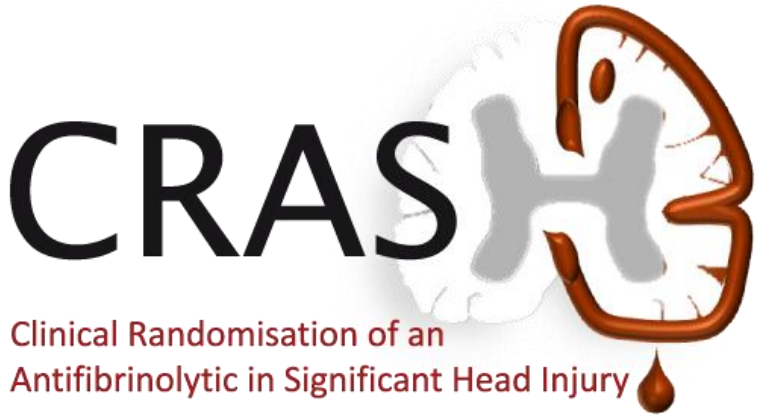

Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial

CLINICAL TRIAL PROTOCOL

Protocol Number: ISRCTN15088122

UNITED KINGDOM

	NUMBER	DATE
FINAL VERSION	1.0	1 October 2011
AMENDMENT (if any)	2.0	6 September 2016

SUMMARY

FULL TITLE OF STUDY:	Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial		
SHORT TITLE:	Clinical randomisation of an antifibrinolytic in significant head injury		
TRIAL ACRONYM:	CRASH-3		
PROTOCOL NUMBER:	ISRCTN15088122		
EUDRACT NUMBER:	2011-003669-14	**CLINICALTRIALS.GOV ID:**	NCT01402882

BACKGROUND: Worldwide, over 10 million people are killed or hospitalised because of traumatic brain injury (TBI) each year. About 90% of deaths from TBI occur in low and middle income countries. TBI mostly affects young adults and many experience long lasting or permanent disability. The social and economic burden of TBI is considerable. Tranexamic acid (TXA) is commonly given to surgical patients to reduce bleeding and the need for blood transfusion. TXA has been shown to reduce the number of patients receiving a blood transfusion by about a third, reduces the volume of blood transfused by about one unit, and halves the need for further surgery to control bleeding in elective surgical patients. The CRASH-2 trial showed that administration of TXA significantly reduces deaths due to bleeding (RR=0.85, 95% CI 0.76–0.96; p=0.008), and all-cause mortality (RR=0.91, 95% CI 0.85–0.97; p=0.0035) in trauma patients with significant extra cranial bleeding, with no increase in vascular occlusive events. A meta-analysis of randomised controlled trials of TXA in TBI showed a significant reduction in haemorrhage growth (RR=0.72; 95% CI 0.55–0.94) and mortality (RR=0.63; 95% CI 0.40–0.99) with TXA. Although the results from these trials are promising, the estimates are imprecise and there are no data on the effect of TXA on disability.

AIM: The CRASH-3 trial will provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with TBI. The effect of TXA on the risk of vascular occlusive events and seizures will also be assessed.

OUTCOME:

PRIMARY OUTCOME: The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause-specific mortality will also be recorded).

SECONDARY OUTCOMES:

(a) Vascular occlusive events (myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis)
(b) Stroke
(c) Disability assessed using the Disability Rating Scale and Patient Orientated Outcome measures
(d) Seizures
(e) Neurosurgical intervention
(f) Days in intensive care
(g) Other adverse events

TRIAL DESIGN: A pragmatic, randomised, double blind placebo controlled trial among 13,000 traumatic brain injury patients

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:

Adults with traumatic brain injury

- who are within eight hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury)
- with any intracranial bleeding on CT scan or who have a GCS of 12 or less, and
- who have no significant extra cranial bleeding (needing immediate blood transfusion)

The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use tranexamic acid in a particular patient with traumatic brain injury.

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: A loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation. A maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given after the loading dose is finished.

SETTING: This trial will be coordinated from the London School of Hygiene & Tropical Medicine (University of London, UK) and conducted worldwide in hospitals in low, middle and high income countries.

DURATION OF TREATMENT AND PARTICIPATION: The loading dose will be given as soon as possible after randomisation and the maintenance dose will be given immediately after the loading dose over 8 hours.

CRITERIA FOR EVALUATION: All patients randomly assigned to one of the treatments will be analysed together, regardless of whether or not they completed or received that treatment, on an intention to treat basis.

CLINICAL PHASE	3		
PLANNED TRIAL START	01 December 2011		
PLANNED DATE OF LAST PATIENT ENROLMENT	31 December 2017	**PLANNED DATE OF LAST OUTCOME**	31 January 2018

SUMMARY OF CHANGES BETWEEN VERSIONS 1.0 AND 2.0

ELIGIBILITY:

Although there is no change to the original eligibility criteria, for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury.

PRIMARY OUTCOME:

The primary outcome will include only patients randomised within 3 hours of injury. The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause-specific mortality will also be recorded).

SAMPLE SIZE

A study with 10,000 traumatic brain injury (TBI) patients randomised within 3 hours of injury would have about 90% power (two sided alpha=1%) to detect a 15% relative reduction (from 20% to 17%) in all-cause mortality. About three thousand patients have been recruited beyond three hours of injury already, therefore the total sample size would be approximately 13,000 patients.

STATISTICAL ANALYSIS:

We expect tranexamic acid (TXA) to be most effective when given soon after injury, when tissue plasminogen activator (TPA) levels are highest, and less effective when given several hours after injury when the risk of thrombotic DIC may be increased. We will examine this hypothesis by conducting a sub-group analysis of the effect of TXA according to the time interval between injury and TXA treatment (≤1, > 1 to ≤ 3, > 3 h). The outcome measure for this subgroup analysis will be death due to head injury.

RATIONALE FOR CHANGES:

New research highlights the importance of treatment in the first few hours after injury:

Since the start of the CRASH-3 trial, new research suggests that TXA is likely to be most effective in the first few hours after injury and less effective when given later. Trauma triggers the early release of TPA, the enzyme that converts plasminogen to the fibrinolytic enzyme plasmin, resulting in increased clot breakdown and bleeding.[1,2] TPA levels peak about 30 minutes after injury and plasmin peaks at one hour.[2] By inhibiting early fibrinolysis, TXA prevents coagulopathic bleeding.[3] However, the effects appear to be short lived. Around 2 hours after injury, plasminogen activator inhibitor (PAI-1) levels increase, reaching a peak at 3 hours.[2] PAI-1 inhibits fibrinolysis resulting in "fibrinolytic shutdown."[4] This might explain why the benefits of TXA in poly-trauma patients appear to be limited to the first three hours.[5] Because recent research shows that the coagulopathy after TBI is similar to that in poly-trauma, a similar time dependent effect might be expected after TBI.[6,7] To ensure that the CRASH-3 trial is large enough to reliably confirm or refute an early (<3 hours) treatment benefit, the sample size has been increased from 10,000 to 13,000 patients with the aim to enrol 10,000 patients within 3 hours of injury. In addition, the primary outcome has been amended to deaths among patients treated within 3 hours of injury. If the pathophysiological mechanisms affected by TXA are most relevant in the early hours after injury, the effect of TXA in this early period is the outcome of greatest importance. Nevertheless, intracranial bleeding can continue for up to 24 hours after injury and so examination of the effects of TXA within and beyond three hours remains an important scientific objective that will be addressed in pre-planned sub-group analyses.

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7. Abdelmalik PA, Boorman DW, Tracy J, Jallo J, Rincon F. Acute Traumatic Coagulopathy Accompanying Isolated Traumatic Brain Injury is Associated with Worse Long-Term Functional and Cognitive Outcomes. Neurocrit Care. 2015 Aug 21. [Epub ahead of print]

NON-SUBSTANTIAL CHANGES:

Membership of the trial Steering Committee has been updated: Dr Manjul Joshipura has left the World Health organisation and resigned from the TSC. He will not be replaced.

Funding: The following has been added to the protocol in Section 3.11: Full funding for the main trial is provided through a grant provided by the UK Department for International Development/Medical research Council/Wellcome Trust through the Joint Global Health Trials Scheme in low-middle income countries and by the National Institute for Health Research, Health Technology Assessment programme for the UK. Funding for recruitment in the European Union and North America is provided by the LSHTM.

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1 INTRODUCTION

Worldwide, over 10 million people are killed or hospitalised because of traumatic brain injury (TBI) each year.[1] Approximately 90% of deaths from TBI occur in low and middle income countries.[2] TBI predominantly affects young adults and many patients experience long lasting or permanent disability. The social and economic burden of TBI is considerable. With rapidly increasing motorisation, the incidence of TBI is predicted to rise in low and middle income countries.[3] An effective, widely practicable and affordable treatment for TBI could save many thousands of lives and substantially reduce the burden of disability. A summary of the relevant evidence to support the rationale for this study in each country is available in Appendix 4 of this Protocol.

The antifibrinolytic agent tranexamic acid (TXA) is commonly given to surgical patients to reduce bleeding and the need for blood transfusion. A systematic review of randomised trials of TXA in elective surgical patients shows that TXA reduces the number of patients receiving a blood transfusion by about a third, reduces the volume of blood transfused by about one unit, and halves the need for further surgery to control bleeding.[4] These differences are all highly statistically significant. Furthermore, there is no evidence of any increased risk of vascular occlusive events with TXA.[4]

More recently, TXA has been shown to reduce mortality in trauma patients with significant extra cranial bleeding. The CRASH-2 trial, which enrolled 20,211 bleeding trauma patients from hospitals in 40 countries, showed that the administration of TXA within 8 hours of injury significantly reduces deaths due to bleeding (RR=0.85, 95% CI 0.76–0.96; p=0.008), and all-cause mortality (RR=0.91, 95% CI 0.85–0.97; p=0.0035) compared to placebo, with no apparent increase in vascular occlusive events.[5] Among patients treated very soon after injury, the reduction in mortality with TXA is even greater.[6] Cost-effectiveness analysis has shown that the administration of TXA to bleeding trauma patients is highly cost effective in low, middle and high income settings.[7] As a consequence of the CRASH-2 trial results, TXA has been incorporated into trauma treatment protocols worldwide and has been included on the WHO List of Essential Medicines.

The knowledge that TXA reduces blood loss in surgery and reduces mortality in traumatic bleeding raises the possibility that it might also be effective in TBI. Intracranial haemorrhage is common after TBI and is associated with increased mortality and disability. In the MRC CRASH-1 trial, which included 10,008 TBI patients, 73% of patients with moderate or severe TBI had intracranial haemorrhage on CT scan.[8] Haemorrhage size is strongly associated with outcome. Patients with a large intracranial haemorrhage, whatever the location, have a substantially higher mortality than patients with a small haemorrhage.[9] In many TBI patients, the intracranial bleeding continues after hospital admission.[10,11] Among patients with moderate or severe TBI, who are found to have intracranial bleeding on a CT scan taken soon after hospital admission, intracranial bleeding progresses in 84% of patients.

Approximately one third of patients with TBI have laboratory evidence of abnormal coagulation at hospital admission.[12] These patients have an increased risk of intracranial haemorrhage and higher mortality. Increased fibrinolysis, as indicated by high levels of fibrinogen degradation products, is common in TBI and is a strong independent predictor of progressive intracranial haemorrhage.[13] These observations raise the possibility that TXA might reduce intracranial haemorrhage and improve patient outcomes in TBI patients.

In addition, it has been shown that progressive tissue damage and oedema develops in regions surrounding intracranial bleeding lesions, and is associated with worse outcome.[14] Tissue plasminogen activator (tPA)

has been shown to be an important factor in this process of peri-lesional oedema.[15–17] By blocking the conversion from plasminogen to plasmin, TXA counteracts the effect of tPA and therefore, it is possible that TXA might also be beneficial in traumatic intracerebral haemorrhage by decreasing peri-lesional oedema through a specific neuroprotective effect.

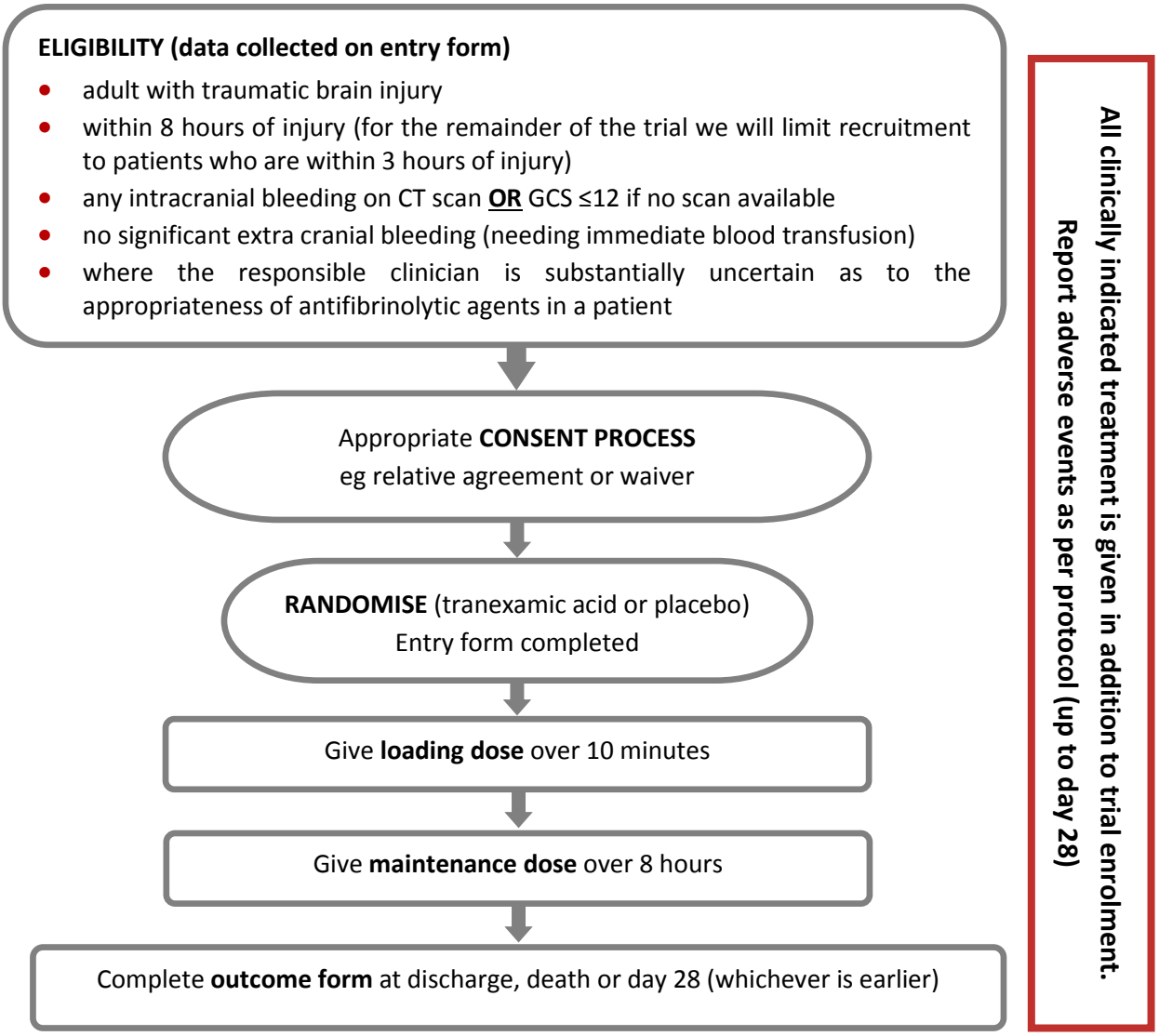
Two studies have evaluated the effect of TXA in traumatic brain injury. The CRASH-2 Intracranial Bleeding Study was a nested randomised trial conducted in 270 trauma patients who had evidence of TBI on a pre-randomisation CT scan. A second scan was conducted 24–48 hours after randomisation. There was a reduction in intracranial haemorrhage growth (RR=0.80; 95% CI 0.59–1.09), fewer ischaemic lesions and lower all-cause mortality (RR=0.60; 95% CI 0.32–1.11) in TXA allocated patients, but these results were not statistically significant.[18] A second randomised trial conducted in 240 patients with isolated TBI also found reductions in haemorrhage growth (RR=0.56; 95% CI 0.32–0.97) and mortality (RR=0.67; 95% CI 0.34–1.32) with TXA but this trial did not collect data on ischaemic lesions.[19] Meta-analysis of the two trials shows a significant reduction in haemorrhage growth (RR=0.72; 95% CI 0.55–0.94) and mortality (RR=0.63; 95% CI 0.40–0.99) with TXA.

Although the results from these trials are promising, the estimates are imprecise and there are no data on the effect of TXA on disability. Furthermore, because patients in the CRASH-2 Intracranial Bleeding Study also had significant extra cranial bleeding, the extent to which the results can be generalised to patients with isolated TBI is open to question. The CRASH-3 trial will provide reliable evidence about the effect of TXA on mortality and disability in patients with TBI. The effect of TXA on the risk of vascular occlusive events and seizures will also be assessed. If such a simple and widely practicable treatment was shown to improve outcomes in patients with TBI, then it could be used in high, middle and low income countries, saving many thousands of lives and reducing the burden of disability.

2 TRIAL DESIGN

2.1 OVERVIEW

FLOW CHART: STUDY OVERVIEW



The CRASH-3 trial is an international, multi-centre, pragmatic, randomised, double blind, placebo controlled trial to quantify the effects of the early administration (within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury) of tranexamic acid (TXA) on death and disability in TBI patients. A total of 13,000 adult TBI patients who fulfil the eligibility criteria will be randomised to receive either TXA or placebo.

Pragmatic design and the uncertainty principle: The pragmatic design will allow us to find out how effective the treatment actually is in routine everyday practice. Ethically, this randomised controlled trial can only be undertaken if there is collective scientific uncertainty about which of the interventions being compared is more likely to benefit patients.[20,21] However, for an individual clinician to be able to recommend enrolment of a patient into a trial, they must be substantially uncertain about the appropriateness of the trial treatment in that particular patient. The eligibility criteria for the CRASH-3 trial are based on this uncertainty principle. This approach to assessing trial eligibility is well established.[22]

A patient can be enrolled if, and only if, the responsible clinician is substantially uncertain as to which of the trial treatments would be most appropriate for that particular patient. A patient should not be enrolled if the responsible clinician or the patient (or his/her representative) are for any medical or non-medical reasons reasonably certain that one of the treatments that might be allocated would be inappropriate for this particular individual (in comparison with either no treatment or some other treatment that could be offered to the patient in or outside the trial). Using the uncertainty principle should allow the process of this trial to be closer to what is appropriate in normal medical practice.

Eligible patients: Adults with TBI who are within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury), with any intracranial bleeding on CT scan OR, if no scan is available, who have a GCS of 12 or less, and no significant extra cranial bleeding (ie not in need of immediate blood transfusion) are eligible, if the responsible clinician is substantially uncertain as to the appropriateness of TXA for them. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use TXA in a particular patient with TBI. This pragmatic approach will allow us to see whether the intervention improves patient outcomes under real-life conditions.

Although some increase in the risk of vascular occlusive events (arterial or venous thrombosis) might be expected with TXA on theoretical grounds, clinical trials in trauma patients have not found any increase.[4–6] In the CRASH-2 trial, in which 20,211 trauma patients were randomly assigned within 8 hours of injury to either TXA (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or placebo, there were fewer vascular occlusive events in patients allocated to receive TXA [168 (1.7%) TXA versus 201 (2.1%) placebo; RR=0.84; 95% CI 0.68–1.02].

Because TXA is eliminated by renal excretion there is a risk of accumulation in patients with renal impairment. However, because the CRASH-3 trial involves a very short course of TXA (a loading dose followed by an infusion over 8 hours) the risk of accumulation should be minimal.

Although high doses of TXA have been associated with seizures in patients undergoing cardiac surgery, there were no reports of serious unexpected adverse events involving seizures in the 20,211 trauma patients randomised into the CRASH-2 trial, half of whom received the dose of TXA that is being used in the CRASH-3 trial.[23]

Even though there are no absolute contraindications to TXA administration in patients with traumatic brain injury, patients with TBI should only be enrolled if their doctor is reasonably 'uncertain' as to whether or not to use TXA for that particular patient. The summary of product characteristics for TXA and an Investigator's Brochure will be provided to investigators to ensure that they have the information needed to assess the balance of harms and benefits in each patient.

Randomisation: Patients will receive all usual treatment for traumatic brain injury. Patients eligible for inclusion should be randomised and the study treatment started as soon as possible. The **Entry Form** (Appendix 1) will be used to assess eligibility and collect baseline information. The next consecutively numbered treatment pack, taken from a box of eight packs, should then be chosen. Once a patient has been randomised, outcome data need to be collected even if the trial treatment is interrupted or is not actually given.

Follow-up: No extra tests are required for the trial but an **Outcome Form** (Appendix 2) should be completed 28 days after randomisation or at death or hospital discharge if either happens sooner. Short

term disability will be assessed on the Outcome Form using the Disability Rating Scale (DRS). This scale measures the level of disability in six diagnostic categories of (1) eye opening, (2) best verbal response, (3) best motor response, (4) self-care ability for feeding, grooming and toileting, (5) level of cognitive functioning and (6) employability, and can be used across the span of recovery. The maximum score a patient can obtain is 29, which represents an extreme vegetative state. A person without disability would score zero.[24]

We will also assess specific patient orientated outcomes that have been identified by patients and their families as being important. They were identified from the literature and then considered and agreed by patient representatives from RoadPeace, the UK national charity for those killed or injured in road crashes.

CT scan study: Selected hospitals will be invited to take part in a CT scan study that will examine the effect of TXA on intracranial pathology in TBI patients. Full details of the CT scan study will be made available in a separate CT scan study protocol. Briefly, CT scans will be obtained before randomisation and up to 72 hours later. These scans will be uploaded for central reading by a radiologist who is blind to both treatment allocation and clinical findings. Data will be collected on the size of intra-parenchymal haemorrhages, haemorrhagic contusions, subdural epidural haematomas, subarachnoid haemorrhage, ischaemic lesions, and mass effect using validated rating scales based on previous work. The CT scan study will evaluate the effect of TXA on total haemorrhage growth (defined as the difference in the combined volume [mL] of all intracranial haemorrhagic lesions between the first and second scan). Outcomes will include i) significant haemorrhage growth (defined as an increase by 25% or more of total haemorrhage in relation to its initial volume); ii) new intracranial haemorrhage (apparent on the second scan but not apparent on the first); iii) mass effect and iv) new focal cerebral ischemic lesions (apparent on the second scan but not apparent on the first).

2.2 SETTINGS

Patients will be recruited from hospitals in high, middle and low income countries. There is no limit to the maximum number of patients to be recruited at each site.

2.3 NUMBER OF PATIENTS NEEDED

Two main factors determine the number of patients needed in a trial: the estimated event rate and size of the treatment effect. The primary end point for CRASH-3 is death in hospital within 28 days.

Estimated event rate: In the CRASH-1 trial, among patients with moderate or severe TBI (GCS of 12 or less), the risk of death in the control group was approximately 20%.

Sample size and size of treatment effect that should be detectable: A study with 10,000 TBI patients randomised within 3 hours of injury would have about 90% power (two sided alpha=1%) to detect a 15% relative reduction (from 20% to 17%) in all-cause mortality. About three thousand patients have been recruited beyond three hours of injury already, therefore the total sample size would be approximately 13,000 patients. With 10,000 patients, the study would also have over 90% power to detect a difference in mean Disability Rating Scale score of 1.0 (assuming a SD of DRS of 9.0). Experience from the CRASH-1 and CRASH-2 trials suggests that the anticipated rates of loss to follow-up (less than 1%) would not impact importantly on study power.

2.4 RECRUITMENT OF COLLABORATING INVESTIGATORS

The trial will recruit hospitals from many countries around the world and we will continue to add hospitals throughout the trial until the sample size is achieved. Suitable collaborating hospitals and investigators will be assessed in terms of the trauma service that they provide and their ability to conduct the trial. Before the trial can begin at any site, the local Principal Investigator must agree to adhere to Good Clinical Practice Guidelines and all relevant national regulations. In addition, all relevant regulatory and ethics approvals should be in place before the trial starts at a site.

2.5 ELIGIBILITY

Inclusion criteria: Adults with traumatic brain injury, who are within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury), and have any intracranial bleeding on CT scan, or if no CT scan is available who have a GCS of 12 or less, can be included if the responsible doctor is substantially uncertain as to whether or not to use TXA in that particular patient, and the appropriate consent procedures have been carried out. Patients with significant extra cranial bleeding (likely to need immediate blood transfusion) will be excluded since there is evidence that TXA improves outcome in these patients.[5] The summary of product characteristics for TXA and an Investigator's Brochure will be provided to investigators to ensure that they have the information needed to assess the balance of risks and benefits in each patient.

2.6 ETHICAL CONSIDERATIONS, INFORMATION GIVING AND WRITTEN INFORMED CONSENT

Ethical considerations: The Glasgow Coma Score (GCS) is a method of assessing the level of consciousness in TBI patients. Patients with a GCS score of 15 are generally considered fully conscious, but those with a GCS score of 12 or less are not fully conscious and would not be mentally capable of giving informed consent to participation in a clinical trial. Intracranial bleeding is a clinical sign indicating significant brain injury and patients with this diagnosis would not be physically or mentally capable of giving informed consent to participation in a clinical trial. Therefore, given that patients are eligible for inclusion in the CRASH-3 trial if they have sustained a traumatic brain injury and have either intracranial bleeding on a CT scan or a GCS of 12 or less, they will, by default, be physically or mentally incapable of giving consent.

Traumatic brain injury is an emergency condition that requires urgent treatment. Because intracranial bleeding occurs soon after injury, any treatment needs to be given as soon as possible. There is evidence from trials in traumatic extra cranial bleeding that TXA is more effective when given early.[25] The need for urgent treatment in the CRASH-3 trial means that the implementation of the research cannot be delayed and that it would be inappropriate to delay treatment until fully informed consent can be obtained from a relative or other legal representative. Patients who are incapable of giving consent in emergency situations are an established exception to the general rule of informed consent in clinical trials. This is clearly acknowledged in the Declaration of Helsinki.

"Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available if

the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative."

WMA Declaration of Helsinki 2008 – Ethical Principles for Medical Research Involving Human Subjects

The following procedure which is in accordance with the Declaration of Helsinki will be used for giving information and obtaining informed consent for the CRASH-3 trial.

Prior information giving: If relatives are present, bearing in mind the clinical situation and their level of distress, they will be provided with brief information about the trial. Specifically, the responsible doctor will explain to the relatives that the patient will receive the usual emergency treatments for traumatic brain injury but that in addition to these, the patient has been enrolled in a research study that aims to improve the treatment of patients with this condition. It will be explained that the study is being done to see whether using a drug called tranexamic acid will help patients with head injury by reducing the amount of bleeding into the brain therefore preventing further brain damage. The relative will be informed that the patient will be given an infusion into a vein over 8 hours of either the tranexamic acid or a dummy medicine (a liquid which does not contain tranexamic acid). The doctor will explain that tranexamic acid has been shown to improve outcome in patients with other types of severe injury and that whilst we hope that it will also improve recovery after head injury, at present we cannot be sure about this. Further information will only be provided on request. If requested, a brief information sheet will be provided (Appendix 3a). If relatives object to the inclusion of the patient in the trial, their views will be respected. If no relatives are present, two doctors (one independent of the trial) will consider the patient's eligibility criteria and any known views of the patient about trial participation. Together they will decide whether or not to enrol the patient into the trial.

Information giving and written informed consent: If and when patients regain the physical and mental capacity to give consent, information will be provided to them (Appendix 3c) and written informed consent will be sought for continuation in the trial (Appendix 3d). If a patient or representative declines to give consent for continuation at this stage, his/her wishes will be respected. For any patient who was included but did not regain full capacity, consent will be sought from a relative or other appropriate representative for continuation of the trial (Appendix 3d). The requirements of the relevant ethics committee will be adhered to at all times.

2.7 RANDOMISATION

Randomisation codes will be generated and secured by an independent statistical consultant from Sealed Envelope Ltd (UK). The codes will be made available to a GMP certified clinical trial supply company explicitly for the treatment packs to be created in accordance with the randomisation list. Eligibility will be determined from the routinely collected clinical information and no trial specific tests are required. Patients eligible for inclusion should be randomised to receive either TXA or placebo (sodium chloride 0.9%) and the trial treatment started as soon as possible.

Baseline information will be collected on the Entry Form (Appendix 1) and the next lowest consecutively numbered pack will be taken from a box of eight treatment packs. When the treatment ampoules are confirmed as being intact, the patient is considered to be randomised into the trial. The entry form data will be sent to the Trial Coordinating Centre as soon as possible after entry. Once a patient has been

randomised, the outcome of the patient should be obtained even if the trial treatment is interrupted or is not actually given.

2.8 TRIAL TREATMENT

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

DOSE SELECTION

TXA has been used to reduce bleeding in elective surgery for many years. A systematic review of randomised trials of tranexamic acid in surgery shows that dose regimens of TXA vary widely.[4] Loading doses range from 2.5 mg/kg to 100 mg/kg and maintenance doses from 0.25 mg/kg/h to 4 mg/kg/h delivered over periods of one to twelve hours. Studies examining the impact of different doses of TXA on bleeding and transfusion requirements showed no significant difference between a high dose and a low dose.[4,26]

In emergency situations, the administration of a fixed dose is more practicable because weighing patients in such situations is difficult. In the CRASH-3 trial, a fixed dose of 1 gram loading dose of TXA, followed by a 1 gram maintenance dose over 8 hours has been selected. This fixed dose is within the dose range which has been shown to inhibit fibrinolysis and provide haemostatic benefit. It should be efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg), as the estimated dose/kg that the latter group would receive has been used in other trials without adverse effects. Furthermore, this fixed dose was used in 20,211 patients enrolled in the CRASH-2 trial and was found to be both effective and safe. The same fixed dose was also used in two studies of TXA in TBI patients, again with no evidence of adverse effects.

DRUG MANUFACTURE, BLINDING AND SUPPLY OF TRIAL TREATMENT

The active trial drug tranexamic acid (Cyklokapron® Injection) will be purchased on the open market. TXA is manufactured by Pfizer Ltd under Marketing Authorisation Number PL00032/0314. The Marketing Authorisation guarantees that the product has been manufactured and released in accordance with the United Kingdom's Good Manufacturing Regulations.

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

Ampoules and packaging will be identical in appearance. The blinding process and first stage Qualified Person (QP) release will be done by the designated clinical trial supply company. The blinding process will involve complete removal of the original manufacturer's label and replacement with the clinical trial label bearing the randomisation number which will be used as the pack identification. Other pack label text will be identical for both TXA and placebo treatments and will be in compliance with requirements for investigational medicinal products.

The designated clinical trial supply company will also be responsible for maintaining the Product Specification File (PSF) until final database lock and unblinding of the trial data. Quality control checks to assure the blinding process will be performed on a random sample of final QP released drug packs. High Performance Liquid Chromatography (HPLC) analyses, separation of known tranexamic acid, will be

assessed against blinded samples to confirm which ampoule contains the placebo and active treatments. The tested samples will be unblinded to assure accuracy of blinding.

The Trial Coordinating Centre (TCC) will be responsible for assuring all relevant approvals are available at the TCC before release of the trial treatment to a site. A separate Manual of Operating Procedures will detail the drug accountability system. The Investigator's Brochure will detail labelling of the trial treatment and other processes for assuring adherence to Good Manufacturing Practice.

ADMINISTRATION OF TRIAL TREATMENT

Each treatment pack will contain:
4 x 500mg ampoules of tranexamic acid or placebo
2 x sterile 10mL syringes and 21FG needles
Labels (for attaching to data forms and patient medical records)
In addition, 100mL bags of sodium chloride 0.9% for administration of the loading dose will be provided by the TCC.

Treatment	Ampoules	Dose (TXA or placebo)	Infusion rate and duration
Loading	2	1 gram	Added to 100 mL sodium chloride 0.9% and infused over 10 minutes
Maintenance	2	1 gram	Added to 500 mL of any isotonic intravenous solution and infused at 120 mg/hr [60 mL/hr] for about 8 hours
The trial treatment injections should not be mixed with blood for transfusion, or infusion solutions containing penicillin or mannitol.			

The loading dose of the trial treatment must be administered by intravenous infusion immediately after randomisation. The maintenance dose (by intravenous infusion) should commence as soon as the loading dose is completed.

2.9 OTHER TREATMENTS FOR TBI

There is a wide spectrum of treatments for TBI. As the trial will be conducted worldwide, each participating site should follow its own clinical guidelines for the treatment of TBI patients. There is no need to withhold any clinically indicated treatment in this trial. TXA or placebo would be provided as an additional treatment to the usual management of TBI.

2.10 ADVERSE EVENTS (AE)

TXA has a well documented safety profile. Although the Summary of Product Characteristics suggests that rare cases of thromboembolic events might be associated with TXA administration, there is no evidence that the TXA treatment regime used in this trial is associated with an increased risk of vascular occlusive events. Nevertheless, data on vascular occlusive events and seizures will be collected as secondary outcomes and will be presented to the independent Data Monitoring Committee (DMC) for unblinded review.

DEFINITIONS

Adverse event (AE): Any untoward medical occurrence affecting a trial participant during the course of a clinical trial

Serious Adverse Event (SAE): A serious adverse event (experience) is any untoward medical occurrence that

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation; or
- results in persistent or significant disability/incapacity

Adverse Reaction (AR): An adverse event when there is at least a possibility that it is causally linked to a trial drug or intervention

Serious Adverse Reaction (SAR): SAE that is thought to be causally linked to a trial drug or intervention

Suspected Unexpected Serious Adverse Reaction (SUSAR): An *unexpected* occurrence of a SAR; there need only be an index of suspicion that the event is a previously unreported reaction to a trial drug or a previously reported but exaggerated or unexpectedly frequent adverse drug reaction.

REPORTING OF ADVERSE EVENTS FOR THIS TRIAL

Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes to be reported in this trial and also to the independent DMC. This clinical trial is being conducted in a critical emergency condition using a drug in common use. It is important to consider the natural history of the critical medical event affecting each patient enrolled, the expected complications of this event, and the relevance of the complications to TXA.

Adverse events to be reported using an adverse event reporting form will be limited to those NOT already listed as primary or secondary outcomes, but which might reasonably occur as a consequence of the trial drug. Events that are part of the natural history of the primary event of TBI or expected complications of TBI should not be reported as adverse events.

If an SAE, SAR or SUSAR occurs, a written report must be submitted within 24 hours. Advice for investigators on reporting of adverse events is available by calling the TCC Emergency Helpline. The TCC will coordinate the reporting of all SAEs/SARs/SUSARs to all relevant Regulatory Agencies, Ethics Committees and local investigators as per local legal requirements.

2.11 UNBLINDING

In general there should be no need to unblind the allocated treatment. If some contraindication to TXA develops after randomisation, eg clinical evidence of thrombosis, the trial treatment should simply be stopped and all usual standard care given. Unblinding should be done only in those rare cases when the clinician believes that clinical management depends importantly upon knowledge of whether the patient received TXA or placebo. In those few cases when urgent unblinding is considered necessary, a 24-hour telephone service will be available and details provided in the Investigator's Study File and wall posters. The caller will be told whether the patient received TXA or placebo. An unblinding report form should be completed by the investigator and sent to the Trial Coordinating Centre within one working day.

2.12 MEASURES OF OUTCOME

After a patient has been randomised, outcome in hospital will be collected even if the trial treatment is interrupted or is not actually given. No extra tests are required but a short Outcome Form (Appendix 2) will be completed 28 days after randomisation, or at prior death or discharge from the randomising hospital.

Primary Outcome: The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause-specific mortality will also be recorded).

Secondary outcomes:

(a) Vascular occlusive events [myocardial infarction (MI), pulmonary embolism (PE), clinical evidence of deep vein thrombosis (DVT)]
(b) Stroke
(c) Disability assessed using the Disability Rating Scale and Patient Orientated Outcome measures
(d) Seizures
(e) Neurosurgical intervention
(f) Days in intensive care
(g) Other adverse events will be described

Cost-effectiveness analysis: A cost-utility analysis performed from a health care perspective will be conducted. Although the constraints of a large pragmatic trial reduce the scope for a comprehensive economic evaluation, the precise estimates of treatment effects from such studies are an important advantage. Data from the CRASH-3 trial will be used to populate a decision analytic model. The assessment of incremental cost-effectiveness requires an estimate of health care costs and QALYs with and without administration of TXA. The incremental cost will be estimated using the data available at 28 days or discharge on ICU days, non-ICU days and health care interventions. If there are any significant differences in vascular events (PE, DVT, MI), stroke, or operative intervention, these can be used to refine the estimate of difference in cost. Life years gained will be modeled using the data on death or discharge in the first 28 days. Initially, it will be assumed that patients at discharge and those in hospital at 28 days have the life expectancy of their age-gender group. However, it will be important to explore alternative assumptions. Any significant differences in complications between the two treatment groups could be used to improve the estimate. Although CRASH-3 will not collect quality of life data directly, the detailed classification of the patient's condition at discharge or 28 days can be used as the basis for a quality of life adjustment. Separate estimates of the incremental cost effectiveness ratio will be produced for the sub-groups identified in the trial protocol. Some of the uncertainty surrounding the estimated cost-effectiveness will be examined using deterministic and probabilistic sensitivity analysis.

2.13 DATA COLLECTION AND MANAGEMENT

This trial will be coordinated from the Trial Coordinating Centre (TCC) at LSHTM and conducted in hospitals in low, middle and high income countries. Data will be collected at each site by local investigators and sent to the TCC. Only data outlined on the entry, outcome, unblinding report and adverse event forms will be collected in this trial.

The **entry form** (Appendix 1) will be used before randomisation to confirm eligibility and collect baseline data. The **outcome form** (Appendix 2) will be completed 28 days after randomisation or at prior death or hospital discharge. These data will be collected from the patient's routine medical records and no special tests will be required.

If a patient or their representative withdraws a previously given informed consent or refuses to consent for continuation in the trial, or if the patient dies and no consent is available, the patient's data will be handled as follows:

- Data collected up to the point of withdrawal will be used in an intention to treat analysis.
- All data on adverse events, including those routinely collected as outcomes, will be collected and reported as required by the relevant authorities.

To allow for variation in available technology for data transfer, a variety of data collection methods will be used in the trial. Data will be collected by the investigator on paper case report forms (CRFs) and transmitted to the TCC either by fax or email or by entering the data directly into the trial database. Original paper CRFs will remain at each trial site. The data will be used in accordance with local law and ethics committee approval.

2.14 MONITORING

GCP section 5.18.3 states in regard to monitoring that, *"the determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."*

The CRASH-3 trial is a large, pragmatic, randomised double blind placebo controlled trial. The intervention (tranexamic acid) has marketing authorisation in many countries and has been in clinical use for decades. Its safety profile is well established and no significant serious adverse events associated with its use have been identified. The trial will routinely collect data on adverse events which may theoretically be associated with this product and the condition under investigation, and these will be reviewed by the independent Data Monitoring Committee (DMC). The trial procedures are based on routine clinical procedures and include (1) the intravenous administration of the trial drug using routine clinical use; (2) collecting routine clinical information from the medical records; and (3) informed consent. There are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in this research study has been assessed as low in each of these categories. Based on the low risks associated with this trial, the Monitoring Procedure to assure appropriate conduct of the trial will utilise 100% central data monitoring in conjunction with procedures such as investigator training and meetings and written guidance. In addition, all data will be subject to statistical monitoring and approximately 10% of data will be subjected to on-site monitoring. Consent Forms will be monitored centrally by the TCC (where permission is given to do so). Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial related and source documents must be kept for at least five years after the end of the trial.

2.15 END OF TRIAL FOR PARTICIPANTS

For the recruited patients the trial ends at death, hospital discharge or at 28 days follow-up, whichever occurs first. If during the treatment phase a patient develops an adverse event, the trial drug should be stopped, the patient should be treated in line with local procedures, and then followed up. The trial may be terminated early by the Trial Steering Committee (TSC). The independent Data Monitoring Committee may give advice/recommendation for the early termination of the trial but the TSC is responsible for the final decision.

2.16 ANALYSIS

The main analyses will compare all those allocated TXA versus those allocated placebo, on an 'intention to treat' basis, irrespective of whether they received the allocated treatment or not. Results will be presented as appropriate effect estimates (relative risks and absolute risks) with a measure of precision (95% confidence intervals). We expect TXA to be most effective when given soon after injury, when tissue plasminogen activator levels are highest, and less effective when given several hours after injury, when the risk of thrombotic DIC may be increased. We will examine this hypothesis by conducting a sub-group analysis of the effect of TXA according to the time interval between injury and TXA treatment (≤1, > 1 to ≤ 3, > 3 h). The outcome measure for this subgroup analysis will be death due to head injury. Subgroup analyses for the primary outcome will also include the severity of TBI (moderate or severe), the location of the intracranial bleeding, and baseline risk. Interaction tests will be used to test whether the effect of treatment (if any) differs across these subgroups. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$) the overall relative risk will be considered as the most reliable guide to the approximate relative risks in all subgroups. Between-sites heterogeneity in effectiveness will also be explored. A secondary analysis will be conducted in which the primary outcome will be adjusted by age, pupil reactivity, blood pressure and Glasgow Coma Score. All analyses will be conducted in STATA. Because all secondary outcomes are non fatal, the effect of TXA on these outcomes could be affected by competing risk by death. We will tackle this potential problem using the principal stratification method for studies with censoring due to death as proposed by Rubin.[27] A detailed Statistical Analysis Plan setting out full details of the proposed analyses will be finalised before the trial database is locked for final analysis.

3 TRIAL ORGANISATION AND RESPONSIBILITIES

3.1 SPONSORSHIP AND TRIAL MANAGEMENT GROUP

The CRASH-3 trial is sponsored by the London School of Hygiene & Tropical Medicine (LSHTM) and its responsibilities coordinated by the Trial Coordinating Centre (TCC). The TCC may delegate responsibilities to third parties which will be outlined in relevant agreements. The responsibilities of the TCC will be overseen by the Trial Management Group (TMG).

3.2 INDEMNITY

LSHTM accepts responsibility attached to its sponsorship of the trial and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this trial. The indemnity is renewed on an annual basis and LSHTM assures that it will continue renewal of the indemnity for the duration of this trial.

3.3 PROTOCOL COMMITTEE

The Protocol Committee consists of the following investigators who are responsible for the development of, and agreeing to, the final protocol. Subsequent changes to the final Protocol will require the agreement of the Trial Steering Committee.

CHIEF INVESTIGATOR	CLINICAL EXPERTS
Ian Roberts (Professor) Clinical Trials Unit, LSHTM London, UK	Yashbir Dewan (Professor) Head of Division of Neurosurgery FLT Lt Rajan Dhall Fortis Hospital New Delhi, India
TRIAL MANAGEMENT	Jorge H Mejía-Mantilla (Dr) Departamento de Anestesia y Reanimación Fundación Valle del Lili Cali, Colombia
Haleema Shakur (Senior Lecturer) Clinical Trials Unit, LSHTM London, UK	Edward O Komolafe (Dr) Obafemi Awolowo University Teaching Hospitals Ife-Ife, Nigeria
STATISTICIAN	Pablo Perel (Dr) Clinical Trials Unit, LSHTM London, UK
Phil Edwards (Senior Lecturer) Clinical Trials Unit, LSHTM London, UK	

3.4 INDEPENDENT DATA MONITORING COMMITTEE (DMC)

MEMBERSHIP

NAME	AFFILIATION	EXPERTISE
Prof Samuel C Ohaegbulam	Memfys Hospital for Neurosurgery, Nigeria	Neurosurgery
Prof Anthony Rodgers	George Institute, Australia	Clinical Trials
Prof Mike Clarke	University of Belfast, UK	Epidemiology and statistics

To provide protection for study participants, an independent DMC has been appointed for this trial to oversee the safety monitoring. The DMC will review on a regular basis accumulating data from the ongoing trial and advise the Trial Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial.

The DMC composition, name, title and address of the chairman and of each member, will be given in the DMC Charter which will be in line with that proposed by the DAMOCLES Study Group (DAMOCLES Study Group 2005). Membership includes expertise in the relevant field of study, statistics and research study design. An independent statistician will be appointed to provide the analysis service required by the DMC. The DMC Charter includes, but is not limited to, defining:

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

STANDARD OPERATING PROCEDURES

The DMC has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup), should be revealed to the TSC. The DMC Charter states that they will do this if, and only if, the following two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of, participants in terms of the major outcome; and (2) the results, if revealed, would be expected to substantially change the prescribing patterns of clinicians who are already familiar with any other trial results that exist. Exact criteria for “proof beyond reasonable doubt” are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. The DMC Charter is in agreement with the Peto-Haybittle stopping rule whereby an interim analysis of a major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure (Haybittle 1971; Peto 1977). An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgment.

3.5 TRIAL STEERING COMMITTEE

MEMBERSHIP

NAME	AFFILIATION	EXPERTISE
Peter Sandercock (Chair)	Western General Hospital Director, Edinburgh Neuroscience, University of Edinburgh, UK	Professor of Medical Neurology; randomised control trials; conduct of large scale international trials
HB Hartzenberg	Tygerberg Academic Hospital Faculty of Health Sciences, University of Stellenbosch, South Africa	Professor and Head of Neurosurgery; previous President of the Society of Neurosurgeons of South Africa
Amy Aeron-Thomas	Executive Director, RoadPeace the national charity for road crash victims, London, UK	Expertise includes developing national road safety action plans, costing crashes and documenting their socio-economic impact on families. Road safety pilot project in Nigeria, intended to improve compensation for road crash victims and increase awareness of the road traffic injury burden.
Ian Roberts	London School of Hygiene & Tropical Medicine, London, UK	Professor of Epidemiology; randomised control trials; conduct of large scale international trials
Pablo Perel	London School of Hygiene & Tropical Medicine, London, UK	Clinical Lecturer; randomised control trials; trial methodology
Haleema Shakur	London School of Hygiene & Tropical Medicine, London, UK	Senior Lecturer; trial methodology; randomised control trials; conduct of large scale international trials

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC must be in agreement with the final Protocol and, throughout the trial, will take responsibility for:

(a) major decisions such as a need to change the protocol for any reason
(b) monitoring and supervising the progress of the trial
(c) reviewing relevant information from other sources
(d) considering recommendations from the DMC
(e) informing and advising the Trial Management Group (TMG) on all aspects of the trial

The TSC consists of people with experience in clinical trials, traumatic brain injury research and patient representatives. Face to face meetings will be held at regular intervals determined by need, but no less than once a year. A TSC Charter will be agreed at the first meeting and will detail how the committee will conduct its business.

When outcome data are available for 500 trial participants, the TSC will review the rate of recruitment into the trial and the overall event rates. The TSC will consider the extent to which the rate of recruitment and the event rates correspond to those anticipated before the trial and will take whatever action is needed in light of this information.

3.6 ADVISORY COMMITTEES

An ad hoc advisory group was established at the Protocol development stage of the CRASH-3 trial with the responsibility of ensuring the Protocol was appropriate to populations in a wide variety of settings. Clinicians and clinical trialists (including neurosurgeons and other trauma specialists) from United Kingdom, Colombia, India and Nigeria were consulted during face to face meetings in each country and their input was incorporated in the final Protocol. A list of those involved in this advisory group is available on the trial website (http://crash3.Lshtm.ac.uk/).

In addition, an International Advisory Committee (IAC) will be convened to fulfil two roles:

(a) to advise the TMG on matters relevant to the trial, and
(b) to enable appropriate representation of each country's views on the trial.

The role of the IAC is advisory only. The IAC will constitute the National Coordinators from participating countries and other individuals with relevant expertise. The IAC will be chaired by Chair of the TMG. New members will be added as new countries join the trial and National Coordinators are appointed.

The IAC will provide advice and comments to the TMG. The TMG will inform the TSC accordingly on matters raised by the IAC that relate either to the protocol or which might have an impact on the progress of the trial. The TMG will convey any relevant comments from the IAC to the TCC on matters relating to the day to day management of the trial. An important function of the IAC is to facilitate the sharing of experience and best practice between its members on how best to conduct the trial efficiently within each country and how to overcome barriers to progress. The IAC's chief role is therefore to report on the progress of the trial within each country and to provide advice to the TMG, TSC and TCC in order to maximise the efficiency of the trial's conduct, and hence the chances of completing the trial on time and within budget.

3.7 COLLABORATORS' RESPONSIBILITIES

Coordination within each participating hospital will be through a local Principal Investigator whose responsibility will be detailed in an agreement in advance of starting the trial and will include:

- Ensure all necessary approvals are in place prior to starting the trial
- Delegate trial related responsibilities only to suitably trained and qualified personnel
- Train relevant medical and nursing staff who see traumatic brain injury patients and ensure that they remain aware of the state of the current knowledge, the trial and its procedures (there are wall charts, pocket summaries and training presentations to assist with this)
- Agree to comply with the final trial protocol and any relevant amendments
- Ensure that all patients with traumatic brain injury are considered promptly for the trial
- Ensure consent is obtained in line with local approved procedures
- Ensure that the patient entry and outcome data are completed and transmitted to the TCC in a timely manner
- Ensure the Investigator's Study File is up to date and complete
- Ensure all Adverse Events are reported promptly to the TCC
- Be accountable for trial treatments at their site
- Ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements

- Allow access to source data for monitoring, audit and inspection
- Be responsible for archiving all original trial documents including the data forms, for five years after the end of the trial

3.8 TRIAL MANAGEMENT GROUP (TMG) / TRIAL COORDINATING CENTRE (TCC) RESPONSIBILITIES

The TMG will consist of at least the following members: Chief Investigator, a trial manager and a clinical expert. The TCC will act on behalf of the Sponsor and will be responsible to the TMG to ensure that all Sponsor's responsibilities are carried out. The responsibilities will include (but are not limited to):

- Reporting to the Trial Steering Committee
- The day to day management of the trial
- Ensuring that all relevant procedures for the conduct of the trial are in place
- Advising the TCC staff on specific aspects as required
- Maintaining the Trial Master File
- Identifying trial sites
- Confirming all approvals are in place before release of trial treatment and the start of the trial at a site
- Providing training about the trial
- Providing study materials
- Acting as the data management centre
- Providing a 24-hour advice and unblinding service
- Giving collaborators regular information about the progress of the study
- Responding to questions (eg from collaborators) about the trial
- Ensuring data security and quality and observe data protection laws
- Safety reporting
- Ensuring the trial is conducted in accordance with the ICH GCP
- Statistical analysis
- Publication of trial results

3.9 CONTACTING THE TCC IN AN EMERGENCY

For urgent enquiries, adverse event reporting and unblinding queries, investigators can contact the 24-hour telephone service provided by the TCC. A central telephone number is given in the Investigator's Study File and posters.

3.10 PUBLICATION AND DISSEMINATION OF RESULTS

All efforts will be made to ensure that the trial protocol and results arising from the CRASH-3 trial are published in an established peer-reviewed journal. At least one publication of the main trial results will be made. All publications will follow relevant external guidance such as the *'Uniform Requirements for Submission of Manuscripts to Biomedical Journals'* issued by the International Committee of Medical Journal Editors (ICMJE) (2008 update) and the CONSORT statement (Moher 2001). Links to the publication will be provided in all applicable trial registers. Dissemination of results to patients will take place via the media, trial website (http://crash3.Lshtm.ac.uk) and relevant patient organisations. In addition, participants and their families will be made aware of the trial results if requested. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients. The success of the trial will be dependent

entirely upon the collaboration of the nurses and doctors in the participating hospitals and those who hold key responsibility for the trial. Hence, the credit for the study will be assigned to the key collaborator(s) from each participating site, as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to trial collaborators. As a large number of hospitals in many countries will contribute to this trial, individual countries or sites cannot restrict the publication of the manuscript relating to the outcomes of this trial. Anonymised data for this trial will be made available for free use at http://freebird.lshtm.ac.uk.

3.11 FINANCIAL SUPPORT

The JP Moulton Charitable Trust, United Kingdom is funding the run-in costs for this trial and up to 500 patients' recruitment. Full funding for the main trial is provided through joint funding by the UK Department for International Development/Medical research Council/Wellcome Trust through the Joint Global Health Trials Scheme (Grant number MR/M009211/1) in low-middle income countries and by the National Institute for Health Research, Health Technology Assessment programme for the UK (Grant number14/190/01). Funding for recruitment in the European Union and North America is provided by the LSHTM. Funding for this trial covers meetings and central organisational costs only. The design and management of the study are entirely independent of the manufacturers of tranexamic acid or the funders.

Large trials of drugs such as TXA, involving many hospitals, are important for future patients, but are practicable only if those collaborating in them do so without payment (except for recompense of any minor local costs that may arise). Agreement for repayment of local costs will be made in advance. This trial will not generate any intellectual property for the Sponsor or collaborating institutions. This trial plans to include over 250 hospitals in about 40 countries. Review by each Ethics Committee and Regulatory Agencies would create a substantial financial burden which could limit the conduct of the trial. We request that payment for review of the Protocol by each Committee be waived or set at a reasonable rate to reflect the actual cost of reviewing the trial Protocol.

4 ABBREVIATIONS USED

AE	Adverse Event
AR	Adverse Reaction
CONSORT	CONsolidated Standards of Reporting Trials
CRF	Case Report Form
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
FG	French Gauge
GCP	Good Clinical Practice
HPLC	High Performance Liquid Chromatography
IAC	International Advisory Committee
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
ICMJE	International Committee for Medical Journal Editors
kg	Kilogram
LSHTM	London School of Hygiene & Tropical Medicine
mg	Milligram
MI	Myocardial Infarction
mL	Millilitre
PE	Pulmonary Embolism
PeR	Personal Representative
PrR	Professional Representative
PSF	Product Specification File
QP	Qualified person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Trial Coordinating Centre
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic Acid
UK	United Kingdom

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6 APPENDICES

Appendix 1: Entry form

Appendix 2: Outcome form

Appendix 3: Country/site specific documents

- Brief information for family (example text)
- Consent procedure overview
- Information sheet for patient and his/her representative
- Informed consent form for patient/representative

Appendix 4: Country specific rationale for study and other relevant protocol information

APPENDIX 1 – ENTRY FORM (PAGE 1)

CRASH-3
Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

ENTRY FORM

PLEASE COMPLETE 1-16 BEFORE RANDOMISING THE PATIENT

ABOUT YOUR HOSPITAL *(please ensure all information below is contained in the medical records)*

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

ABOUT THE PATIENT

3. Patient's initials *(first name/last name)*			**4.** Patient hospital ID		
5. Age *(years – approximate if unknown)*			**6.** Sex *(circle)*	**MALE**	**FEMALE**

ABOUT THE INJURY AND PATIENT'S CONDITION

7.	Time since injury *(insert hours)*		*Best estimate from history*			
8.	Systolic Blood Pressure		*mmHg (most recent measurement prior to randomisation)*			
9.	Glasgow Coma Score (GCS) *(circle one response for each category)* *First measurement in hospital of GCS (if unknown give value at randomisation)*	**9A–EYE OPENING** 4 SPONTANEOUS 3 TO SOUND 2 TO PAIN 1 NONE		**9B–MOTOR RESPONSE** 6 OBEYS COMMANDS 5 LOCALISING 4 NORMAL FLEXION 3 ABNORMAL FLEXION 2 EXTENDING 1 NONE	**9C–VERBAL RESPONSE** 5 ORIENTATED 4 CONFUSED SPEECH 3 WORDS 2 SOUNDS 1 NONE	*IF GCS MORE THAN 12 AND NO CT SCAN AVAILABLE – **DO NOT RANDOMISE*** *IF GCS MORE THAN 12, CT SCAN **IS** AVAILABLE AND INTRACRANIAL BLEEDING=YES – **RANDOMISE***
10.	This GCS is *(circle one)*	**BEFORE**	**AFTER**	intubation/sedation		
11.	Pupil reaction	**BOTH REACT**		**ONE REACTS**	**NONE REACT**	**UNABLE TO ASSESS**
12.	Any significant extracranial bleeding?	**YES**	**NO**	*Patients with extracranial trauma who are likely to need an early blood transfusion in the view of the attending doctor after taking into account mechanism of injury, findings from secondary survey, physiology and response to fluid infusion – **DO NOT RANDOMISE***		
13.	Any intracranial bleeding on CT scan (before randomisation)? *(circle one)*	**YES**	**NO**	**NO CT SCAN AVAILABLE**	*IF CT SCAN AVAILABLE AND INTRACRANIAL BLEEDING=NO – **DO NOT RANDOMISE***	
14.	Location of intracranial haemorrhage on CT Scan *(circle one response for each line)*					
	a) Epidural	**YES**	**NO**			
	b) Subdural	**YES**	**NO**			
	c) Subarachnoid	**YES**	**NO**			
	d) Parenchymal	**YES**	**NO**			
	e) Intraventricular	**YES**	**NO**			

RANDOMISATION INFORMATION

Eligible if adult, with TBI, no significant extracranial bleeding, within 8h of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury) (GCS=12 or less, or any intracranial haemorrhage on CT scan)

15. Eligible? *(circle)*	**YES**	*Get the lowest available number treatment pack and follow instructions*			**NO**	*Do not randomise, record on screening log*	
16. Consent process for entry used? *(circle)*	**WAIVER**			**OTHER REPRESENTATIVE**		**RELATIVE**	
17. Insert treatment pack number here	**BOX**					**PACK**	
18. Date of randomisation	*day*	*month*	*year*	**19.** Time of randomisation *(24-hour clock)*		*hours*	*minutes*
20. Name of person randomising				**21.** Signature			

SEE GUIDANCE OVERLEAF

Protocol Code: ISRCTN15088122 Page 1 of 2 Entry Form v 2.0 dated 28 September 2016

APPENDIX 1 – ENTRY FORM (PAGE 2)

DATA FORMS GUIDANCE

AFTER COMPLETING THIS PAPER FORM PLEASE SEND THE DATA BY ANY METHOD LISTED:

- Enter these data directly into the trial database (username and password required)
- Upload as a secure scanned document (see Study File for details)
- Fax to +44 20 7299 4663

PLEASE STORE THE ORIGINAL FORM IN THE INVESTIGATOR'S STUDY FILE

PLEASE GIVE A COPY OF THIS COMPLETED FORM TO THE PERSON RESPONSIBLE FOR COMPLETING THE OUTCOME FORM AT YOUR HOSPITAL.

FOR UNBLINDING, ADVICE ON SERIOUS ADVERSE EVENT REPORTING AND OTHER URGENT ENQUIRIES PLEASE TELEPHONE +44(0)7768 707500

APPENDIX 2 – OUTCOME FORM (PAGE 1)

OUTCOME FORM

COMPLETE AT DISCHARGE FROM THE RANDOMISING HOSPITAL, DEATH IN HOSPITAL OR 28 DAYS AFTER INJURY, WHICHEVER OCCURS FIRST

Attach here a sticker from the lid of the treatment pack or write box/pack number below: ____ / ____

1. HOSPITAL (Hospital code)

2. PATIENT a) BOX | b) PACK | c) INITIALS

3. OUTCOME

3.1 DEATH IN HOSPITAL

a) Date of death (DAY (DD) / MONTH (MM) / YEAR (YYYY)) | b) Time of death (HOUR (HH) / MIN (MM))

c) Primary Cause of death *(tick one option)*

- ☐ Head injury
- ☐ Bleeding
- ☐ Pulmonary embolism
- ☐ Stroke
- ☐ Myocardial Infarction
- ☐ Multi organ failure
- ☐ Other/describe here (only one)_____

3.2 PATIENT ALIVE

a) Still in this hospital now *(28 days after randomisation)* – Date (DAY (DD) / MONTH (MM) / YEAR (YYYY))

b) Discharged to another hospital – Date of discharge (DAY (DD) / MONTH (MM) / YEAR (YYYY))

c) Discharged home – Date of discharge (DAY (DD) / MONTH (MM) / YEAR (YYYY))

3.3 IF ALIVE – DISABILITY RATING SCALE *(tick one response for each box) – see overleaf for guidance*

a) EYE OPENING	b) COMMUNICATION ABILITY	c) MOTOR RESPONSE	d) FEEDING *(cognitive ability only)*	e) TOILETING *(cognitive ability only)*
☐ Spontaneous	☐ Oriented	☐ Obeying	☐ Complete	☐ Complete
☐ To Speech	☐ Confused	☐ Localizing	☐ Partial	☐ Partial
☐ To Pain	☐ Inappropriate	☐ Withdrawing	☐ Minimal	☐ Minimal
☐ None	☐ Incomprehensible	☐ Flexing	☐ None	☐ None
	☐ None	☐ Extending		
		☐ None		

f) GROOMING *(cognitive ability only)*	g) LEVEL OF FUNCTIONING *(physical, mental, emotional or social function)*	h. "EMPLOYABILITY" *(as a full time worker, homemaker, or student)*
☐ Complete	☐ Completely independent	☐ Not restricted
☐ Partial	☐ Independent in special environment	☐ Selected jobs, competitive
☐ Minimal	☐ Mildly dependent – limited assistance	☐ Sheltered workshop, non-competitive
☐ None	☐ Moderately dependent – moderate assistance	☐ Not employable
	☐ Markedly dependent – assist all major activities, all times	
	☐ Totally dependent – 24-hour nursing care	

3.4 IF ALIVE: *Assessed by doctor/nurse/relative based on their knowledge of the patient, or patient if able (tick one response for each box)*

SEE GUIDANCE OVERLEAF

a) WALKING	b) WASHING / DRESSING	c) PAIN / DISCOMFORT	d) ANXIETY / DEPRESSION	e) AGITATION / AGGRESSION	f) FATIGUE
☐ No problems	☐ No problems	☐ None	☐ None	☐ None	☐ None
☐ Some problems	☐ Some problems	☐ Moderate	☐ Moderate	☐ Moderate	☐ Moderate
☐ Confined to bed	☐ Unable	☐ Extreme	☐ Extreme	☐ Extreme	☐ Extreme

4. MANAGEMENT

a) DAYS IN INTENSIVE CARE UNIT *(if no ICU or not admitted to ICU, write '0' here)*	
b) TYPE OF NEUROSURGICAL OPERATION	
i) Haematoma evacuation	YES / NO
ii) Other	YES / NO
c) BLOOD LOSS DURING NEUROSURGICAL OPERATION	
Estimated Volume (ml)	

5. TRIAL TREATMENT

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

6. COMPLICATIONS

(circle one option on every line)

Pulmonary embolism	YES	NO
Deep vein thrombosis	YES	NO
Stroke	YES	NO
Myocardial infarction	YES	NO
Renal failure	YES	NO
Sepsis	YES	NO
Seizure	YES	NO
Gastro intestinal bleeding	YES	NO

7. OTHER COMPLICATIONS

YES / NO

IF YES, REPORT AS PER PROTOCOL USING ADVERSE EVENT FORM

8. PERSON COMPLETING FORM

THE PRINCIPAL INVESTIGATOR IS RESPONSIBLE FOR ALL DATA SUBMITTED

a) Name		b) Position	
c) Signature		d) Date	

Protocol Code: ISRCTN15088122 — Outcome form version 1.0 dated 1 October 2011

APPENDIX 2 – OUTCOME FORM (PAGE 2)

GUIDANCE – HOW TO COMPLETE THE DISABILITY RATING SCALE, QUESTION 3.3 OVERLEAF

A. EYE OPENING

0–SPONTANEOUS: eyes open with sleep/wake rhythms indicating active arousal mechanisms, does not assume awareness

1–TO SPEECH AND/OR SENSORY STIMULATION: response to any verbal approach, spoken/shouted, not necessarily the command to open the eyes. Also response to touch, mild pressure

2–TO PAIN: tested by a painful stimulus

3–NONE: no eye opening even to painful stimulation

B. COMMUNICATION ABILITY

0–ORIENTED: implies awareness of self and the environment. Patient able to tell you a) who he is; b) where s/he is; c) why he is there; d) year; e) season; f) month; g) day; h) time of day

1–CONFUSED: attention can be held and patient responds to questions but responses are delayed and/or indicate varying degrees of disorientation and confusion

2–INAPPROPRIATE: intelligible articulation but speech is used only in an exclamatory or random way (such as shouting and swearing); no sustained communication exchange is possible

3–INCOMPREHENSIBLE: moaning, groaning or sounds without recognizable words, no consistent communication signs

4–NONE: no sounds or communications signs from patient

C. MOTOR RESPONSE

0–OBEYING: obeying command to move finger on best side. If no response or not suitable try another command such as "move lips," "blink eyes," etc. Do not include grasp or other reflex responses

1–LOCALIZING: a painful stimulus at more than one site causes limb to move (even slightly) in an attempt to remove it. It is a deliberate motor act to move away from or remove the source of noxious stimulation. If there is doubt as to whether withdrawal or localization has occurred after 3 or 4 painful stimulations, rate as localization

2–WITHDRAWING: any generalized movement away from a noxious stimulus that is more than a simple reflex response

3–FLEXING: painful stimulation results in either flexion at the elbow, rapid withdrawal with abduction of the shoulder or a slow withdrawal with adduction of the shoulder. If there is confusion between flexing and withdrawing, then use pinprick on hands

4–EXTENDING: painful stimulation results in extension of the limb

5–NONE: no response can be elicited. Usually associated with hypotonia. Exclude spinal transection as an explanation of lack of response; be satisfied that an adequate stimulus has been applied

D.FEEDING, E.TOILETING, F.GROOMING (COGNITIVE ABILITY ONLY FOR EACH)

Does the patient show awareness of how and when to perform this activity? Ignore motor disabilities that interfere with carrying out this function (rated under Level of Functioning below.)

- Rate best response for toileting based on bowel and bladder behavior
- Grooming refers to bathing, washing, brushing of teeth, shaving, combing or brushing of hair and dressing

0–COMPLETE: continuously shows awareness that he knows how to feed and can convey unambiguous information that he knows when this activity should occur

1–PARTIAL: intermittently shows awareness that he knows how to carry out this activity and/or can intermittently convey reasonably clearly information that he knows when the activity should occur

2–MINIMAL: shows questionable or infrequent awareness that he knows in a primitive way how to carry out this activity and/or shows infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur

3–NONE: shows virtually no awareness at any time that he knows how to carry out this activity and cannot convey information by signs, sounds, or activity that he knows when the activity should occur

G.LEVEL OF FUNCTIONING (PHYSICAL, MENTAL, EMOTIONAL OR SOCIAL FUNCTION)

0–COMPLETELY INDEPENDENT: able to live as he wishes, requiring no restriction due to physical, mental, emotional or social problems

1–INDEPENDENT IN SPECIAL ENVIRONMENT: capable of functioning independently when needed requirements are met (mechanical aids)

2–MILDLY DEPENDENT: able to care for most of own needs but requires limited assistance due to physical, cognitive and/or emotional problems (e.g., needs non-resident helper)

3–MODERATELY DEPENDENT: able to care for self partially but needs another person at all times (person in home)

4–MARKEDLY DEPENDENT: needs help with all major activities and the assistance of another person at all times

5–TOTALLY DEPENDENT: not able to assist in own care and requires 24-hour nursing care

H.'EMPLOYABILITY'(AS A FULL TIME WORKER, HOMEMAKER, OR STUDENT)

0–NOT RESTRICTED: can compete in the open market for a relatively wide range of jobs commensurate with existing skills; or can initiate, plan execute and assume responsibilities associated with homemaking; or can understand and carry out most age relevant school assignments

1–SELECTED JOBS, COMPETITIVE: can compete in a limited job market for a relatively narrow range of jobs because of limitations of the type described above and/or because of some physical limitations; or can initiate, plan, execute and assume many but not all responsibilities associated with homemaking; or can understand and carry out many but not all school assignments

2–SHELTERED WORKSHOP, NON-COMPETITIVE: cannot compete successfully in a job market because of limitations described above and/or because of moderate or severe physical limitations; or cannot without major assistance initiate, plan, execute and assume responsibilities for homemaking; or cannot understand and carry out even relatively simple school assignments without assistance

3–NOT EMPLOYABLE: completely unemployable because of extreme psychosocial limitations of the type described above, or completely unable to initiate, plan, execute and assume any responsibilities associated with homemaking; or cannot understand or carry out any school assignments

GUIDANCE – HOW TO COMPLETE THE ASSESSMENT IN QUESTION 3.4 OVERLEAF

To indicate which statement best describes the patient's status on discharge or day 28 (if still in hospital), place a tick ✓ in one box in each group. **Do not tick more than one box in each group.**

APPENDIX 3A – BRIEF INFORMATION FOR FAMILY

BRIEF INFORMATION FOR THE PATIENT'S FAMILY
THE CRASH-3 TRIAL

Tranexamic acid for the treatment of significant traumatic brain injury;
an international randomised, double blind placebo controlled trial

Your relative has a head injury that needs urgent care. He/she will get all the usual emergency care for head injury that we provide at this hospital. As well as this, we would like to include him/her in an international study. This study will see whether a drug called tranexamic acid reduces bleeding inside the head after head injury. We hope that the drug will lead to a better recovery. We know that the drug reduces bleeding in other types of severe injury and without side effects, but as yet we don't know if it works in head injury.

As part of the study, your relative will receive an injection into a vein followed by a drip over eight hours. Half the patients in the study will get the tranexamic acid and half a dummy drug (a liquid which does not contain tranexamic acid). We will not know until the end of the study who received which treatment. We will need to collect some information about your relative'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 happy for us to go ahead with the study treatment?

Yes, I am happy for you to go ahead.

Name: _____

Signature: _____

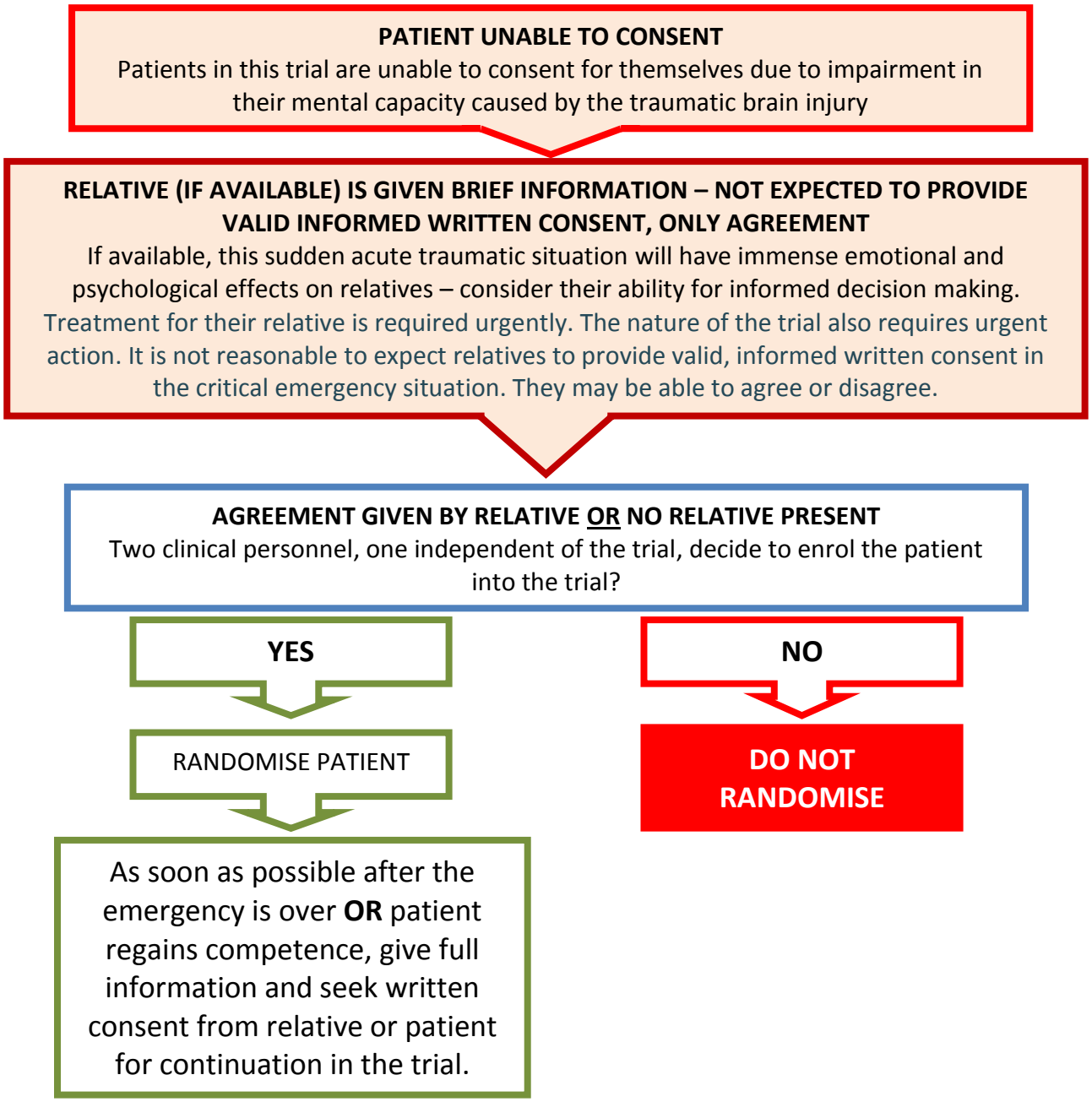
Relationship to Patient: _____

Date: _____

Complete only where required. ***PLEASE NOTE:*** *This is not a consent form; please consider Waiver of Consent.*

CRASH-3 trial – Brief information leaflet v 1.0, 1 October 2011

APPENDIX 3B – CONSENT PROCEDURE OVERVIEW



APPENDIX 3C – INFORMATION SHEET FOR PATIENT AND REPRESENTATIVE (PAGE 1)

[HOSPITAL CONTACT DETAILS]

INFORMATION FOR REPRESENTATIVES AND PATIENTS
THE CRASH-3 TRIAL

Trial title	Tranexamic acid for the treatment of significant traumatic brain injury; an international randomised, double blind placebo controlled trial
Trial site number	
Leaflet version	Version number 1.2; Version date 06/09/2016

This hospital is taking part in an international study to find better treatments for head injury.
(One of the following two options apply to you)

(1) **As a patient representative:** This leaflet gives information about the study to help you to make a decision on the patient's behalf.

(2) **As the patient:** After your head injury, you got all the usual emergency care for head injury that we provide at this hospital. The decision was also taken for you to be part of an international study to find better treatments for head injury. Because of your injury you could not make this decision yourself but now that your condition has improved, we would like to tell you about the study and ask whether you want to stay part of it.

Before you decide, it is important that you know why the study is being done and what it involves. Please read the information below and ask as many questions as you like before deciding. This leaflet explains why we are doing the study and outlines the benefits and risks of taking part. The Doctor or Nurse will be happy to talk to you about the study and answer any questions.

1) What is the purpose of this study?

In this hospital, patients with head injury are given the usual emergency treatments. The aim of this study is to find a better treatment to improve recovery. We hope that the study treatment (tranexamic acid) will prevent or reduce bleeding into the head after head injury and so lead to better outcomes. In general, there are no medical reasons why tranexamic acid should not be given to patients with head injury but if the doctor felt that it was not suitable in your particular case they would not include you (the patient) in the study. We hope that the treatment will do more good than harm but we don't yet know this.

2) Why have you/the patient been chosen to take part?

This study is being done to see if a drug called tranexamic acid improves outcome after head injury. You (the patient) have been included because you suffered a serious head injury which could cause bleeding into the brain. You (the patient) are one of about 13,000 patients with head injury from all around the world taking part in this study.

APPENDIX 3C – INFORMATION SHEET FOR PATIENT AND REPRESENTATIVE (PAGE 2)

3) A patient cannot be in this study if:

- the doctor thinks there is a particular reason why tranexamic acid definitely **should not** be given
- the doctor thinks there is a particular reason why tranexamic acid definitely **should** be given
- he/she is not an adult
- he/she was injured more than 8 hours before arriving at the hospital

4) What does taking part in this study involve?

All the usual emergency treatments for head injury are given. We do not know whether giving tranexamic acid on top of all the other treatments will help or not, so half the patients in the study will get tranexamic acid and the other half will get a placebo (dummy treatment). The treatment will be/was given over a period of eight hours. The choice of what to give (active treatment or dummy treatment) is made randomly (like a lottery), and you/the patient will have an equal chance of receiving either one. The doctors looking after you/the patient do not know whether you/the patient received tranexamic acid or the dummy medicine. You/the patient will not need to undergo any extra tests or spend any extra time in hospital as a result of taking part in this study. The study treatment is free.

5) What are the possible risks of being in the study?

Tranexamic acid is not a new drug. It has been used for years to reduce bleeding after operations and more recently to treat other types of serious injury. It works by stopping the breakdown of the blood clots which are needed to control bleeding. Studies have shown that it does not cause unwanted clotting and there are no serious side effects with short term use. However, the doctor will monitor you/the patient closely and will report to the study organisers if there are any unexpected problems.

6) What are the possible benefits of being in the study?

We hope that tranexamic acid will help reduce bleeding into the head after head injury, which is a common cause of death and disability after head injury. The knowledge that we gain from this study will help people with similar injuries in the future.

7) What if I don't want to be a part of this study anymore?

You can always withdraw from the study at any time. You just need to say for example *"I've decided I don't want to be in this study now"*. We hope that you will let us use information about how you/the patient got on, but if you do not want us to use it please tell the doctor.

8) Will the information you collect be kept private?

All information about you/the patient and the injury will be kept private. The only people allowed to look at the information will be the doctors running the study and the staff at the Trial Coordinating Centre at LSHTM (University of London) and the regulatory authorities who check that the study is being carried out correctly. Your doctor will send brief details about you/the patient to the Trial Coordinating Centre at LSHTM. Personal information will be used in strict confidence by the people working on the study and will not be released under any circumstance. We will publish the results of the study in a medical journal so that other doctors can benefit from the knowledge, but your/the patient's personal information will not be included and there will be no way that you/the patient can be identified. The study data will be made freely available to researchers worldwide so that it can be used to advance medical knowledge and improve patient care. However, no personal information will be included and it will not be possible to identify individuals.

The Trial Coordinating Centre may want to collect or copy some trial documents which will have your name and will include the signed Consent Form. This will help them to ensure that the trial is being carried out correctly.

APPENDIX 3C – INFORMATION SHEET FOR PATIENT AND REPRESENTATIVE (PAGE 3)

9) Who can you/the patient contact about any questions or problems?

If you have any questions or concerns about any aspect of this study, you should ask to speak with the study doctors who will do their best to answer your questions. Dr [insert name] is in charge of this study at this hospital. You can contact the doctor at:

Address	
Telephone	

If you remain unhappy and would rather complain formally, you can do this through the NHS complaints procedure. Contact details can be obtained from the hospital. Participation in this study does not affect your normal rights to complain about any aspect of your treatment and care.

This study is co-ordinated by doctors and a trial team at the London School of Hygiene & Tropical Medicine (LSHTM) at the University of London.

10) Who has reviewed the study?

To protect your interests, all research in the NHS is looked at by an independent group of people called a Research Ethics Committee. This study has been reviewed and given favourable ethical opinion by the NRES Committee East of England – Essex Research Ethics Committee.

11) What happens afterwards?

We would like to hear if you/the patient develop(s) any medical problems after discharge from this hospital and at any time up to 28 days. You will be given a card with the contact details of the doctor who is responsible for the study at this hospital, which should be kept in a safe place and presented to anyone who may be treating you/the patient for any illness.

If you would like to have a summary of the results of this study, please let the doctor treating you know and s/he will ensure you receive a copy. You may also visit the trial website to keep up to date with the progress of the trial: **crash3.Lshtm.ac.uk**

12) What else do you need to know?

- The study is organised by the University of London and funded by public and charitable funds, not the makers of tranexamic acid.
- In the event that something does go wrong and you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation. The London School of Hygiene & Tropical Medicine who are organising the study would be responsible for claims for any non-negligent harm suffered as a result of participating in this study. The NHS will be liable for clinical negligence and other negligent harm as a result of the clinical procedure being undertaken. You may have to pay your legal costs.
- We will ask you to sign a separate consent form and give you a copy to keep and you can also keep this information sheet.

APPENDIX 3D – INFORMED CONSENT FORM FOR PATIENT AND REPRESENTATIVE

CRASH-3 TRIAL CONSENT FORM

[HOSPITAL CONTACT DETAILS]

CONSENT FORM FOR PATIENT AND REPRESENTATIVE
THE CRASH-3 TRIAL

Title of Research: Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial

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

Version Number: 1.2 / Version Date: 06/09/2016

1. I confirm that I have read and understood the information sheet Version Number 1.2, version date 06/09/2016, for the above study and have had the opportunity to ask questions. ☐
2. I understand that my consent is voluntary and that I am free to withdraw this consent at any time, without giving any reason and without my/the patient's medical care or any legal rights being affected. ☐
3. I understand that sections of my/the patient's medical notes may be looked at by responsible individuals involved in the study. I give permission for these individuals to have access to these records. ☐
4. I give permission for a copy of this consent form, which contains my/the patient's personal information, to be made available to the Trial Coordinating Centre in London for monitoring purposes only. ☐
5. I give permission for the data collected about me in this trial (with my personal information removed) to be used by researchers worldwide. ☐
6. I agree to me/the patient taking part in the above study, the CRASH-3 trial. ☐

Name of Patient/Representative	Date	Signature (thumbprint or other mark if unable to sign)
Name of person taking consent	Date	Signature
Name of site Principal Investigator	Date	Signature

The patient/representative is unable to sign. As a witness, I confirm that all the information about the trial was given and the patient/representative consented to taking part.

Name of witness	Date	Signature

Original to be filed in the Investigator's Study File; 1 copy for patient; 1 copy to be kept with patient's hospital records

APPENDIX 4 – COUNTRY SPECIFIC RATIONALE FOR STUDY AND OTHER RELEVANT PROTOCOL INFORMATION: UNITED KINGDOM

Public health relevance: Injury is the leading cause of death and disability in young adults in the United Kingdom. Among trauma patients who survive to reach hospital, traumatic brain injury is a common cause of death. Annually there are approximately 1,000,000 TBI patients attending emergency departments; of these over 150,000 are admitted to hospitals with an average cost of £15,000 per hospitalisation.

Minimum age considered as adult for recruitment: 16 years

Local organisation: The trial will be organised centrally by the Trial Coordinating Centre at LSHTM.

References:

Kay A, Teasdale G. Head injury in the United Kingdom. World Journal of Surgery 2001; 25: 1210–20.

Morris, S., Ridley, S., Lecky, F. E., Munro, V. and Christensen, M. C. Determinants of hospital costs associated with traumatic brain injury in England and Wales. Anaesthesia 2008, 63: 499–508.