

CRASH₂

Clinical Randomisation of an
Antifibrinolytic in Significant Haemorrhage 

PROTOCOL EU

A large randomised placebo controlled trial among trauma patients with or at risk of significant haemorrhage, of the effects of antifibrinolytic treatment on death and transfusion requirement

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CRASH2

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage



A LARGE RANDOMISED PLACEBO CONTROLLED TRIAL AMONG TRAUMA PATIENTS WITH OR AT RISK OF SIGNIFICANT HAEMORRHAGE, OF THE EFFECTS OF ANTIFIBRINOLYTIC TREATMENT ON DEATH AND TRANSFUSION REQUIREMENT

1. Background

Introduction: For people at ages 5 to 45 years, trauma is second only to HIV/AIDS as a cause of death. Each year, worldwide, about three million people die as a result of trauma, many after reaching hospital.¹ Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths.² Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding.³

Mechanisms: The haemostatic system helps to maintain the integrity of the circulatory system after severe vascular injury, whether traumatic or surgical in origin.⁴ Major surgery and trauma trigger similar haemostatic responses and the consequent massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma, in any patient, is stimulation of clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) in some.⁴ Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparently increasing the risk of post-operative complications, most notably there is no increased risk of venous thromboembolism.⁵

Existing knowledge: Systemic antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and thus reduce surgical blood loss. A recent systematic review⁶ of randomised controlled trials of antifibrinolytic agents (mainly aprotinin or tranexamic acid) in elective surgical patients identified 89 trials including 8,580 randomised patients (74 trials in cardiac, eight in orthopaedic, four in liver, and three in vascular surgery). The results showed that these treatments reduced the numbers needing transfusion by one third, reduced the volume needed per transfusion by one unit, and halved the need for further surgery to control bleeding. These differences were all highly

statistically significant. There was also a statistically non-significant reduction in the risk of death (RR=0.85: 95% CI 0.63 to 1.14) in the antifibrinolytic treated group.

Hypothesis: Because the coagulation abnormalities that occur after injury are similar to those after surgery, it is possible that antifibrinolytic agents might also reduce blood loss, the need for transfusion and mortality following trauma. However, to date there has been only one small randomised controlled trial (70 randomised patients, drug versus placebo: 0 versus 3 deaths) of the effect of antifibrinolytic agents in major trauma.⁷ As a result, there is insufficient evidence to either support or refute a clinically important treatment effect. Systemic antifibrinolytic agents have been used in the management of eye injuries where there is some evidence that they reduce the rate of secondary haemorrhage.⁸

Need for a trial: A simple and widely practicable treatment that reduces blood loss following trauma might prevent thousands of premature trauma deaths each year and secondly could reduce exposure to the risks of blood transfusion. Blood is a scarce and expensive resource and major concerns remain about the risk of transfusion-transmitted infection. Trauma is common in parts of the world where the safety of blood transfusion is not assured. A recent study in Uganda estimated the population-attributable fraction of HIV acquisition as a result of blood transfusion to be around 2%, although some estimates are much higher.^{9,10} Only 43% of the 191 WHO member states test blood for HIV and hepatitis C and B viruses. Every year unsafe transfusion and injection practices are estimated to account for 8–16 million Hepatitis B infections, 2.3–4.7 million Hepatitis C infections and 80,000–160,000 HIV infections.¹¹ A large randomised trial is therefore needed of the use of a simple, inexpensive, widely practicable antifibrinolytic treatment such as tranexamic acid (aprotinin is considerably more expensive and is a bovine product with consequent risk of allergic reaction and hypothetically transmission of disease), in a wide range of trauma patients who, when they reach hospital are thought to be at risk of major haemorrhage that could significantly affect their chances of survival.

DOSE SELECTION

The systematic review of randomised controlled trials of antifibrinolytic agents in surgery showed that dose regimens of tranexamic acid vary widely.⁶ Loading doses range from 2.5mg/kg to 100 mg/kg and maintenance doses from 0.25 mg/kg/hr to 4 mg/kg/hr delivered over time periods of one to twelve hours. Studies examining the impact of different doses of tranexamic acid on bleeding

and transfusion requirements showed no significant difference between a high dose and a low dose.

Studies in cardiac surgery have shown that a 10 mg/kg initial dose of tranexamic acid followed by an infusion of 1 mg/kg/hour produces plasma concentrations sufficient to inhibit fibrinolysis in vitro.¹² The dose–response relationship of tranexamic acid was examined by Horrow et al (1995) who concluded that 10 mg/kg followed by 1 mg/kg/hour decreases bleeding after extracorporeal circulation and that larger doses did not provide any additional haemostatic benefit.¹³

In this emergency situation, administration of a fixed dose would be more practicable as determining the weight of a patient would be impossible. Therefore a fixed dose within the dose range which has been shown to inhibit fibrinolysis and provide haemostatic benefit is being used for this trial. The fixed dose chosen would be efficacious for larger patients (>100 kgs) but also safe in smaller patients (<50 kgs), as the estimated dose/kg the latter group would receive has been applied in other trials without adverse effects. The planned duration of administration allows for the full effect of tranexamic acid on the immediate risk of haemorrhage without extending too far into the acute phase response seen after surgery and trauma.

2. Study design

SUMMARY

CRASH 2 is a large pragmatic randomised placebo controlled trial of the effects of the early administration of the antifibrinolytic agent tranexamic acid on death, vascular events and transfusion requirements. Adults with trauma who are within 8 hours of injury and have either significant haemorrhage, or who are considered to be at risk of significant haemorrhage, are eligible if the responsible doctor is for any reason substantially uncertain whether or not to use an antifibrinolytic agent. Numbered drug or placebo packs will be available in each participating emergency department. Randomisation will involve calling a 24-hour freecall randomisation service. The call should last only a minute or two and at the end of it the randomisation service will specify which numbered treatment pack to use. For hospitals where telephone randomisation is not feasible, randomisation will be by taking the next consecutively numbered treatment pack. No extra tests are required but a short form must be completed one month later or on discharge or on death (whichever occurs first).

NUMBER OF PATIENTS NEEDED

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

Estimated event rate: In the Medical Research Council (MRC) CRASH trial of corticosteroids in head injury, the overall risk of death was 20%.¹⁴ The MRC CRASH trial was the largest international randomised controlled trial in trauma patients and it would be reasonable to expect a similar risk of death in CRASH 2.

Size of treatment effect that should be detectable: Because even a 2% survival advantage for an intervention as simple and widely practicable as tranexamic acid would represent a worthwhile benefit, the current trial has been planned to be able to detect a benefit of this size.

Sample size: If the real mortality difference is 20% versus 18% then there is about an 85% chance that a trial involving 20,000 patients will achieve $2P < 0.01$ (and a 95% chance that it will achieve $2P < 0.05$). If however, the trial were only half as big then there would be a 50% chance of failing to achieve $2P < 0.01$ (and a 28% chance of failing to achieve $2p < 0.05$), which is not good enough.

Effects on other outcomes: With such large numbers randomised, even moderate effects on the numbers needing transfusion or on the mean volume per transfusion will be determined very accurately, as will any substantial effects on non-fatal vascular events (haemorrhagic or occlusive).

ELIGIBILITY

- *Adult trauma patients with ongoing significant haemorrhage or at risk of significant haemorrhage, within 8 hours of injury, except those for whom antifibrinolytic agents are thought to be clearly indicated or clearly contra-indicated.*

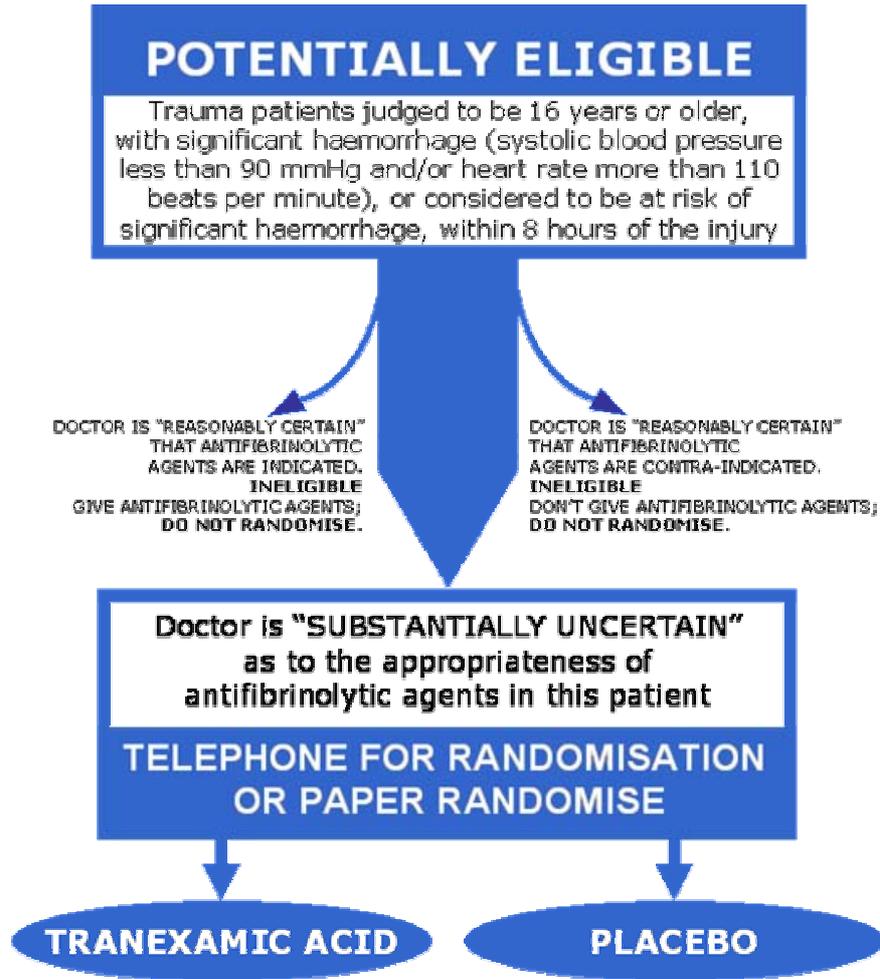
Inclusion criteria: All trauma patients with ongoing significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or who are considered to be at risk of significant haemorrhage, and are within 8 hours of the injury, are eligible for trial entry if they appear to be at least 16 years old. Although entry is allowed up to 8 hours from injury, the earlier that patients can be treated the better.

Exclusion criteria: The fundamental eligibility criterion is the responsible doctor's 'uncertainty' as to whether or not to use an antifibrinolytic agent in a particular adult with traumatic haemorrhage. Patients for whom the responsible doctor considers there is a clear indication for antifibrinolytic therapy should not be randomised. Likewise, patients for whom there is considered to be a clear contraindication to antifibrinolytic therapy (such as, perhaps, those who have clinical evidence of a thrombotic disseminated intravascular coagulation) should not be randomised. Where the responsible doctor is substantially uncertain as to whether or not to use an antifibrinolytic, all these patients are eligible for randomisation and should be considered for the trial. There are no other pre-specified exclusion criteria.

Heterogeneity of the patients entering such a trial is a particular strength in terms of the analysis. If a wide range of patients are randomised then it may be possible for a really big trial such as this one to help determine which (if any) particular types of patient are most likely to benefit from treatment.

Special eligibility considerations: None. In the setting of acute severe haemorrhage the routine exclusion of patients with a history of thrombo-embolic disease is unnecessary, unless the responsible doctor considers these to be a definite contraindication. Brief details of patients assessed but not randomised in the trial will be recorded on a Patient Screening Log at each collaborating unit.

Figure 1: Eligibility



CONSENT

Patients with significant trauma may have impaired consciousness and may be unable to give properly informed consent. In this emergency situation it may not be medically appropriate to delay the start of treatment. Consent will be obtained from either a personal legal representative or a professional legal representative where relevant. The requirements of the relevant ethics committee will be adhered to at all times. An information leaflet on the study for patients (Appendix 1a) will be available in all drug packs in addition to a form for Legal Representative Consent (Appendix 1b).

RANDOMISATION

Patients eligible for inclusion should be randomised, and the study treatment started, as soon as possible. Randomisation is done by telephoning a 24-hour freecall service and takes only about two minutes. The patient entry form (Appendix 2) shows the questions that will be asked by the telephone operator prior to allocation of the treatment pack. The study computer will then

randomly assign a treatment pack number that will identify one of the CRASH 2 treatment packs stored in the emergency department. If telephone randomisation is not feasible a local pack system will be used. At such hospitals, baseline information will be collected on the trial entry form and the next consecutively numbered treatment pack taken from a box of eight packs. Once a patient has been randomised, we will definitely wish to learn the outcome in hospital, even if the trial treatment is interrupted or is not actually given.

TREATMENT

Each CRASH 2 treatment pack contains:

- 4 x 500 mg ampoules of Tranexamic Acid or placebo
- 1 x 100mL bag of 0.9% NaCl (for use with loading dose)
- Stickers (for attaching to infusion bags and patient notes)
- Patient information leaflet and Consent forms
- Patient entry form and Outcome form

TREATMENT	AMPOULES	DOSE (TRANEXAMIC ACID OR PLACEBO)	INFUSION RATE AND DURATION
Loading	2	1 gram	100 mL over 10 minutes
Maintenance	2	1 gram	120 mg/hr [60 mL/hr] for about 8 hours

SERIOUS UNEXPECTED SUSPECTED ADVERSE EVENTS

If a “SUSAR” (Serious Unexpected Suspected Adverse Reaction) occurs and is believed to be related to the study medicine, this should be logged by calling the 24-hour randomisation service, who will inform the Co-ordinating Centre in London. The Co-ordinating Centre will then contact you within 24 hours so that a written SUSAR report can be completed.

EXPECTED SIDE EFFECTS

In general, vascular events such as pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, gastrointestinal bleeding and multiorgan failure, do not need to be reported in this way because some increase in their incidence might be expected with antifibrinolytic agents. Likewise, the various medical events that are to be expected in severely injured patients do not need to be reported by telephone. However, all such events are routinely monitored among all patients on the outcome form (Appendix 3).

UNBLINDING

In general there should be no need to unblind the allocated treatment. If some contra-indication to antifibrinolytic therapy develops after randomisation (e.g. clinical evidence of thrombosis), the trial treatment should simply be stopped. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received antifibrinolytic or placebo. In those few cases when urgent unblinding is considered necessary, the randomisation service should be telephoned, giving the name of the doctor authorising unblinding and the treatment pack number. The caller will then be told whether the patient received antifibrinolytic or placebo.

MEASURES OF OUTCOME

The primary outcome measure is:

- *Death in hospital within four weeks of injury (causes of death will be described to assess whether deaths were due to haemorrhage or vascular occlusion).*

Secondary outcome measures are: receipt of a blood products transfusion, the number of units of blood products transfused, surgical intervention, and the occurrence of thrombo-embolic episodes (stroke, myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis).

Data collection: In-hospital deaths, transfusion requirement, complications and short-term recovery are to be recorded on the outcome form (Appendix 3) which can be completed entirely from the hospital notes — no extra tests are needed. The outcome form should be completed at death, discharge or four weeks post randomisation whichever occurs first.

End of trial for patients: Death, discharge or four weeks post randomisation whichever occurs first.

ANALYSIS

Comparisons will be made of the primary outcome measure, comparing all those allocated antifibrinolytic treatment versus those allocated placebo, on an ‘intention to treat’ basis. Analyses will be stratified on time from injury to the initiation of treatment (less than one hour, one to three hours, more than three hours), on severity of haemorrhage as assessed by capillary refill time (0–2, 3–4, ≥ 5 seconds) and systolic blood pressure (<75, 76–89, >89 mmHg). Comparisons will also be made of the risks of blood product transfusion, need for operation and thrombo-embolic complications.

3. Organisation

DATA MONITORING COMMITTEE

Professor Rory Collins, chair
Professor Adrian Grant
Professor John A Myburgh

Standard Operating Procedures: The Data Monitoring and Ethics Committee (DMEC) 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 Trial Steering Committee (TSC). The DMEC terms of reference state that they will do this if, and only if, two conditions are satisfied: (1) the results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of patients, in terms of the major outcome; (2) the results would, if revealed, be expected to substantially change the prescribing patterns of doctors 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. DMEC members have expressed sympathy with the stopping rule proposed in Part I of the 1976 report to the MRC Leukaemia Committee, whereby an interim analysis of major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure. An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules (as successfully applied in other trials including the MRC International Stroke Trial, which randomised 19,436 acute stroke patients) require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgement.

STEERING COMMITTEE

Professor Ian Franklin (chair), University of Glasgow and Scottish Blood Transfusion Service

Ms Brigitte Chaudhry, RoadPeace

Professor Tim Coats, University of Leicester

Dr Charles Deakin, Southampton General Hospital

Dr Steve Goodacre, University of Sheffield

Dr Beverley J Hunt, Guy's & St Thomas' Hospital NHS Trust

Dr David Meddings, World Health Organization

Professor Sir Richard Peto, University of Oxford

Professor Ian Roberts, London School of Hygiene & Tropical Medicine

Professor Peter Sandercock, University of Edinburgh

The steering committee consists of respected and experienced trauma and haematology experts, clinical trialists as well as a lay representative. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email and post.

Standard Operating Procedures: The Steering Committee, in the development of this protocol and throughout the trial, will take responsibility for:

- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial
- reviewing relevant information from other sources
- considering recommendations from the DMEC
- informing and advising the management group on all aspects of the trial

COLLABORATORS' RESPONSIBILITIES

Co-ordination within each participating hospital will be through a local collaborator who will:

- Discuss the trial with medical and nursing staff who see trauma 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 a set of slides to assist with this)
- Ensure that adults with trauma are considered promptly for the trial
- Ensure that the patient entry forms (in non–telephone randomising centres) and single sided outcome forms are completed
- Ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements
- Allow access to source data for audit and verification

CO–ORDINATING CENTRE RESPONSIBILITIES

- Provide study materials and a 24–hour randomisation (and unblinding) service
- Give collaborators regular information about the progress of the study
- Help ensure complete data collection at discharge
- Respond to any questions (e.g. from collaborators) about the trial
- Assure data security and quality and observe data protection laws
- Ensure trial is conducted in accordance with ICH GCP

PUBLICATION

The success of CRASH 2 will be dependent entirely upon the collaboration of nurses and doctors in the participating hospitals. Hence, the chief credit for the study will be assigned to the collaborators from each participating centre and they will be named personally in the main publications. The results of the trial will be reported first to trial collaborators. Dissemination of results to patients will take place via the media, trial website (www.crash2@Lshtm.ac.uk) and relevant patient organisations.

INDEMNITY

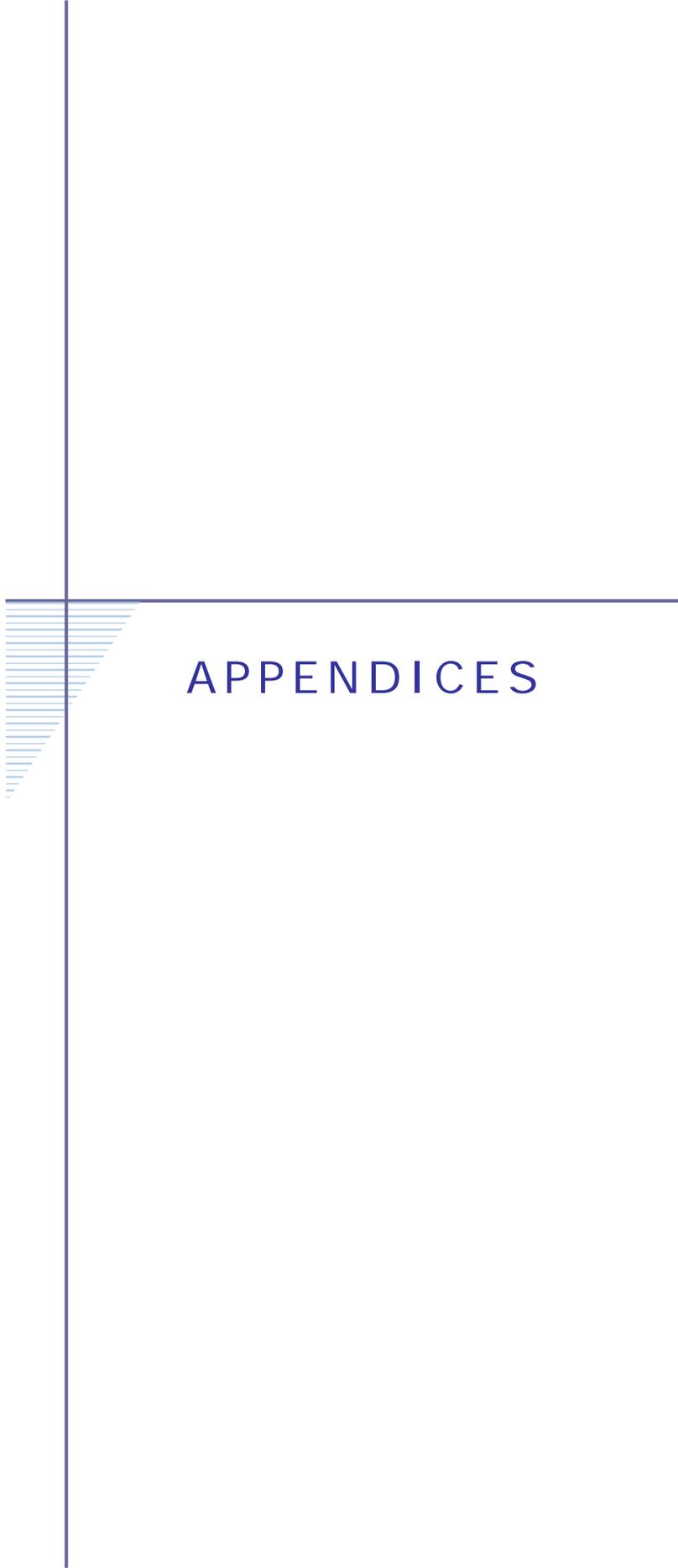
CRASH 2 is funded by the London School of Hygiene & Tropical Medicine (LSHTM) and the World Health Organization (WHO) and not the manufacturers of tranexamic acid. LSHTM as the Co–ordinating Centre for the trial accepts responsibility attached to its sponsorship of the trial and, as such, would be responsible for claims for any non–negligent harm suffered by anyone as a result of participating in this trial.

FINANCIAL SUPPORT

LSHTM and WHO funding covers meetings and central organisational costs only. The design, management and finance of the study are entirely independent of the manufacturers of tranexamic acid, which is not a new product. Large trials of such drugs, involving many hospitals, are important for future patients but are practicable only if those collaborating in them do so without payment (except for recompense of any minor local costs that may arise).

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APPENDICES

Appendix 1a

PATIENT INFORMATION SHEET (page1)

(HOSPITAL LETTERHEAD)

INFORMATION FOR PATIENTS

INTERNATIONAL STUDY OF BLEEDING AFTER INJURY

This hospital is taking part in a research study to find ways to reduce severe bleeding after serious injury. You have been included in this study.

WHAT YOU SHOULD KNOW ABOUT RESEARCH STUDIES:

This form gives information about the study including the aims, risks and benefits of taking part.

In this hospital, patients with severe bleeding are given the usual emergency treatment for bleeding. The aim of this research study is to find a better treatment. We hope that the study treatment (tranexamic acid) will help clotting and so lessen the amount of blood lost and reduce the need for a blood transfusion. But the study treatment may cause clots where they are not needed. We hope to find that the treatment will do a little more good than harm but we don't yet know this. Please read the information below carefully and ask the doctor looking after you any questions you have.

1) Why is this research being done?

Severe bleeding is a common cause of death after injury and it is important to find better ways of reducing the amount of blood lost.

2) What is the purpose of this study?

Tranexamic acid is often used to reduce bleeding after major surgery such as heart operations. This study is being done to see if it can also reduce bleeding after major injury. Tranexamic acid is not a new drug and is an approved treatment for many common conditions that involve bleeding.

3) Who is doing the study?

Dr _____ is in charge of this study at this hospital. The study is co-ordinated by doctors at The University of London.

4) A patient cannot be in this study if:

- he/she is known to be under 16
- he/she was injured more than 8 hours before arriving in hospital
- 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

PATIENT INFORMATION SHEET (page2)

5) What has happened to you after you were included in this study?

You were given all the usual emergency treatments for bleeding, including fluids to replace the blood that you lost. You were also given a dose of either the active tranexamic acid or an inactive dummy medicine called saline. The dose was given over a period of eight hours. The choice of what to give (active treatment or dummy treatment) was made randomly by a computer at the University of Oxford, UK. The doctors looking after you do not know whether you got the active or the dummy medicine. This information is kept on a confidential list in another hospital. The study involves no extra tests but your doctor will send brief details about how you have been to the Co-ordinating Centre in London. This information will be used in strict confidence by the people working on the study and will not be released under any circumstance.

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

Tranexamic acid is widely used and at the moment there is no conclusive evidence of serious side effects with short term use. Tranexamic acid is NOT a new drug.

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

We hope that tranexamic acid may help reduce blood loss. The knowledge that we gain from this study will help people with similar injuries in the future.

8) If you have any questions or problems, who can you call?

If you have any questions you can contact

Dr _____ by telephoning _____

9) What information do we keep private?

All information about you and your injury will be kept private. The only people allowed to look at the information will be the doctors who are running the study, the staff at the Co-ordinating Centre and the regulatory authorities who check that the study is being carried out correctly. We will publish the results of the study in a medical journal so that other doctors can benefit from the knowledge, but your personal information will not be included and there will be no way that you can be identified.

10) Can the study end early for the participant?

The study treatment was given in the emergency situation. We hope that you will let us use information about how you got on, but if you do not want us to use it then please tell your doctor.

11) What else do you need to know?

- The study is funded by the University of London and the World Health Organisation, not the makers of tranexamic acid.
- The London School of Hygiene & Tropical Medicine (University of London) as the Co-ordinating Centre for the study accepts responsibility attached to its sponsorship of the study and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this study.
- We will ask you to sign a separate consent form and give you a copy to keep.

STUDY CO-ORDINATING CENTRE:

International Study of Bleeding After Injury, Room 180
 London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT
 Tel 020 7299 4684
 WWW.CRASH2.LSHTM.AC.UK

Appendix 1b

LEGAL REPRESENTATIVE INFORMATION SHEET (page 1)

(HOSPITAL LETTERHEAD)

LEGAL REPRESENTATIVE CONSENT FORM (PERSONAL /PROFESSIONAL) INTERNATIONAL STUDY OF BLEEDING AFTER INJURY

This hospital is taking part in a research study to find ways to reduce severe bleeding after serious injury. We are asking for your permission to enrol into a research study or continue study treatment

for _____ (the participant). You are being asked because the patient is unable to give consent.

WHAT YOU SHOULD KNOW ABOUT RESEARCH STUDIES:

This form gives information about the study including the aims, risks and benefits of taking part.

In this hospital, patients with severe bleeding are given the usual emergency treatment for bleeding. The aim of this research study is to find a better treatment. We hope that the study treatment (tranexamic acid) will help clotting and so lessen the amount of blood lost and reduce the need for a blood transfusion. But the study treatment may cause clots where they are not needed. We hope to find that the treatment will do a little more good than harm but we don't yet know this. Please read the information below carefully and ask the doctor looking after the participant any questions you have.

- 1) **Why is this research being done?**
Severe bleeding is a common cause of death after injury and it is important to find better ways of reducing the amount of blood lost.
- 2) **What is the purpose of this study?**
Tranexamic acid is often used to reduce bleeding after major surgery such as heart operations. This study is being done to see if it can also reduce bleeding after major injury. Tranexamic acid is not a new drug and is an approved treatment for many common conditions that involve bleeding.
- 3) **Who is doing the study?**
Dr _____ is in charge of this study at this hospital. The study is co-ordinated by doctors at the University of London.
- 4) **A patient cannot be in this study if:**
 - he/she is known to be under 16
 - he/she was injured more than 8 hours before arriving in hospital
 - 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

LEGAL REPRESENTATIVE INFORMATION SHEET (page 2)

5) What will happen to the participant if you decide to allow him or her to be included in this study?

The participant was given all the usual emergency treatments for bleeding, including fluids to replace the blood that he/she lost. He/she was also given a dose of either the active tranexamic acid or an inactive dummy medicine called saline. The dose was given over a period of eight hours. The choice of what to give (active treatment or dummy treatment) was made randomly by a computer in the University of Oxford, UK. The doctors looking after the participant do not know whether he/she got the active or the dummy medicine. This information is kept on a confidential list in another hospital. The study involves no extra tests but the treating doctor will send brief details to the Co-ordinating Centre in London about how the participant has been. This information will be used in strict confidence by the people working on the study and will not be released under any circumstance.

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

Tranexamic acid is widely used and at the moment there is no conclusive evidence of serious side effects with short term use. Tranexamic acid is NOT a new drug.

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

We hope that tranexamic acid may help reduce blood loss. The knowledge that we gain from this study will help people with similar injuries in the future.

8) If you have any questions or problems, who can you call?

If you have any questions you can contact

Dr _____

by telephoning _____

9) What information do we keep private?

All information about the participant and his/her injury will be kept private. The only people allowed to look at the information will be the doctors who are running the study, the staff at the Co-ordinating Centre and the regulatory authorities who check that the study is being carried out correctly. We will publish the results of the study in a medical journal so that other doctors can benefit from the knowledge, but personal information will not be included and there will be no way that the participants can be identified.

10) Can the study end early for the participant?

The study treatment can be stopped at any time in the 8 hours if necessary. We hope that you will let us use information about how the participant got on, but if you do not want us to use it then please tell the treating doctor.

11) What else do you need to know?

- The study is funded by the University of London and the World Health Organisation, not the makers of tranexamic acid.
- The London School of Hygiene & Tropical Medicine (University of London) as the Co-ordinating Centre for the study accepts responsibility attached to its sponsorship of the study and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this study.
- We will give you a copy of this consent form to keep.

STUDY CO-ORDINATING CENTRE:

International Study of Bleeding After Injury, Room 180
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT
 Tel 020 7299 4684
 WWW.CRASH2.LSHTM.AC.UK

LEGAL REPRESENTATIVE CONSENT

Hospital Name:
Patient Hospital ID:
Randomisation Number:
Name of Principal Investigator:

LEGAL REPRESENTATIVE CONSENT FORM

INTERNATIONAL STUDY OF BLEEDING AFTER INJURY

PLEASE INITIAL

I confirm that I have read and understood the information sheet Version 2, dated 9 December 2004, for the above study and have had the opportunity to ask questions.

The research study described in this consent form, including the risks and benefits, has been explained to me and all of my questions have been answered to my satisfaction.

I consent to the participation of
in this research study.

To my knowledge, participation would not conflict with his/her religious or personal beliefs.

I may withdraw this consent at any time.

.....
Name of Legal Representative Date Signature

.....
Name of Person taking consent Date Signature
(if different from researcher)

.....
Researcher Date Signature

ORIGINAL FOR RESEARCHER
COPY FOR PATIENT
COPY FOR LEGAL REPRESENTATIVE
COPY TO BE KEPT WITH HOSPITAL NOTES

Appendix 2

PATIENT ENTRY FORM

CRASH2 PATIENT ENTRY INTERNATIONAL

ALL QUESTIONS BELOW NEED TO BE ANSWERED BEFORE CALLING THE RANDOMISATION SERVICE

INFORMATION ABOUT YOUR HOSPITAL

1. Country	
2. Name of hospital (or your hospital code)	
3. Name of caller	

INFORMATION ABOUT THE PATIENT

4. Patient sex (please circle)	Male	Female	5. Patient initials	
6. Patient hospital identification number				
7. Do you know patient's date of birth?				
a. YES – date of birth	YEAR	MONTH	DAY	b. NO – approximate age

INFORMATION ABOUT THE INJURY

8.	Estimated number of hours since injury	hours		
9.	Type of injury (please circle)	1 Blunt	2 Penetrating	3 Both

FIRST MEASUREMENT IN HOSPITAL OF THE FOLLOWING (IF UNKNOWN GIVE VALUE AT RANDOMISATION)

10.	Systolic BP (mmHg)		11.	Respiratory rate (per min)																						
12.	Central capillary refill time (sec)		13.	Heart rate (per min)																						
14.	Glasgow Coma Score (max 15)		<table border="1"> <thead> <tr> <th>EYE OPENING</th> <th>MOTOR RESPONSE</th> <th>VERBAL RESPONSE</th> </tr> </thead> <tbody> <tr> <td>4 Spontaneous</td> <td>6 Obeyes commands</td> <td>5 Orientated</td> </tr> <tr> <td>3 To sound</td> <td>5 Localising</td> <td>4 Confused speech</td> </tr> <tr> <td>2 To pain</td> <td>4 Normal flexion</td> <td>3 Words</td> </tr> <tr> <td>1 None</td> <td>3 Abnormal flexion</td> <td>2 Sounds</td> </tr> <tr> <td></td> <td>2 Extending</td> <td>1 None</td> </tr> <tr> <td></td> <td>1 None</td> <td></td> </tr> </tbody> </table>			EYE OPENING	MOTOR RESPONSE	VERBAL RESPONSE	4 Spontaneous	6 Obeyes commands	5 Orientated	3 To sound	5 Localising	4 Confused speech	2 To pain	4 Normal flexion	3 Words	1 None	3 Abnormal flexion	2 Sounds		2 Extending	1 None		1 None	
EYE OPENING	MOTOR RESPONSE	VERBAL RESPONSE																								
4 Spontaneous	6 Obeyes commands	5 Orientated																								
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2 To pain	4 Normal flexion	3 Words																								
1 None	3 Abnormal flexion	2 Sounds																								
	2 Extending	1 None																								
	1 None																									

Now call **Randomisation Service** with these answers and write down the treatment pack number given at the end of the phone call

Box **Pack**

Get this pack and follow the instructions on it carefully

Or paper randomise as per instructions in site file

PATIENT ENTRY FORM reverse

WHAT TO DO IF A TREATMENT PACK IS LOST OR DAMAGED

Telephone Randomisation Service

(number in your site file)

- Ask for **CRASH2 “LOST OR DAMAGED TREATMENT PACK”**
- Give hospital name or ID code and treatment box/pack number

TO REPORT ADVERSE EVENTS

Telephone Randomisation Service

(number in your site file)

- Ask for **CRASH2 “ADVERSE EVENTS”**
- Give hospital name or ID code and treatment box/pack number
- Give **name** of the person who reported the adverse event
.....
- Give **telephone number** of the person who reported the adverse event
.....

TO UNBLIND ALLOCATED TREATMENT

In general there should be no need to unblind the allocated treatment. Unblinding should only be done in those rare cases when management depends importantly upon knowledge of whether the patient received tranexamic acid or placebo.

Telephone Randomisation Service

(number in your site file)

- Ask for **CRASH2 “UNBLINDING”**
- Give hospital name or ID code and treatment box/pack number
- A Co-ordinating Centre team member will be contacted and will help

NOTES:

PLEASE GIVE THIS COMPLETED FORM TO THE PERSON RESPONSIBLE FOR COMPLETING THE OUTCOME FORM AT YOUR HOSPITAL

Appendix 3

OUTCOME FORM



OUTCOME FORM

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

Attach treatment pack sticker here

1. HOSPITAL

2. PATIENT

Patient Initials	<input type="text"/>	Hospital ID Number	<input type="text"/>	Sex	<input type="checkbox"/> M	<input type="checkbox"/> F
Date of Birth	<input type="text" value="YEAR"/>	/	<input type="text" value="MONTH"/>	/	<input type="text" value="DAY"/>	

3. OUTCOME

<p>3.1 DEATH IN HOSPITAL</p> <p>Date of death <input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/></p> <p>Cause of death</p> <p><input type="checkbox"/> Bleeding</p> <p><input type="checkbox"/> Head injury</p> <p><input type="checkbox"/> Myocardial Infarction</p> <p><input type="checkbox"/> Stroke</p> <p><input type="checkbox"/> Pulmonary Embolism</p> <p><input type="checkbox"/> Multi organ failure</p> <p><input type="checkbox"/> Other – describe <input type="text"/></p>	<p>3.2 PATIENT ALIVE</p> <p><input type="checkbox"/> Discharged – Date of discharge <input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/></p> <p><input type="checkbox"/> Still in this hospital now (28 days after injury) – Date <input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/></p>
<p>3.3 IF ALIVE TICK ONE BOX THAT BEST DESCRIBES THE PATIENT'S CONDITION (at 28 days or prior discharge)</p> <p><input type="checkbox"/> No symptoms</p> <p><input type="checkbox"/> Minor symptoms</p> <p><input type="checkbox"/> Some restriction in lifestyle but independent</p> <p><input type="checkbox"/> Dependent, but not requiring constant attention</p> <p><input type="checkbox"/> Fully dependent, requiring attention day and night</p>	

4. MANAGEMENT

a) Days in Intensive Care Unit (if not admitted to ICU, write '0' here)	<input type="text"/>
b) Significant Head Injury	<input type="checkbox"/> YES <input type="checkbox"/> NO
c) Operation site - Tick one box on every line	
<input type="checkbox"/> Neurosurgical	<input type="checkbox"/> YES <input type="checkbox"/> NO
<input type="checkbox"/> Chest	<input type="checkbox"/> YES <input type="checkbox"/> NO
<input type="checkbox"/> Abdomen	<input type="checkbox"/> YES <input type="checkbox"/> NO
<input type="checkbox"/> Pelvis	<input type="checkbox"/> YES <input type="checkbox"/> NO

7. TRANSFUSION

a) Blood products transfusion	<input type="checkbox"/> YES	<input type="checkbox"/> NO
b) Units transfused in 28 days		
<input type="checkbox"/> Red cell products	<input type="text"/>	units
<input type="checkbox"/> Fresh frozen plasma	<input type="text"/>	units
<input type="checkbox"/> Platelets	<input type="text"/>	units
<input type="checkbox"/> Cryoprecipitate	<input type="text"/>	units
<input type="checkbox"/> Recombinant Factor VIIa	<input type="checkbox"/> YES	<input type="checkbox"/> NO

5. COMPLICATIONS

Tick one box on every line		
<input type="checkbox"/> Pulmonary Embolism	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<input type="checkbox"/> Deep Vein Thrombosis	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<input type="checkbox"/> Stroke	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<input type="checkbox"/> Operation for bleeding	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<input type="checkbox"/> Myocardial Infarction	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<input type="checkbox"/> Gastrointestinal bleeding	<input type="checkbox"/> YES	<input type="checkbox"/> NO

8. PERSON COMPLETING FORM

NAME	<input type="text"/>
POSITION	<input type="text"/>
DATE	<input type="text"/>

NOW SEND THIS FORM TO THE CO-ORDINATING CENTRE IN ONE OF THE FOLLOWING WAYS:

- SECURE WEBSITE
 - ELECTRONIC DATA FORMS / EMAIL
 - FAX +44 (0)20 7299 4663
- SEE INSTRUCTIONS IN YOUR SITE FILE

6. TRIAL TREATMENT

a) Complete loading dose given	<input type="checkbox"/> YES	<input type="checkbox"/> NO
b) Complete maintenance dose given	<input type="checkbox"/> YES	<input type="checkbox"/> NO

ISRCTN86750102

Appendix 4

PROTOCOL SUMMARY

TRAUMA AND SIGNIFICANT HAEMORRHAGE

CONSIDER FOR CRASH 2 TRIAL OF ANTIFIBRINOLYTIC TREATMENT OF HAEMORRHAGE AFTER TRAUMA



ELIGIBILITY

- All adult trauma patients (appearing to be at least 16 years old) with ongoing significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or considered to be at risk of significant haemorrhage, within 8 hours of the injury
- No clear indication for, or contraindication to antifibrinolytic agents, in view of clinician

RANDOMISATION

TELEPHONE CENTRES

Telephone freecall randomisation service and give:

- patient initials and sex
 - birth date (if known) or approximate age
 - hours since injury and type of injury
 - GCS, SBP, respiratory rate, central capillary refill time, heart rate
- Treatment pack number will be allocated – get treatment pack and follow instructions on it

NON-TELEPHONE CENTRES

Complete patient entry form with:

- patient initials and sex
- birth date (if known) or approximate age
- hours since injury and type of injury
- GCS, SBP, respiratory rate, central capillary refill time, heart rate

Get lowest available number treatment pack and follow instructions on it

TREATMENT

- 10-minute loading infusion of 100mL (1g tranexamic acid or placebo)
- 8-hour infusion of 60mL/hr (120mg/hour tranexamic acid or placebo for about 8 hours)

DATA COLLECTION

One single-sided outcome form completed from hospital notes at discharge, death in hospital or four weeks from injury, whichever occurs first

FOR 24-HOUR RANDOMISATION

TELEPHONE CENTRES

FREECALL

(see number in your site file)

NON-TELEPHONE CENTRES

SECURE WEBSITE, ELECTRONIC DATA FORMS, EMAIL OR FAX

(see instructions in your site file)

INFORMATION AND STUDY MATERIALS:

CRASH Trials Co-ordinating Centre, LSHTM, Keppel Street, London WC1E 7HT
Tel +44(0)20 7299 4684, Fax +44(0)20 7299 4663, email CRASH@Lshtm.ac.uk
WWW.CRASH2.LSHTM.AC.UK

ISRCTN86750102

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Ms Haleema Shakur (Trial Manager)

Ms Barbara Farrell (Clinical Trials)

Dr Phil Edwards (Statistician)

Ms Maria Ramos (Administrator)



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