryceland and Lisa McClelland.

**Salford Royal Hospital (n = 83)**

Martin Thomas, Kate Clayton and Angiy Michael.

**Great Western Hospital (n = 80)**

Stephen Haig, Saif Al-Nahas and Tim Godfrey.

**Southampton General Hospital (n = 80)**

Philip Boger, Rachel Comer and Barbara Watkins.

**Darlington Memorial Hospital (n = 79)**

Ola Afolabi, Shazad Afzal and Amanda Cowton.

**St James University Hospital Leeds (n = 79)**

Simon Everett, Ruth Fazakerley and Felicia Onoviran.

**Poole Hospital (n = 77)**

Jonathon Snook, Jackie Berry and Diane Simpson.

**King's College Hospital (n = 73)**

Jeff Keep, Hannah Cotton and Sinead Helyar.

**University Hospital of North Tees (n = 73)**

Matthew Rutter, Tracey Johnston and Laura O'Rourke.

**Basingstoke and North Hampshire Hospital (n = 72)**

Louisa Chan, Joanna Tambellini and Dawn Trodd.

**Dorset County Hospital (n = 68)**

James Shutt, Sarah Moreton and Abby Oglesby.

**Addenbrooke's Hospital (n = 67)**

Adrian Boyle, Nicola Haeger and Susie Hardwick.

**Southmead Hospital (n = 67)**

Jason Kendall, Beverley Faulkner and Ruth Worner.

**Royal Victoria Infirmary (n = 64)**

Sarah Hearnshaw, Mary Doona and Maria Price.

**St Thomas' Hospital (n = 64)**

Laura Hunter, Maggie Bell and Vania Loureiro.

**Derriford Hospital (n = 61)**

Anthony Kehoe, Alison Jefferey and Rosalyn Squire.

**Ipswich Hospital (n = 60)**

David Hartin, Stephanie Bell and Alexandra Newman.

**Musgrove Park Hospital (n = 59)**

James Gagg, Jayne Foot and Sue Wakeford.

**Royal Oldham Hospital (n = 58)**

Gabrielle May, Thomas Bartram and Paul Cumpstay.

**Whittington Hospital (n = 58)**

Lucy Parker, Rita Das and Sheik Pahary.

**Basildon University Hospital (n = 57)**

Gavin Wright, Georgina Butt and Natasha Christmas.

**Wexham Park Hospital (n = 56)**

Sarah Wilson, Mohammed Ashfaq and Louise Chandler.

**Royal United Hospital Bath (n = 50)**

Saif Al-Nahas, Carrie Demetriou and Philip Kaye.

**Manchester Royal Infirmary (n = 48)**

Simon Carley and Andrew Brown.

**Chesterfield Royal Hospital (n = 44)**

Lucy Jones and Amanda Whileman.

**James Cook University Hospital (n = 44)**

John Greenaway and Julie Tregonning.

**Newham University Hospital (n = 44)**

Timothy Harris and Geoffrey Bellhouse.

**Northern General Hospital (n = 44)**

Avril Kuhrt and Steve Goodacre.

**Royal Shrewsbury Hospital (n = 43)**

John Jones and Charlotte Owen.

**Charing Cross Hospital (n = 41)**

Anu Mitra and Abby Harper-Payne.

**Sandwell General Hospital (n = 37)**

Nigel Trudgill and Anne Hayes.

**South Tyneside District Hospital (n = 36)**

Faheem Butt and Gayle Clifford.

**Victoria Hospital, Fife (n = 35)**

Andrew Kinnon and Susan Fowler.

**Chelsea and Westminster Hospital (n = 34)**

Kris Pillay and Shweta Gidwani.

**Queen Elizabeth Hospital Woolwich (n = 34)**

Alistair McNair and Omer Omer.

**Gloucestershire Royal Hospital (n = 31)**

Tanya de Weymarn and Adnan Amin.

**Royal Hampshire County Hospital (n = 31)**

Louisa Chan and Jane Martin.

**Torbay Hospital (n = 31)**

Nick Mathieu and Simon Barnes.

**York Hospital (n = 31)**

James Turvill and Helen Sweeting.

**University Hospital Crosshouse (n = 29)**

Morten Draegebo and Marion McNaught.

**Worthing Hospital (n = 29)**

Mandy Grocutt and Jordi Margalef.

**Barnsley Hospital (n = 27)**

Julia Humphrey and Richard Jackson.

**North Devon District Hospital (n = 27)**

Fionn Bellis and Jane Hunt.

**St Mary's Hospital (n = 24)**

Anu Mitra.

**University Hospital Ayr (n = 22)**

Alastair Stevenson.

**King's Mill Hospital (n = 19)**

Nicholas Watson.

**Royal Sussex County Hospital (n = 19)**

Steven Barden.

**Forth Valley Royal Hospital (n = 16)**

Stuart Paterson.

**New Cross Hospital (n = 16)**

Andrew Veitch.

**Cumberland Infirmary Hospital (n = 14)**

Chris Macdonald.

**Sunderland Royal Hospital (n = 14)**

David Hobday.

**West Cumberland Hospital (n = 13)**

Olu Orugun.

**Yeovil District Hospital (n = 13)**

Andrew Allison.

**Northampton General Hospital (n = 12)**

Tristan Dyer.

**Royal Lancaster Infirmary (n = 12)**

Samuel McBride.

**Royal Liverpool University Hospital (n = 12)**

Wojciech Sawicki.

**Hull Royal Infirmary (n = 10)**

Ben Rayner.

**Frimley Park Hospital (n = 8)**

Lynsey Flowerdew.

**Queen Elizabeth Hospital - Gateshead (n = 7)**

Jamie Barbour.

**Salisbury District Hospital (n = 7)**

Jason Klein.

**Aintree University Hospital (n = 6)**

Stephen Hood.

**University Hospital of Wales (n = 5)**

Nicola Palmer.

**Northwick Park Hospital (n = 4)**

Jacob de Wolff.

**Colchester General Hospital (n = 3)**

Achuth Shenoy.

**Birmingham City Hospital (n = 2)**

Nigel Trudgill.

**Royal Bournemouth Hospital (n = 1)**

Peter Swallow.

**University Hospital Lewisham (n = 1)**

Rajaventhana Srirajaskanthan.



**Pakistan (n = 4420)****King Edward Medical University, Mayo Hospital Lahore (n = 539)**

Irshad Hussain, Hamza Arshad, Naeem Aslam, Anam Bangash, Muhammad Qamar and Haroon Zahoor.

**Rawalpindi Medical University Pakistan, Holy Family Hospital, Unit II (n = 501)**

Muttiullah Mutti, Saba Arshad, Quratul ain Ghalib, Tehseen Hameed, Tayyaba Saif and Wajahat Shafi.

**Services Institute of Medical Sciences/Services Hospital GI/Medical Unit III Lahore (n = 443)**

Muhammad Arif Nadeem, Abid Ali, Shehroze Khan, Muhammad Muaaz and Ahmad Taj.

**Lady Reading Hospital (n = 386)**

Aamir Ghafoor, Aamir Afridi, Mansoor Ahmad, Mujahid Aslam and Sandeep Kumar.

**Asian Institute of Medical Sciences (n = 360)**

Majid Soomro, Mohsin Ali, Ubedullah Bughio, Adil Chang and Sana Shaikh.

**Jinnah Postgraduate Medical Centre Karachi (n = 296)**

Syed Ahmad, Zeeshan Ali, Marium Waqar, Aiman Mushir and Sadaf Sattar.

**DHQ Teaching Hospital Sargodha (n = 207)**

Saifullah Goraya, Sharmeen Aslam, Nighat Fatima, Saadia Noreen and Sheraz Saleem.

**Rawalpindi Medical University Pakistan, Benazir Bhutto Hospital Unit I (n = 196)**

Fazal Rahman, Nadeem Iqbal, Mohammad Khalid and Umar Riaz.

**Rawalpindi Medical University Pakistan, Holy Family Hospital, Unit I (n = 169)**

Muhammad Umar, Tayyab Akhter, Javaria Khan and Noureen Misbah.

**Aziz Bhatti Shaheed Teaching Hospital (n = 160)**

Muhammad Afzal, Mobeen Kayani, Syed Shah and Shahida Tarar.

**Bolan Medical Complex Hospital (n = 149)**

Sherbat Khan, Yasir Iqbal, Essa Khan and Maqbool Reki.

**Rawalpindi Medical University Pakistan, Benazir Bhutto Hospital Unit II (n = 120)**

Tanveer Hussain, Shafqat Iqbal, Muhammad Khurram and Muhammad Shafi.

**Ghulam Muhammad Mahar Medical College and Teaching Hospital Unit I (n = 120)**

Abrar Shaikh, Aijaz Ahmed, Ameet Kumar and Pinkey Sachdev.

**Jinnah Hospital Unit I (n = 88)**

Khalid Mahmood Nasir, Zafar Iqbal Chaudhry and Muhammad Zubair.

**Lahore General Hospital Medical Unit I (n = 84)**

Ghias Tayyab, Junaid Mushtaq and Muhammad Nasir.

**Mardan Medical Complex and Teaching Hospital (n = 80)**

Amir Khan, Amjad Ali and Sajjad Ali.

**POF Hospital (n = 76)**

Wasim Uddin, Sohaib Ahmed and Tazaeen Kazmi.

**Ghulam Muhammad Mahar Medical College Teaching Hospital (n = 58)**

Saleh Channa, Adeeqa Aman and Mouzam Shaikh.

**DHQ Hospital Faisalabad (n = 47)**

Tahir Rizvi and Amjad Hussain.

**Rawalpindi Medical University Pakistan, DHQ Hospital Rawalpindi (n = 47)**

Haider Zaigham Baqai and Zakawat Rasheed.

**Shifa International Hospital (n = 41)**

Abdus Khan and Adeela Irfan.

**Allied Hospital Faisalabad Medical Unit III (n = 38)**

Aamir Husain and Asifa Aslam.

**Madinah Teaching Hospital Faisalabad (n = 34)**

Khalid Yahya and Salman Azhar.

**Liaquat National Hospital and Postgraduate Medical Centre (n = 33)**

Mansoor Ul Haq and Adeel Afzal.

**Services Institute of Medical Sciences/Services Hospital GI/Medical Unit II Lahore (n = 33)**

Muhammad Imran and Iram Saeed.

**Shaukat Khanum Memorial Hospital and Research Centre (n = 29)**

Aasim Yusuf and Mariam Hassan.

**Hayatabad Medical Complex (n = 25)**

Mumtaz Marwat and Muhammad Ishfaq.

**Sir Ganga Ram Hospital Medical Unit III (n = 20)**

Tahir Bashir.

**Liaquat University of Medical and Health Sciences Medical Unit II (n = 17)**

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**DHQ Hospital, Narowal (n = 16)**

Sajjad Yaqoob.

**DHQ Hospital Khuzdar (n = 8)**

Abdul Wahid.

**Nigeria (n = 770)**

**University College Hospital Ibadan (n = 143)**

Adegboyega Akere, Tinuola Fakoya, Temitope Oke and Edries Tejan.

**National Hospital Abuja (n = 109)**

Oluwole Olaomi, Olawale Badejo, Okafor Nnaemaka and Nancy Ukwu.

**Obafemi Awolowo University Teaching Hospital, Ile-Ife (n = 99)**

Olukayode Arowolo, Adewale Aderounmu and Funmilola Wuraola.

**University of Benin Teaching Hospital (n = 74)**

Rose Ugiagbe, Alexander Atiri and Enadeghe Eghaghe.

**Olabisi Onabanjo University Teaching Hospital (n = 49)**

Adeleke Adekoya, Adedayo Oluyomi Tade and Olatunji Shonoiki.

**University of Ilorin Teaching Hospital (n = 49)**

Samuel Olatoke and Toafiq Raji.

**Federal Medical Centre, Owerri (n = 46)**

Christopher Ekwunife and Chigozirim Onyekpere.

**Ahmadu Bello University Teaching Hospital (n = 40)**

Adamu Ahmed and Daniyan Muhammad.

**Lagos University Teaching Hospital (n = 37)**

Emuobor Odeghe, Olufunmilayo Lesi and Azeberoje Osueni.

**Aminu Kano Teaching Hospital (n = 25)**

Adamu Samaila and Aminu Nahuche.

**Ekiti State University Teaching Hospital (n = 24)**

Akande Ajayi.

**Irrua Specialist Teaching Hospital (n = 24)**

Andrew Dongo.

**University of Nigeria Teaching Hospital, Enugu (n = 18)**

Uchenna Ijoma.

**Federal Medical Centre, Abeokuta (n = 8)**

Ademola Tolulope Adebajo.

**Lagos State University Teaching Hospital (n = 7)**

Rufina Igetei.

**University of Abuja Teaching Hospital (n = 7)**

Monday Yilkudi.

**Maitama District Hospital (n = 6)**

Kehinde Osisanya.

**Jos University Teaching Hospital (n = 3)**

Edith Nonyelum Okeke.

**Imo State University Teaching Hospital (n = 2)**

Oguamanam Okezie Enwere.

**Egypt (n = 709)****Kasr Al Aini Internal Medicine Hospital, Cairo University (n = 641)**

Serag Esmat, Omar Ashoush, Mazen Naga, Fady Nagy, Mostafa Saïid and Ahmed Shaker.

**Mataria Teaching Hospital (n = 60)**

Hussein Khamis, Ashraf Helmy and Saafan Saafan.

**Badr Hospital, Helwan University (n = 8)**

Mohammed Abdel Monem.

**Malaysia (n = 464)**

**Hospital Tengku Ampuan Afzan (n = 123)**

Jiffre Din, Khairul Azis, Muhyuddin Brukan and Sanjay Singh.

**Hospital Universiti Sains Malaysia (n = 110)**

Andee Zakaria, Shaik Farid, Nizam Hashim and Masykurin Mafauzy.

**Hospital Sultanah Bahiyah (n = 71)**

Wan Najmi, Nil Amri and Xin Yi.

**Hospital Raja Permaisuri Bainun (n = 63)**

Mohammad Hisyam, Elaine Ng and Zuhrihimi Ramli.

**Pulau Pinang General Hospital (n = 55)**

Shyang Yee Lim, Kelvin Voon and Sir Young Yam.

**Sungai Buloh Hospital (n = 42)**

Mohammad Jahit and Lee Joon.

**Georgia (n = 425)**

**High Technology Medical Centre, University Clinic (n = 364)**

Besik Melikidze, Davit Kazaishvili, Tamar Gogichaishvili, Nino Grubelashvili and Baadur Mosidze.

**Centre of Emergency Surgery and Traumatology (n = 61)**

Gia Tomadze and Avto Megreladze.

**Romania (n = 287)**

**Clinical Emergency Hospital Bucharest – SCUB Floreasca (n = 128)**

Ruxandra Oprita, Dorina Pestroiu Calescu, Camèlia Chioncel and Andrei Ragea.

**Colentina Clinical Hospital (n = 58)**

Bogdan Mateescu, Bogdan Busuioc and Andrei Voiosu.

**Municipal Emergency Hospital Moinesti (n = 45)**

Adrian Cotirlet and Iulia Pintilie.

**Central University Emergency Military Hospital, ‘Carol Davila’ University of Medicine and Pharmacy, Bucharest (n = 38)**

Mariana Jinga and Daniel Balaban.

**Regional Institute of Gastroenterology and Hepatology ‘Prof Dr Octavian Fodor’ (n = 11)**

Marcel Tanțău.

**University Hospital of Emergency Bucharest (n = 5)**

Lucian Negreanu.

**Emergency County Hospital Mures (n = 2)**

Simona Bataga.

**Nepal (n = 50)****Lifeline Hospital (n = 16)**

Khushboo Priya.

**Gandaki Medical College and Teaching Hospital (n = 12)**

Shankar Baral.

**Nepal Medical College and Teaching Hospital (n = 12)**

Anuj KC.

**Janaki Medical College (n = 4)**

Vijay Sah.

**National Medical College and Teaching Hospital (n = 4)**

Vijay Yadav.

**Lumbini Medical College and Teaching Hospital (n = 2)**

Ajay Adhikaree.

**Sudan (n = 40)****Ibn Sina Hospital (n = 40)**

Abdelmounem Abdo and Dalia Ahmed.

**Saudi Arabia (n = 19)****Prince Mohammed Bin Abdulaziz Hospital (n = 19)**

Marzouqah Al Anazi and Areej Al Balkhi.

**Ireland (n = 17)****Cork University Hospital (n = 17)**

Conor Deasy.

**Spain (n = 17)****Hospital Nuestra Señora del Prado (n = 9)**

Joaquín Álvarez Gregori.

**TorreCardenas Hospital (n = 8)**

Helio Fornieles Pérez.

**Albania (n = 16)****University Hospital Centre 'Mother Teresa' (n = 16)**

Arben Beqiri.

*Papua New Guinea (n = 13)*

**Port Moresby General Hospital (n = 13)**

Bobby Welsh.

*Australia (n = 11)*

**The Townsville Hospital (n = 11)**

Luke Lawton.

## Appendix 2 Brief information sheet

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

### THE HALT-IT TRIAL BRIEF INFORMATION ABOUT THE RESEARCH



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.]*

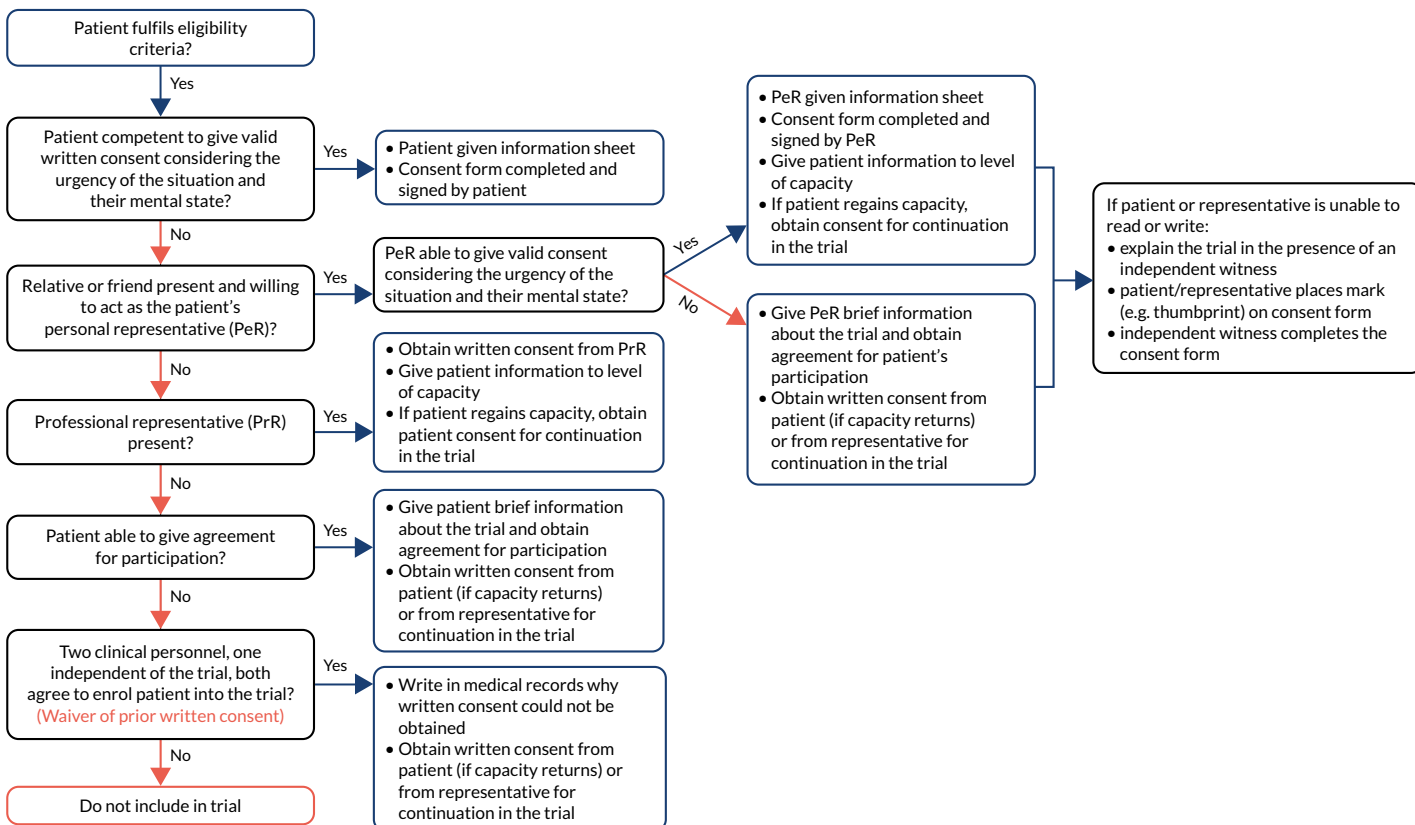
Brief information leaflet v1.1 dated 01/03/2013

Protocol ISRCTN11225767






## Appendix 3 Consent procedure overview



# Appendix 4 Entry form



## ENTRY

**PLEASE COMPLETE 1–19 BEFORE RANDOMISING THE PATIENT**

### ABOUT THE HOSPITAL

<b>1.</b> Country	
<b>2.</b> Hospital code <i>(in your Study File)</i>	

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

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

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

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

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

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### 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@Lshmt.ac.uk](mailto:haltit.data@Lshmt.ac.uk)
- ❖ Send as a secure scanned document by email to [haltit.data@Lshmt.ac.uk](mailto:haltit.data@Lshmt.ac.uk) or upload a scanned copy at <http://ctu-files.Lshmt.ac.uk>.
- ❖ Fax to **020 7299 4663**
- ❖ Store original form in the Investigator's Study File Section 15.
- ❖ **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 5 Total number of randomisations by geographical region and treatment group

Geographical region	Treatment group (n)		Total (N)
	TXA	Placebo	
Africa	756	763	1519
Asia	2479	2474	4953
Europe, Australia and North America	2752	2772	5524
Caribbean, Central and South America	0	0	0
Oceania	7	6	13
Total	5994	6015	12,009



# Appendix 6 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	<i>first</i>	<i>last</i>	
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	<i>dd</i>	<i>mm</i>	<i>yyy</i>	
b) Time of death (24-hr clock)	<i>hours</i>	<i>minutes</i>		
c) Main cause of death (tick one option only)	<input type="checkbox"/> Haemorrhage <input type="checkbox"/> Malignancy			
	<input type="checkbox"/> Myocardial infarction <input type="checkbox"/> Pneumonia			
	<input type="checkbox"/> Stroke <input type="checkbox"/> Pulmonary embolism			
	<input type="checkbox"/> 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)	<i>dd</i>	<i>mm</i>	<i>yyy</i>	
b) Still in hospital at day 28? (Date)	<i>dd</i>	<i>mm</i>	<i>yyy</i>	

### 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
<input type="checkbox"/> Erosion or peptic ulcer	<input type="checkbox"/> Diverticular disease
<input type="checkbox"/> Varices	<input type="checkbox"/> Colitis
<input type="checkbox"/> Vascular lesion	<input type="checkbox"/> Vascular lesion
<input type="checkbox"/> Malignancy	<input type="checkbox"/> Malignancy
<input type="checkbox"/> Other/unknown	<input type="checkbox"/> Infection
	<input type="checkbox"/> 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)	<i>units</i>	
c) Frozen plasma (part unit = 1 unit)	<i>units</i>	
d) Platelets (part unit = 1 unit)	<i>units</i>	

### 9. MANAGEMENT (if none enter 0)

a) Days in Intensive Care Unit (ICU)	<i>days</i>
b) Days in High Dependency Unit (HDU)	<i>days</i>

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

a) Re-bleeding (up to point of outcome)	YES	NO
i) If yes, number of re-bleeding episodes		
ii) Date of episode 1	<i>dd</i>	<i>mm</i> / <i>yyy</i>
<i>Additional episodes to be recorded on reverse</i>		
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	<i>first name</i>	<i>family name</i>
b) Date of birth	<i>dd</i>	<i>mm</i> / <i>yyy</i>
c) Post code		
d) NHS number		

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

a) Name	<i>first name</i>	<i>last name</i>
b) Position		
c) Signature		
d) Date	<i>dd</i>	<i>mm</i> / <i>yyy</i>

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## 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		
2	dd	mm	yyyy
3	dd	mm	yyyy
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

**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@Lshmt.ac.uk](mailto:haltit.data@Lshmt.ac.uk)
- ❖ Send as a secure scanned document by email to [haltit.data@Lshmt.ac.uk](mailto:haltit.data@Lshmt.ac.uk) or upload a scanned copy at <http://ctu-files.Lshmt.ac.uk>.
- ❖ Fax to +44 20 7299 4663

**STORE THIS ORIGINAL FORM IN YOUR SITE FILE**



## Appendix 7 Adverse events between groups

Adverse event	TXA group	Placebo group	Total
Abdominal distension	0	1	1
Abdominal pain	2	3	5
Abscess	1	1	2
Acute confusion state	3	1	4
Acute enterocolitis	1	0	1
Adenocarcinoma	0	1	1
Alcohol intoxication	1	0	1
Alcoholic withdrawal symptoms	1	2	3
Allergic reaction	5	6	11
Anaemia	5	13	18
Angina pectoris	2	0	2
Angiodysplasia	1	0	1
Appendicitis	1	0	1
Arterioenteric fistula	1	0	1
Ascites	2	4	6
Aspiration	0	1	1
Atrial fibrillation	0	2	2
Bowel infarction	0	1	1
Bowel perforation	0	1	1
Brain lesion	0	1	1
COPD exacerbation	3	2	5
Calculus biliary	1	0	1
Cardiac arrest	0	1	1
Cardiac failure congestive	0	3	3
Cellulitis	3	4	7
Cerebral infarction	1	0	1
Chemotherapy NOS	0	2	2
Chest pain	2	2	4
Cholangiocarcinoma	0	1	1
Cholangitis	1	0	1
Cholecystitis	0	1	1
Chronic venous insufficiency	0	1	1
<i>Clostridium difficile</i> infection	2	6	8
Coagulopathy	1	0	1
Colorectal cancer	0	1	1
Conjunctivitis	1	0	1

## APPENDIX 7

Adverse event	TXA group	Placebo group	Total
Constipation	5	3	8
Contusion	1	0	1
Crohn's disease	0	1	1
Crystal arthropathy	0	1	1
Cyanosis	0	1	1
Deep-vein thrombosis	4	1	5
Dehydration	0	1	1
Delirium	1	2	3
Diarrhoea	3	2	5
Diverticular disease	3	1	4
Duodenal perforation	1	0	1
Dyspepsia	0	1	1
Embolus in foot	1	0	1
Encephalopathy	2	2	4
Enterocutaneous fistula	1	0	1
Epistaxis	1	1	2
Erythema	1	1	2
Fall	6	9	15
Febrile neutropenia	2	0	2
Fluid overload	1	1	2
Fluid retention	1	0	1
Fracture of unspecified intracapsular femur	0	1	1
Frailty	1	0	1
Gallbladder polyp	1	0	1
Gastric cancer	1	0	1
Gastric ulcer	1	0	1
Gastritis	1	4	5
Gastroenteritis	1	1	2
GI haemorrhage	66	80	146
Gout	3	1	4
Groin pain	1	0	1
Haematoma	1	0	1
Haematuria traumatic	0	1	1
Haemodilution	1	0	1
Haemorrhoids	2	2	4
Head injury	1	0	1
Heart failure	0	1	1
Hemicolectomy	0	1	1
Hepatic cirrhosis	6	3	9

Adverse event	TXA group	Placebo group	Total
Hepatic encephalopathy	0	1	1
Hepatitis	0	1	1
Hepatocellular carcinoma	0	1	1
Hepatorenal syndrome	1	0	1
Humerus fracture	0	1	1
Hydrocele	0	1	1
Hypernatraemia	0	1	1
Hypoglycaemia	2	2	4
Hypokalaemia	2	1	3
Hypomagnesaemia	1	0	1
Hyponatraemia	1	2	3
Hypotension	1	0	1
Hypoxia	0	1	1
Infected skin ulcer	0	1	1
International normalised ratio abnormal	1	0	1
Intestinal stoma leak	0	1	1
Ischaemic heart disease	0	1	1
Ischaemic hepatitis	0	1	1
Ischaemic stroke	3	3	6
Jaundice	0	1	1
Large bowel obstruction	1	0	1
Leg ischaemia	0	1	1
Liver abscess	0	1	1
Liver carcinoma ruptured	1	0	1
Liver cirrhosis	1	0	1
Lower respiratory tract infection	1	1	2
Lung cancer	1	0	1
Mallory-Weiss tear	0	1	1
Mastoid effusion	0	1	1
Meningioma	1	0	1
Multiorgan failure	2	0	2
Myocardial infarction	2	1	3
Nasogastric tube irritation	1	0	1
Necrotising otitis externa	0	1	1
Neuropathy peripheral	0	1	1
Obstructive jaundice	0	1	1
Oedema	1	3	4
Oesophageal cancer	1	1	2
Oesophageal candida	0	3	3

## APPENDIX 7

Adverse event	TXA group	Placebo group	Total
Oesophagitis	0	3	3
Overdose	1	1	2
Pain	1	0	1
Palpitations	1	0	1
Pancreatitis	1	0	1
Panic attack	1	0	1
Perforated gastric ulcer	1	0	1
Pericardial effusion	1	0	1
Peritonitis	4	0	4
Pharyngitis	1	0	1
Phlebitis	2	0	2
Pleural effusion	0	2	2
Pneumonia	9	3	12
Portal vein thrombosis	1	1	2
Postural hypotension	1	2	3
Pressure sore	1	1	2
Pulmonary embolism	3	3	6
Pulmonary haemorrhage	1	0	1
Pulmonary oedema	1	0	1
Pyelonephritis	0	1	1
Pyrexia	3	3	6
Rash	1	0	1
Refeeding syndrome	0	2	2
Renal failure	2	1	3
Respiratory infection	12	1	13
Seizure	3	1	4
Sepsis	6	7	13
Shingles	0	1	1
Shortness of breath	1	0	1
Small bowel obstruction	2	2	4
Staphylococcal bacteraemia	1	0	1
Stoma site bleeding	1	0	1
Suicidal ideation	0	1	1
Supraventricular tachycardia	0	1	1
Swollen lips	1	0	1
Syncope	1	1	2
Thoracic aneurysm, ruptured	0	1	1
Thrombocytopenia	1	1	2
Thrombosis	2	1	3

Adverse event	TXA group	Placebo group	Total
Transfusion reaction	0	1	1
Transient ischaemic attack	1	2	3
Type 2 diabetes mellitus	1	0	1
Upper GI haemorrhage	1	0	1
Urinary incontinence	0	1	1
Urinary retention	1	1	2
Urinary tract infection	12	12	24
Ventricular tachycardia	1	0	1
Vomiting	1	2	3
Total	273	281	554

COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified.



## Appendix 8 Dissemination plan

### Background

Gastrointestinal bleeding, from peptic ulcers, dilated gullet veins and cancer, is a common medical emergency that causes hundreds of thousands of deaths worldwide. Patients can either vomit blood or pass blood in the stools, and up to 10% of affected patients die. Some patients stop bleeding only to start bleeding again a short time later, and these patients have particularly high death rates. Treatment includes blood transfusion and emergency surgery to tie off the bleeding vessels.

Tranexamic acid reduces bleeding in surgery and reduces deaths from bleeding after serious injury and childbirth, in both cases without increasing side effects. TXA is licensed for the treatment of GI bleeding. Only a few small trials have looked at the effect of TXA in stomach bleeding but, when these trials were added together, there appeared to be a large reduction in deaths with TXA. For many doctors, this evidence was conclusive; indeed, many were so convinced that they refused to take part in the trial given that this would mean that half of their patients would receive a placebo. However, doctors at LSHTM were sceptical and decided to carry out a large international clinical trial.

### The HALT-IT trial

The HALT-IT trial is a randomised, blinded, placebo-controlled trial in 12,009 patients with severe GI bleeding. Patients were recruited from 164 hospitals across 15 countries. The aim was to assess the effects of TXA in patients with GI bleeding. The primary outcome was death due to bleeding within 5 days of randomisation.

### Objectives of dissemination

The results showed that TXA does not reduce deaths from stomach bleeding but increases the risk of thromboembolic events (clots in the veins of the legs that can move to the lungs). There were also more seizures with TXA. Rebleeding was similar in both groups.

Although it is often assumed that a treatment that works in one bleeding situation will probably work in another, these results highlight the need for clinical trials that target specific causes of bleeding. Stomach bleeding may respond differently, particularly in patients with underlying liver disease, who may be more prone to side effects from unwanted clotting.

Given that TXA is already in use for the treatment of GI bleeding, these results have the potential to change medical practice.

### *Help our collaborators to disseminate the results in their respective countries*

Dissemination tools will be developed that collaborators can use for national and international audiences. We need to upgrade our trial website and make sure that it hosts all of the trial dissemination materials that can be downloaded and used locally. Dissemination tools for collaborating investigators will be created so they can raise awareness about the trial results. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients in their countries.

## Specific outputs

1. Main publication of the trial results in *The Lancet* is expected on 20 June 2020.
2. Links to the publication will be made available in all applicable trial registers, the trial and CTU websites.
3. A PowerPoint presentation of the results will be prepared and made available for use by doctors and other health-care professionals.
4. Dissemination of results to patients will take place via the media and the trial website ([haltit.lshtm.ac.uk](http://haltit.lshtm.ac.uk)).
5. A lay result summary is being prepared for sharing with trial participants.
6. A social media strategy is being prepared. However, it is important to note that the trial results are being published during the COVID-19 pandemic and this may limit the impact of our dissemination plan.
7. Upgrade the trial website: make sure that it hosts trial-related materials that can be downloaded by investigators and others and used for dissemination.
8. A podcast with the breakdown of the trial results and interview with Professor Ian Roberts will be broadcasted at The Resus Room (@TheResusRoom).
9. Once all prespecified analyses are completed, totally anonymised data will be shared via the LSHTM CTU data-sharing platform at [freebird.lshtm.ac.uk](http://freebird.lshtm.ac.uk). This will allow for maximum utilisation of the data to improve patient care and advance medical knowledge. The trial protocol, statistical analysis plan and trial publications will be freely available online.





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