



**NETSCC, HTA**

**15<sup>th</sup> February 2011**

# CRASH<sub>2</sub>

Clinical Randomisation of an  
Antifibrinolytic in Significant Haemorrhage 

## PROTOCOL UK

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



# CONTENTS

|  | <i>page</i> |
|--|-------------|
| <b>1. BACKGROUND</b>   |             |
| ○ Introduction; Mechanisms; Existing knowledge   | 1           |
| ○ Hypothesis; Need for a trial   | 2           |
| Dose selection   | 2           |
| <b>2. STUDY DESIGN</b>   |             |
| Summary  | 4           |
| ○ Number of patients needed  | 4           |
| ○ Estimated event rate; Size of treatment effect that should be detectable; Sample size; Effects on other outcomes | 4           |
| Eligibility  | 5           |
| ○ Inclusion criteria; Exclusion criteria; Special eligibility considerations                                       | 5           |
| ○ Eligibility graph  | 6           |
| Consent  | 6           |
| Randomisation  | 6           |
| Treatment  | 7           |
| Serious unexpected suspected adverse events  | 7           |
| Expected side effects  | 7           |
| Unblinding   | 8           |
| Measures of outcome  | 8           |
| ○ Primary outcome measure; Secondary outcome measures; Data collection; End of trial for patients                  | 8           |
| Analysis   | 8           |
| <b>3. ORGANISATION</b>   |             |
| Data Monitoring Committee  | 9           |
| ○ Standard Operating Procedures  | 9           |
| Steering Committee   | 10          |
| ○ Standard Operating Procedures  | 10          |
| Collaborators' responsibilities  | 10          |
| Co-ordinating Centre responsibilities  | 11          |
| Publication  | 11          |
| Indemnity  | 11          |
| Financial support  | 11          |
| <b>4. REFERENCES</b>   | 12          |
| <b>APPENDICES</b>  |             |
| 1a Patient Information Sheet & Consent form  | 14          |
| 1b Legal Representative Information Sheet & Consent form   | 17          |
| 2 Patient entry form   | 20          |
| 3 Outcome form   | 22          |
| 4 Procedure for obtaining consent  | 23          |
| 5 Protocol Summary   | 25          |



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.<sup>1</sup> 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.<sup>2</sup> Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding.<sup>3</sup>

**Mechanisms:** The haemostatic system helps to maintain the integrity of the circulatory system after severe vascular injury, whether traumatic or surgical in origin.<sup>4</sup> 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.<sup>4</sup> 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.<sup>5</sup>

**Existing knowledge:** Systemic antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and thus reduce surgical blood loss. A recent systematic review<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup>

**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.<sup>9,10</sup> 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.<sup>11</sup> 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.<sup>6</sup> 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.<sup>12</sup> 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.<sup>13</sup>

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

CRASH2 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%.<sup>14</sup> 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 CRASH2.

**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.*

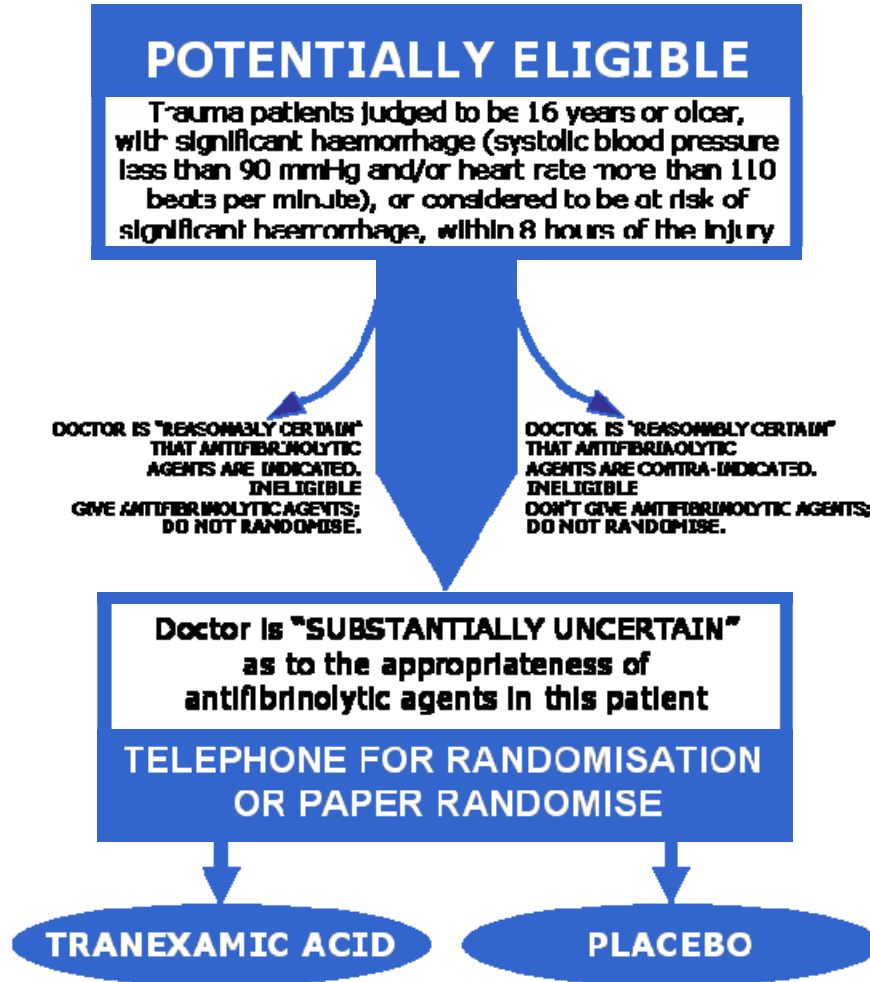
**Inclusion criteria:** All trauma patients with ongoing significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or who are considered to be at risk of significant haemorrhage, and are within 8 hours of the injury, are eligible for trial entry 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 CRASH2 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 CRASH2 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:

- o *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,  $\geq 5$  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 CRASH2 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](http://www.crash2@lshtm.ac.uk)) and relevant patient organisations.

## INDEMNITY

CRASH2 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.

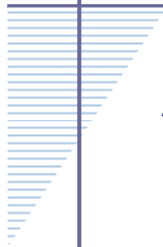
## FINANCIAL SUPPORT

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).

## 4. References

1. Murray CJL, Lopez AD. Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions. Harvard School of Public Health, Boston: Harvard University Press, 1996.
2. Sauaia A, Moore FA, Moore E, Moser K, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. *J Trauma* 1995;38:185–193.
3. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Hypotension. *J Neurotrauma*. 2000;17(6–7):591–5.
4. Lawson JH, Murphy MP. Challenges for providing effective hemostasis in surgery and trauma. *Semin Hematol* 2004;41:55–64.
5. Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002; 62: 2193–211.
6. Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM, Sly K, Laupacis A, Fergusson D. Antifibrinolytic use for minimising perioperative allogeneic blood transfusion (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
7. Coats T, Roberts I, Shakur H. Antifibrinolytic drugs for acute traumatic injury (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.
8. Aylward GW, Dunlop IS, Little BC. Meta-analysis of systemic antifibrinolytics in traumatic hyphema. *Eye* 1994;8:440–442.
9. Kiwanuka N, Gray RH, Serwadda D, et al. The incidence of HIV-1 associated with injections and transfusions in a prospective cohort, Raki, Uganda. *AIDS* 2004;18:342–343.
10. Heymann SJ, Brewer TF. The problem of transfusion associated acquired immunodeficiency syndrome in Africa: a quantitative approach. *Am J Infection Control* 1992;20:256–62.
11. Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. *Lancet* 2003; 361: 161–9.
12. Fiechtner BK, Nuttall GA, Johnson ME, Dong Y; Sujirattanawimol N, Oliver WC Jr, Sarpal RS, Oyen LJ, Ereth MH. Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesth Analg*. 2001; 92(5): 1131–6
13. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL. The dose-response relationship of tranexamic acid. *Anesthesiology* 1995;82:383–92.
14. WWW.CRASH.LSHTM.AC.UK





# 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

## PATIENT CONSENT

Hospital Name:

Patient Hospital ID:

Randomisation Number:

Name of Principal Investigator:

# PATIENT CONSENT FORM

## INTERNATIONAL STUDY OF BLEEDING AFTER INJURY

PLEASE INITIAL BOX

1. 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.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from The London School of Hygiene & Tropical Medicine or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study / for my information to be used in this trial
5. I understand that I can withdraw my consent at any time and my medical care will not be affected in anyway by my withdrawal






\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

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

# 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

### CLINICAL RANDOMISATION OF AN ANTIFIBRINOLYTIC IN SIGNIFICANT HAEMORRHAGE

1. 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.
2. 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.
3. I may withdraw this consent at any time.

PLEASE INITIAL BOX




\_\_\_\_\_  
Name of Legal Representative                      Date                      Signature

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

\_\_\_\_\_  
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 UK  
 Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage  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)         | <b>EYE OPENING</b> |     |                            |  | <b>MOTOR RESPONSE</b> |  | <b>VERBAL RESPONSE</b> |  |
|     |                                     | 4 Spontaneous      |     | 6 Obeys 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             |     |                            |  |                       |  |                        |  |

Now call  **0800 585 323** 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



## PATIENT ENTRY FORM reverse

### WHAT TO DO IF A TREATMENT PACK IS LOST OR DAMAGED

**Telephone**  
**0800 585 323**

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

### TO REPORT ADVERSE EVENTS

**Telephone**  
**0800 585 323**

- 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**  
**0800 585 323**

- 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 you with the unblinding

**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

3.1 DEATH IN HOSPITAL

Date of death  /  /

Cause of death

- Bleeding
- Head injury
- Myocardial Infarction
- Stroke
- Pulmonary Embolism
- Multi organ failure
- Other – describe

3.2 PATIENT ALIVE

Discharged – Date of discharge  /  /

Still in this hospital now (28 days after injury) – Date  /  /

3.3 IF ALIVE TICK ONE BOX THAT BEST DESCRIBES THE PATIENT'S CONDITION (at 28 days or prior discharge)

- No symptoms
- Minor symptoms
- Some restriction in lifestyle but independent
- Dependent, but not requiring constant attention
- Fully dependent, requiring attention day and night

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

## PROCEDURE FOR OBTAINING CONSENT

### INTRODUCTION AND BACKGROUND

The CRASH2 Trial involves patients who have suffered serious injuries and are at risk of life threatening haemorrhage. In this situation, most patients will have some impairment in their level of consciousness caused either by blood loss or coexisting head injury. In this emergency situation patients may not be able to provide written informed consent. In addition, the trial treatment has to be administered as soon as possible after injury.

From 1 May 2004 it is necessary that trials be compliant with Directive 2001/20/EC in the UK. To implement this directive, the UK regulation titled “**The Medicines for Human Use (Clinical Trials) Regulations (2004)**” was published, which requires that certain conditions and principles are applied to enable an incapacitated adult to be part of a clinical trial. (See **Conditions** on this page.) For the full regulation please visit the following website:

<http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/ctregsdraft.pdf>

The EU Directive (2001/20/EC) requires that, prior to participation in a trial, written consent from a legal representative of any person unable to consent for him or herself be obtained.

In the first instance, the legal representative of a person unable to give consent should be close to that person, aware of his/her wishes and independent of the research. This person would be termed the *Personal Legal Representative (PeLR)*.

If this is not possible and there is no one sufficiently close to the potential subject who is willing or able to take on the role, or if a person close enough to the potential subject cannot be contacted before it is medically necessary to give the intervention, then someone nominated by the NHS Trust as a *Professional Legal Representative (PrLR)* will fulfil this role.

The CRASH2 Trial is conducted in **an emergency situation** and the protocol requires that treatment is administered **as soon as possible after injury**. In the majority of cases patients are unaccompanied. In addition, it can take time for the police to identify and contact someone who can potentially be a PeLR. In most cases it is expected that consent for participation will have to be obtained from a PrLR for patients to be enrolled.

### OBTAINING LEGAL REPRESENTATIVE CONSENT FOR THE CRASH2 TRIAL

- It is the responsibility of each NHS Trust collaborating in the CRASH2 Trial to nominate suitable personnel to act as PrLR.
- It is the responsibility of each NHS Trust collaborating in the CRASH2 Trial to provide general training about the role of a PrLR.
- It is the responsibility of each NHS Trust collaborating in the CRASH2 Trial to provide Indemnity for PrLRs.
- It is the responsibility of each Principal Investigator and the Trial Co-ordinating Centre to provide written trial specific information about the trial to PrLRs to allow them to make an informed decision.

PROCESS FOR OBTAINING CONSENT

PATIENT FULFILLS ELIGIBILITY CRITERIA



Is a person who has a close personal relationship with the patient available and knowledgeable about their wishes?

**YES**



**NO**



**Is this person willing and able to take on the responsibilities of PeLR in this emergency situation?**

**NO** →

- If **YES**, explanation to be given in person by a member of the trial team.
- Written consent to be signed by PeLR (Appendix 1b).
- If PeLR not present in person, verbal consent to be obtained by telephone (to be witnessed and recorded in medical records). Written consent to be obtained as soon as possible (Appendix 1b).
- If / when patient regains competence, inform of participation, provide patient information sheet (Appendix 1a) and obtain consent for use of information

**Is there any reason to presume that this patient would NOT be willing to participate?**

- If **NO**, Trial Team to contact identified PrLR and obtain written consent (Appendix 1b).
- If no PrLR is available in the emergency situation (e.g during night time hours), patient can be randomised into the trial, if there is local agreed pre-arrangement, and written consent obtained from PrLR as soon as possible thereafter (Appendix 1b).
- If / when patient regains competence, or should a PeLR be identified, inform of participation, provide patient information sheet (Appendix 1a) and obtain consent for use of information

STATUTORY INSTRUMENTS – MEDICINES

The Medicines for Human Use (Clinical Trials) Regulations (2004)

PART 5: CONDITIONS AND PRINCIPLES WHICH APPLY IN RELATION TO AN INCAPACITATED ADULT

**Conditions**

1. The subject's legal representative has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.
2. The legal representative has been provided with a contact point where he may obtain further information about the trial.
3. The legal representative has been informed of the right to withdraw the subject from the trial at any time.
4. The legal representative has given his informed consent to the subject taking part in the trial.
5. The legal representative may, without the subject being subject to any resulting detriment, withdraw the subject from the trial at any time by revoking his informed consent.
6. The subject has received information according to his capacity of understanding regarding the trial, its risks and its benefits.
7. The explicit wish of a subject who is capable of forming an opinion and assessing the information referred to in the previous paragraph to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator.
8. No incentives or financial inducements are given to the subject or their legal representative, except provision for compensation in the event of injury or loss.
9. There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit to the subject outweighing the risks or produce no risk at all.
10. The clinical trial is essential to validate data obtained—
  - a) in other clinical trials involving persons able to give informed consent, or
  - b) by other research methods.
11. The clinical trial relates directly to a life-threatening or debilitating clinical condition from which the subject suffers.

**Principles**

12. Informed consent given by a legal representative to an incapacitated adult in a clinical trial shall represent that adult's presumed will.
13. The clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the cognitive abilities of the patient.
14. The risk threshold and the degree of distress have to be specially defined and constantly monitored. The interests of the patient always prevail over those of science and society

# Appendix 5

## 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

## MANAGEMENT GROUP

**Professor Tim Coats, Clinical expert Trauma Care**

Professor of Emergency Medicine, University of Leicester

**Dr Beverley Hunt, Clinical expert Haematology and Fibrinolysis**

Consultant in Departments of Haematology and Rheumatology, Guy's and St Thomas' NHS Trust; Honorary Senior Lecturer in Clinical Haematology, Guy's, King's and St Thomas' Medical School, London

**Professor Ian Roberts, Clinical Trials Expert**

Overall responsibility for the conduct of the trial

**Ms Haleema Shakur, Trial Manager**

Overall responsibility for day-to-day management of the trial. First contact in the event of questions about the conduct of the trial.

**Ms Barbara Farrell, Clinical trial management expert**

National Co-ordinator for the UK Trial Managers' Network, MRC Clinical Trials Unit, London

**Dr Phil Edwards, Statistician**

Responsibility for trial statistics and the development of the database. Responsible for running statistical checks to assure data validity.

**Ms Maria Ramos, Administrator**

Overall administration, trial budget monitoring, responsibility for organising trial treatment and other materials.



CRASH TRIALS CO-ORDINATING CENTRE

London School of Hygiene & Tropical Medicine

Keppel Street, London WC1E 7HT

Tel +44(0)20 7299 4684

Fax +44(0)20 7299 4663

Email [CRASH@LSHTM.AC.UK](mailto:CRASH@LSHTM.AC.UK)

[WWW.CRASH2.LSHTM.AC.UK](http://WWW.CRASH2.LSHTM.AC.UK)

ISRCTN86750102