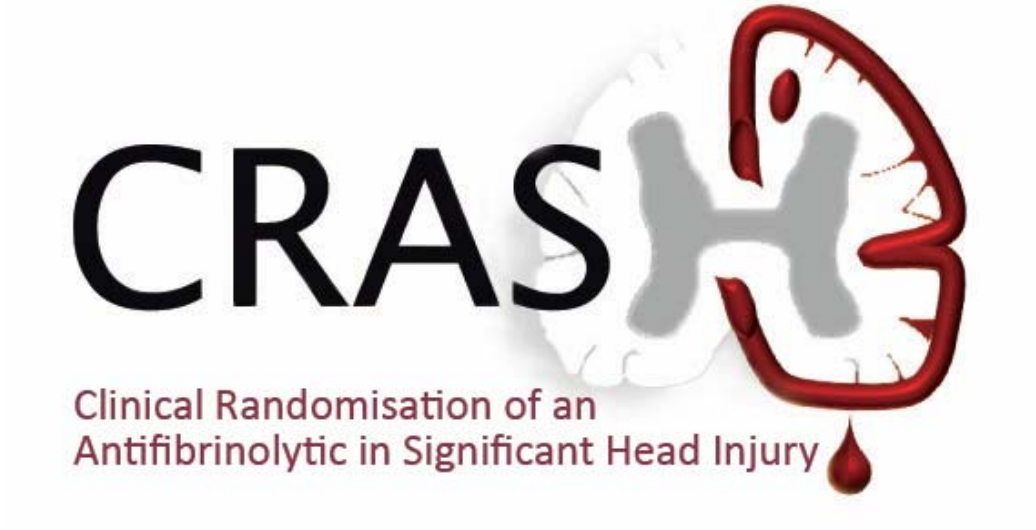


Assessing Eligibility

Protocol Code: ISRCTN15088122
V 1.0 date 30 Jan 2012

Eligibility Overview

Of adult age	*The age a person is considered an adult varies from country to country. See Protocol Appendix 4 for your country's minimum age for a person to be considered as an eligible adult*
Within 8 hours of injury	*Evidence in trauma trials; TXA more effective when given early. Early intervention needed in TBI to reduce extent of brain damage*
Any intracranial bleeding on CT scan **OR** GCS ≤ 12 if no scan is available	*Not all hospitals will have access to CT scans early enough; previous TBI trial shows that about 80% of patients with GCS ≤12 will have an intracranial bleed*
No significant extra cranial bleeding (needing immediate transfusion)	*Patients with significant extra cranial bleeding (eg needing immediate transfusion) will be excluded as there is evidence that TXA improves outcomes in these patients. As the trial treatment is either TXA or placebo, it is not appropriate to include patients that are known to benefit from TXA where the possibility exists that they may receive placebo.*
Where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in that particular patient	• *If clinician is certain or there is a clear indication for the use of TXA, the patient should **NOT** be randomised* • *If there is a clear contraindication to the use of TXA, the patient should **NOT** be randomised* • *If the clinician is uncertain about the use of TXA in a particular patient, the patient **SHOULD** be randomised*

Assessing eligibility for CRASH-3

Adult — NO → DO NOT RANDOMISE
↓ YES

Within 8 hours of injury — NO → DO NOT RANDOMISE
↓ YES

Bleeding on CT scan or GCS ≤12 if no scan available — NO → DO NOT RANDOMISE
↓ YES

Significant extracranial injury (needing immediate transfusion) – as TXA is clearly indicated in this case — YES → DO NOT RANDOMISE
↓ NO

Consent process followed eg agreement or waiver — NO → DO NOT RANDOMISE
↓ YES

Complete Entry Form
↓ YES

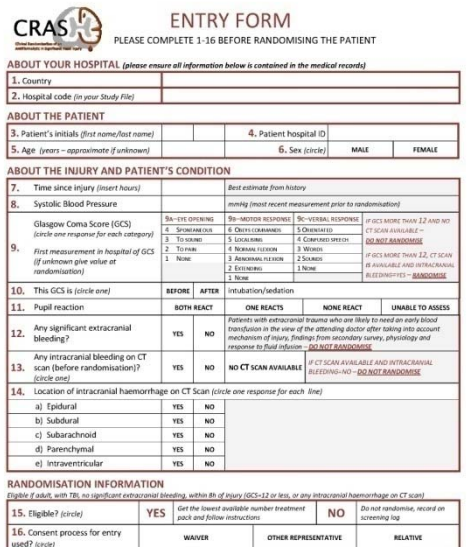
Clinician substantially uncertain regarding the use of TXA in this patient — NO → DO NOT RANDOMISE
↓ YES

RANDOMISE

DO NOT RANDOMISE

Record on screening log

- Eligibility for the trial should be determined from routine information (eg age, GCS, time since injury) recorded in patient medical records.
- Use the Entry Form (Questions 1–16) to help guide your assessment of eligibility and to record the information.



CRASH-3 ENTRY FORM

PLEASE COMPLETE 1-16 BEFORE RANDOMISING THE PATIENT

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

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

ABOUT THE PATIENT

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

ABOUT THE INJURY AND PATIENT'S CONDITION

7.	Time since injury (insert hours)		Best estimate from history
8.	Systolic Blood Pressure		mmHg (most recent measurement prior to randomisation)
9.	Glasgow Coma Score (GCS) (circle one response for each category)	9a–EYE OPENING: 4 Spontaneous; 3 To sound; 2 To pain; 1 None	9b–MOTOR RESPONSE: 6 Obeys commands; 5 Localising; 4 Normal flexion; 3 Abnormal flexion; 2 Extending; 1 None	9c–VERBAL RESPONSE: 5 Orientated; 4 Confused speech; 3 Words; 2 Sounds; 1 None
	First measurement in hospital of GCS (if unknown give value at randomisation)			IF GCS MORE THAN 12 AND NO CT SCAN AVAILABLE – DO NOT RANDOMISE; IF GCS MORE THAN 12, CT SCAN IS AVAILABLE AND INTRACRANIAL BLEEDING=YES – RANDOMISE
10.	This GCS is (circle one)	BEFORE / AFTER	Intubation/sedation	
11.	Pupil reaction	BOTH REACT	ONE REACTS	NONE REACT / UNABLE TO ASSESS
12.	Any significant extracranial bleeding?	YES / NO	Patients with extracranial trauma who are likely to need an early blood transfusion in the view of the attending doctor after taking into account mechanism of injury, findings from secondary survey, physiology and response to fluid infusion – DO NOT RANDOMISE	
13.	Any intracranial bleeding on CT scan (before randomisation)? (circle one)	YES / NO	NO CT SCAN AVAILABLE	IF CT SCAN AVAILABLE AND INTRACRANIAL BLEEDING=NO – DO NOT RANDOMISE

14. Location of intracranial haemorrhage on CT Scan (circle one response for each line)

a) Epidural	YES	NO
b) Subdural	YES	NO
c) Subarachnoid	YES	NO
d) Parenchymal	YES	NO
e) Intraventricular	YES	NO

RANDOMISATION INFORMATION

Eligible if adult, with TBI, no significant extracranial bleeding, within 8h of injury (GCS=12 or less, or any intracranial haemorrhage on CT scan)

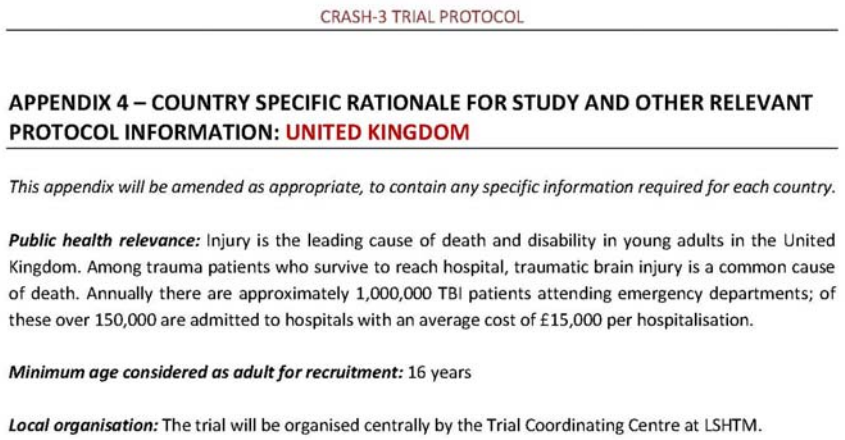
15. Eligible? (circle)	YES	Get the lowest available number treatment pack and follow instructions	NO	Do not randomise, record on screening log
16. Consent process for entry used? (circle)	WAIVER		OTHER REPRESENTATIVE	RELATIVE

Assessing eligibility – Adult

- In this trial, an **adult** will be defined by the relevant Ethics Committee, but patients should be at least 16 years old.

- The primary reason for limiting the trial to 'adults' is that the trial uses a fixed dose which would not be suitable for children. Dosage for children needs to be adjusted based on their body mass.

- Appendix 4 details the minimum age for an adult for your country.



CRASH-3 TRIAL PROTOCOL

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

This appendix will be amended as appropriate, to contain any specific information required for each country.

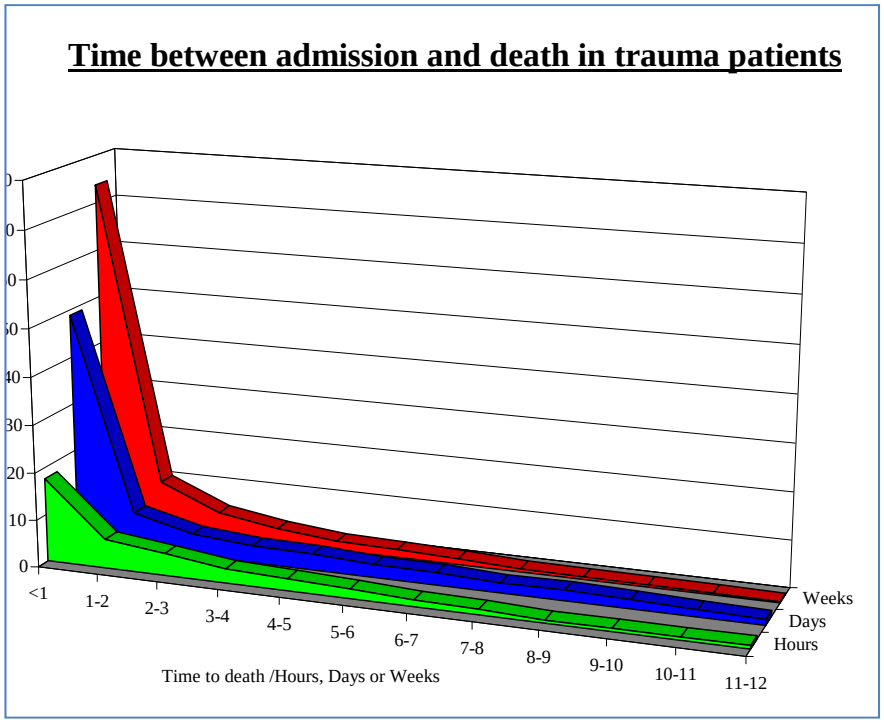
Public health relevance: Injury is the leading cause of death and disability in young adults in the United Kingdom. Among trauma patients who survive to reach hospital, traumatic brain injury is a common cause of death. Annually there are approximately 1,000,000 TBI patients attending emergency departments;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

Minimum age considered as adult for recruitment: 16 years

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

Assessing eligibility – Within 8 hours of injury

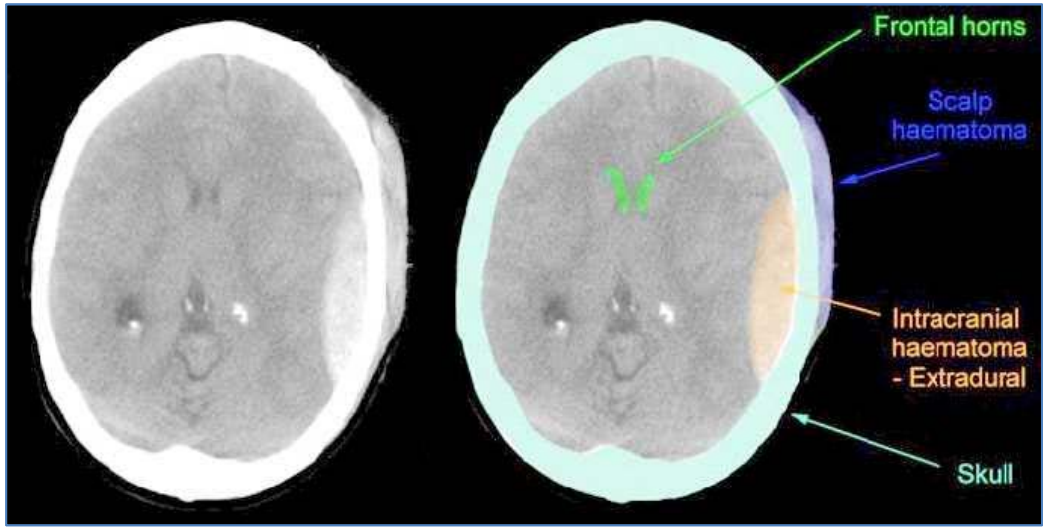
- Obtain best estimate from patient history
- Most deaths from TBI occur soon after injury – earliest possible intervention is needed for impact
- If patient sustained injury more than 8 hours ago, do not randomise (record on screening log)



Assessing eligibility – Severity of TBI

IF CT SCAN AVAILABLE:

- Any evidence of bleeding on CT scan ➡ randomise, regardless of GCS score
- If no bleeding on CT scan ➡ DO NOT RANDOMISE, even if GCS is ≤ 12



IF **NO** CT SCAN AVAILABLE:

- GCS ≤ 12 ➡ randomise
- GCS > 12 ➡ DO NOT RANDOMISE

Assessing eligibility – Glasgow Coma Score

Best Eye Response (4)
1. No eye opening
2. Eye opening to pain
3. Eye opening to verbal command
4. Eyes open spontaneously

Best Verbal Response (5)
1. No verbal response
2. Incomprehensible sounds
3. Inappropriate words
4. Confused
5. Orientated

Best Motor Response (6)
1. No motor response
2. Extension to pain
3. Flexion to pain
4. Withdrawal from pain
5. Localising pain
6. Obeys Commands

GLASGOW COMA SCALE
- Mild 13 to 15
- Moderate 9 to 12
- Severe 3 to 8

Patients with a GCS of 12 or less fall into the moderate to severe category and are eligible for randomisation (unless CT scan is available that shows NO bleeding present)

Assessing eligibility – Glasgow Coma Score

Which recording to use?

- Ideally, record the measurement done before initiation of intubation or other resuscitative measures.
- Otherwise, use the measurement obtained just before randomisation.

Assessing eligibility – No extra cranial bleeding

- If patient has sustained extra cranial injuries that require an immediate blood transfusion, then **DO NOT RANDOMISE**

- The CRASH-2 trial showed that tranexamic acid improves outcomes in patients with or at risk of significant extracranial bleeding. Therefore these patients should receive tranexamic acid and should not be randomised.

CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

For more information go to www.crash2.Lshtm.ac.uk

Assessing eligibility – The uncertainty principle

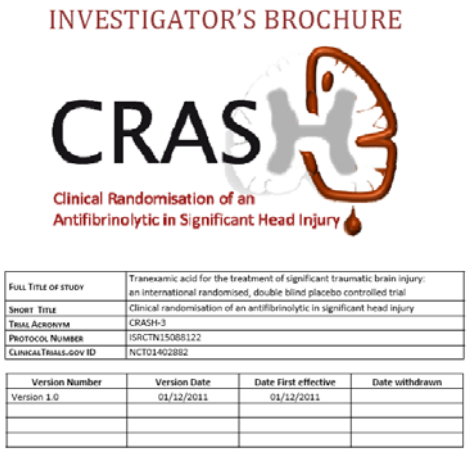
- **Uncertainty principle:** The fundamental eligibility criterion for the trial is the responsible clinician's uncertainty as to whether or not to use an antifibrinolytic agent in a particular patient with TBI.
  This approach to trial eligibility is well established.
- A patient can be enrolled if, and only if, the responsible clinician is substantially uncertain as to which of the trial treatments would be most appropriate for that particular patient.
- A patient should not be enrolled if the responsible clinician is for any medical or non-medical reasons reasonably certain that one of the treatments that might be allocated would be inappropriate for this particular individual (in comparison with either no treatment or some other treatment that could be offered to the patient in or outside the trial).
- Using the uncertainty principle should allow the process of this trial to be closer to what is appropriate in normal medical practice.

Assessing eligibility – The uncertainty principle

Information about the available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on TXA should allow you to decide whether it is indicated or contraindicated for a particular patient.

Information is provided in the Protocol and more comprehensively in:

1. **Investigator's Brochure** (contained in Study File Folder 1 section 4 – Trial drug guidance and information)
2. **Manufacturer's Summary of Product Characteristics** (contained within the Investigator's Brochure)


INVESTIGATOR'S BROCHURE

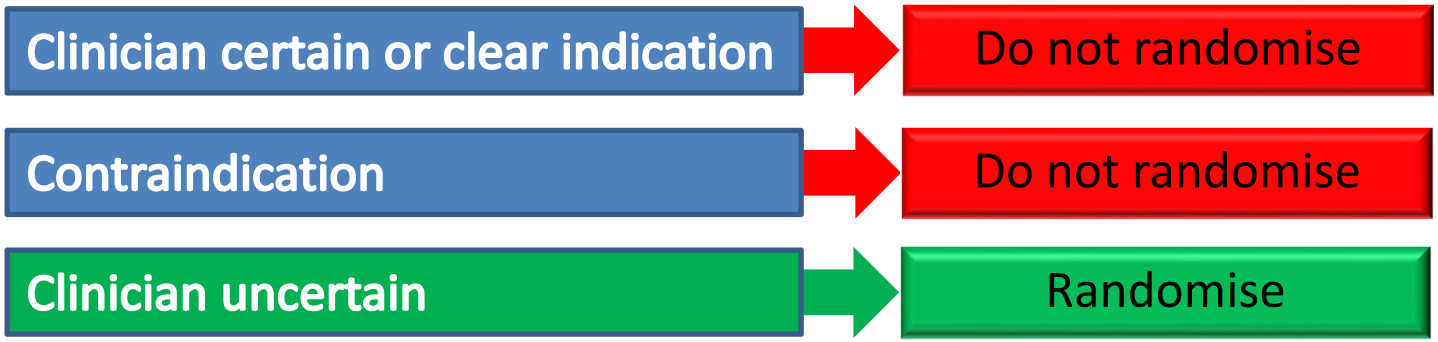
CRASH-3

Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

Full Title of study	Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial
Short Title	Clinical randomisation of an antifibrinolytic in significant head injury
Trial Acronym	CRASH-3
Protocol Number	ISRCTN15088122
ClinicalTrials.gov ID	NCT01402882

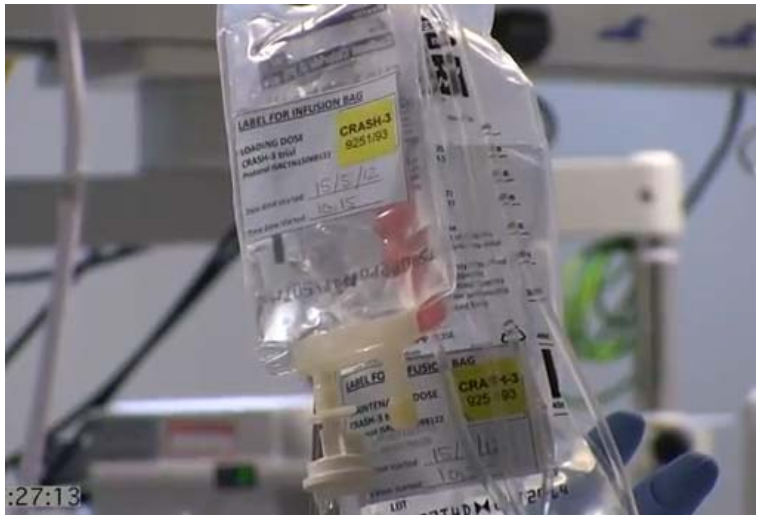
Version Number	Version Date	Date First effective	Date withdrawn
Version 1.0	01/12/2011	01/12/2011	

It is important that all trial team members familiarise themselves with these documents.



Points to remember

- All clinically indicated treatment available **MUST** be given.
- The treatment given in this trial is **ADDITIONAL** to all other treatments and is NOT a substitute for any other clinically indicated treatments.
- At the same time as you are starting treatments for TBI, consider inclusion in the trial.
- Aim to give the trial treatment as soon as possible after diagnosis of TBI.



CRASH

Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

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