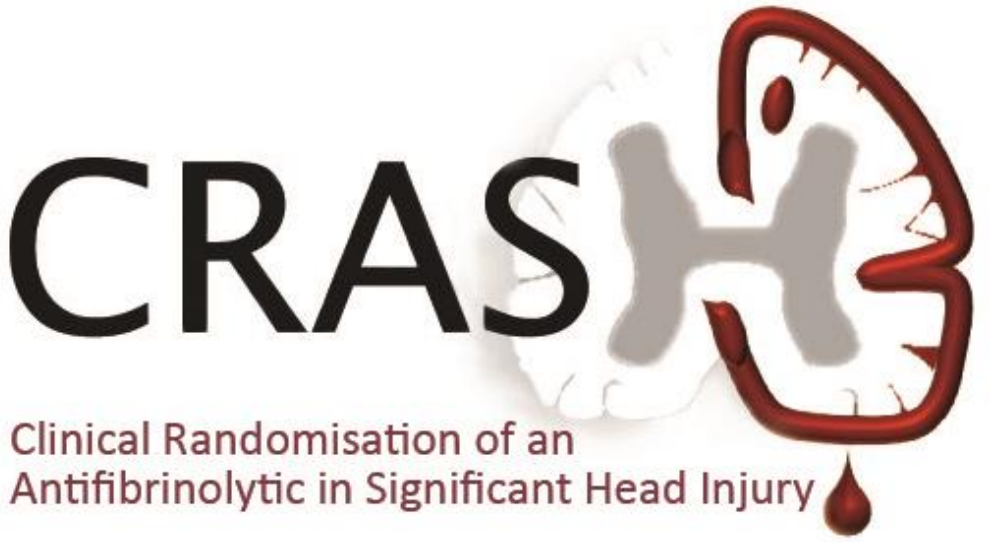


Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial

RATIONALE AND OVERVIEW

Protocol Code: ISRCTN15088122
V 1.1 date 27 Sep 2016

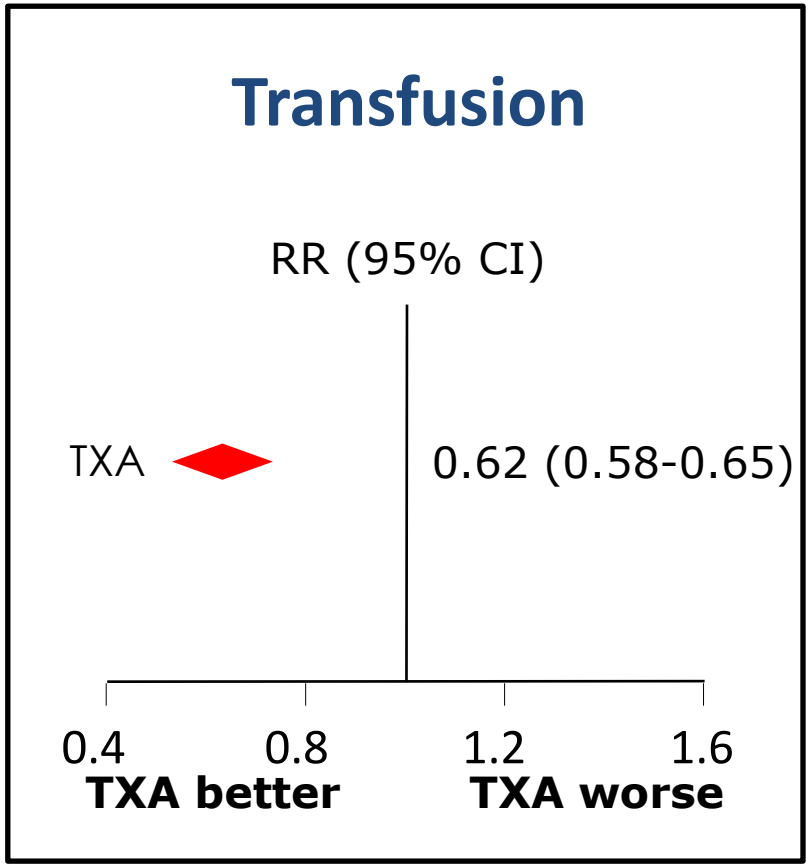
Traumatic brain injury

- 10 million killed or hospitalised every year
- 90% in low and middle income countries
- Mostly young adults and long lasting disability
- The incidence of TBI is predicted to rise

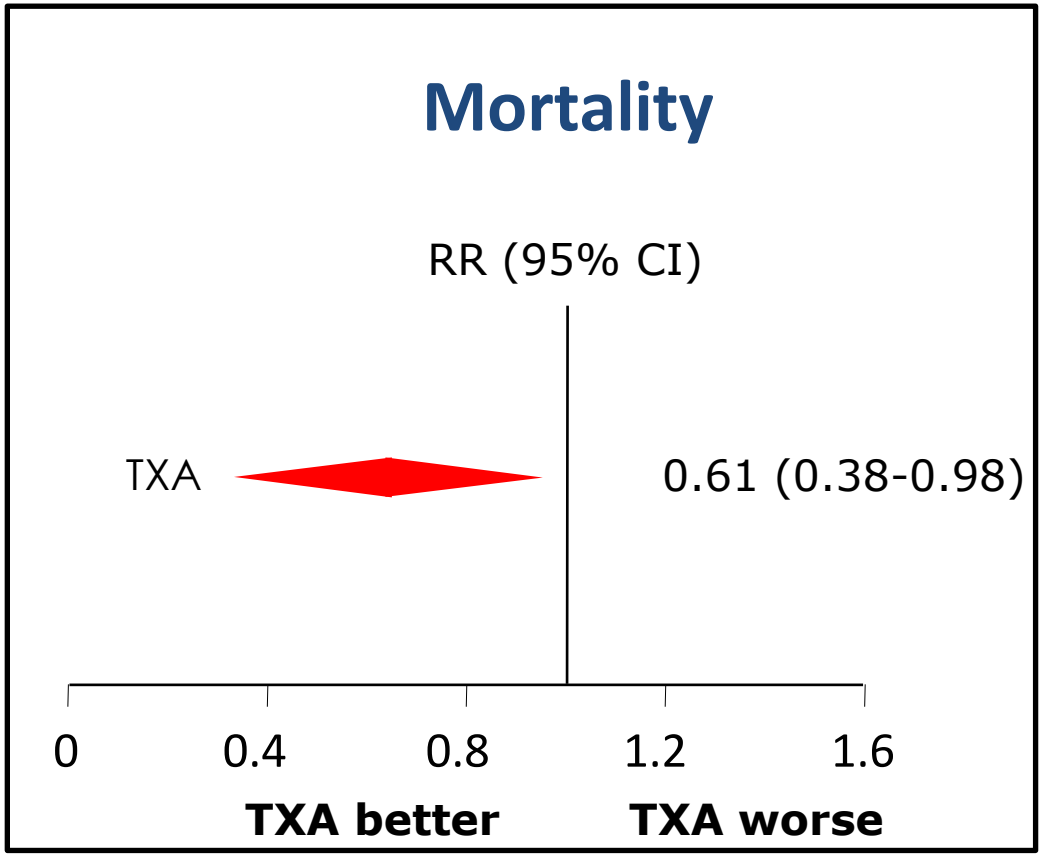
•*Bruns J, Hauser W. The epidemiology of traumatic brain injury: a review. Epilepsia 2003;44: Supplement 10:2-10.*
•*Peden M, Scurfield R, Sleet D, et al. World Report on Road Traffic Injury Prevention. Geneva: World Health Organization, 2004.*

Tranexamic acid and bleeding

TXA reduces bleeding in surgery



95 trials

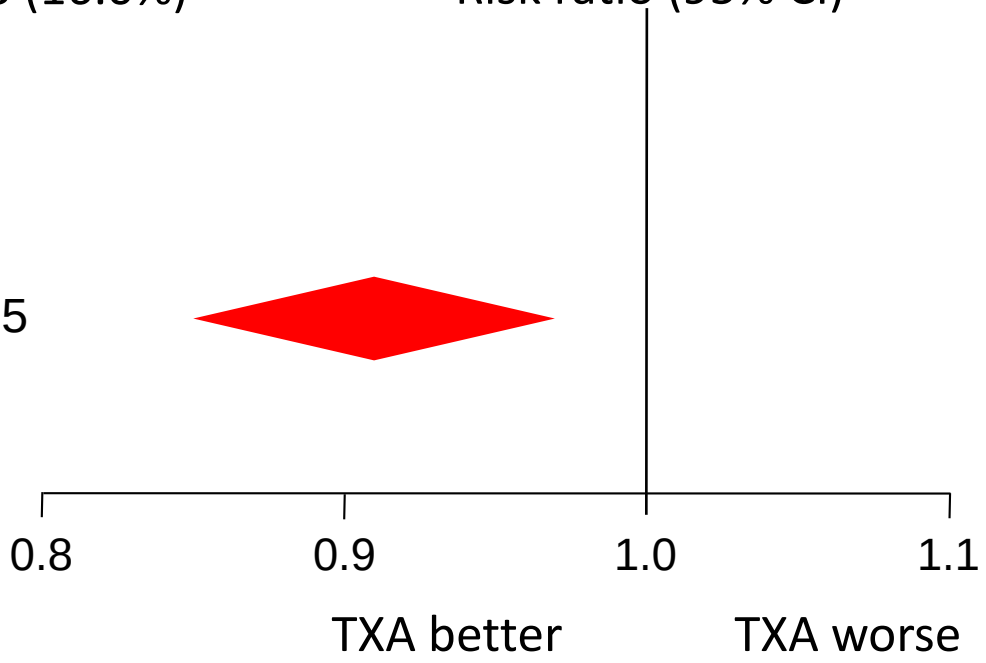


72 trials

Ker et al. BMC Emergency Medicine 2012, 12:3

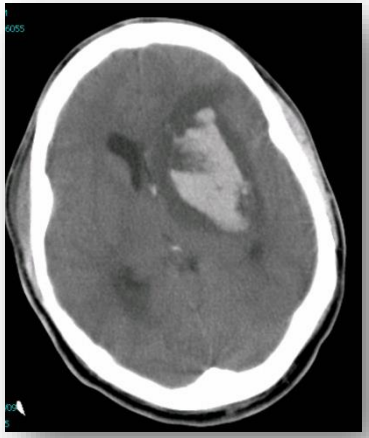
CRASH-2 trial results

TXA-allocated (n=10,060)	Placebo-allocated (n=10,067)	Risk ratio (95% CI)
1,463 (14.5%)	1,613 (16.0%)	
0.91 (0.85–0.97) 2P=0.0035		



•*The CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet. 2010; 376(9734):23-32.*

Traumatic Intracranial Bleeding



- Bleeding is a common complication of traumatic brain injury
- It is associated with poor outcome
- It can develop or worsen after hospital admission
- Early intervention may prevent enlargement

•Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: A prognostic study. BMC Emergency Medicine 2009, 9:15

•Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. J Neurosurg. 2002;96(1):109-16.

•Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN, Marshall LF. Progression of traumatic intracerebral hemorrhage: a prospective observational study. J Neurotrauma. 2008; 25(6):629-39.

Why TXA and intracranial bleeding?

- Coagulopathy affects about one third of patients with TBI
- Increased fibrinolysis is a common feature of coagulopathy
- Two randomised controlled trials of TXA in TBI

•*Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien). 2008;150(2):165-75.*
•*Bayir A, Kalkan E, Koçak S, Ak A, Cander B, Bodur S. Fibrinolytic markers and neurologic outcome in traumatic brain injury. Neurol India. 2006; 54(4):363-5.*

CRASH-2 Intracranial Bleeding Study (IBS)

	TXA n (%)	Placebo n (%)	OR (95% CI) n=249
Significant haemorrhage growth (n 123/126)	44 (36)	56 (44)	0.70 (0.42–1.16)
New focal ischaemic regions (n 123/126)	6 (5)	12 (9)	0.49 (0.18–1.35)
Death (n 133/137)	14 (10.5)	24 (17.5)	0.55 (0.27–1.22)

•*CRASH-2 collaborators (Intracranial Bleeding Study). Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ 2011; 343:d3795.*

Thai Study of TXA in TBI

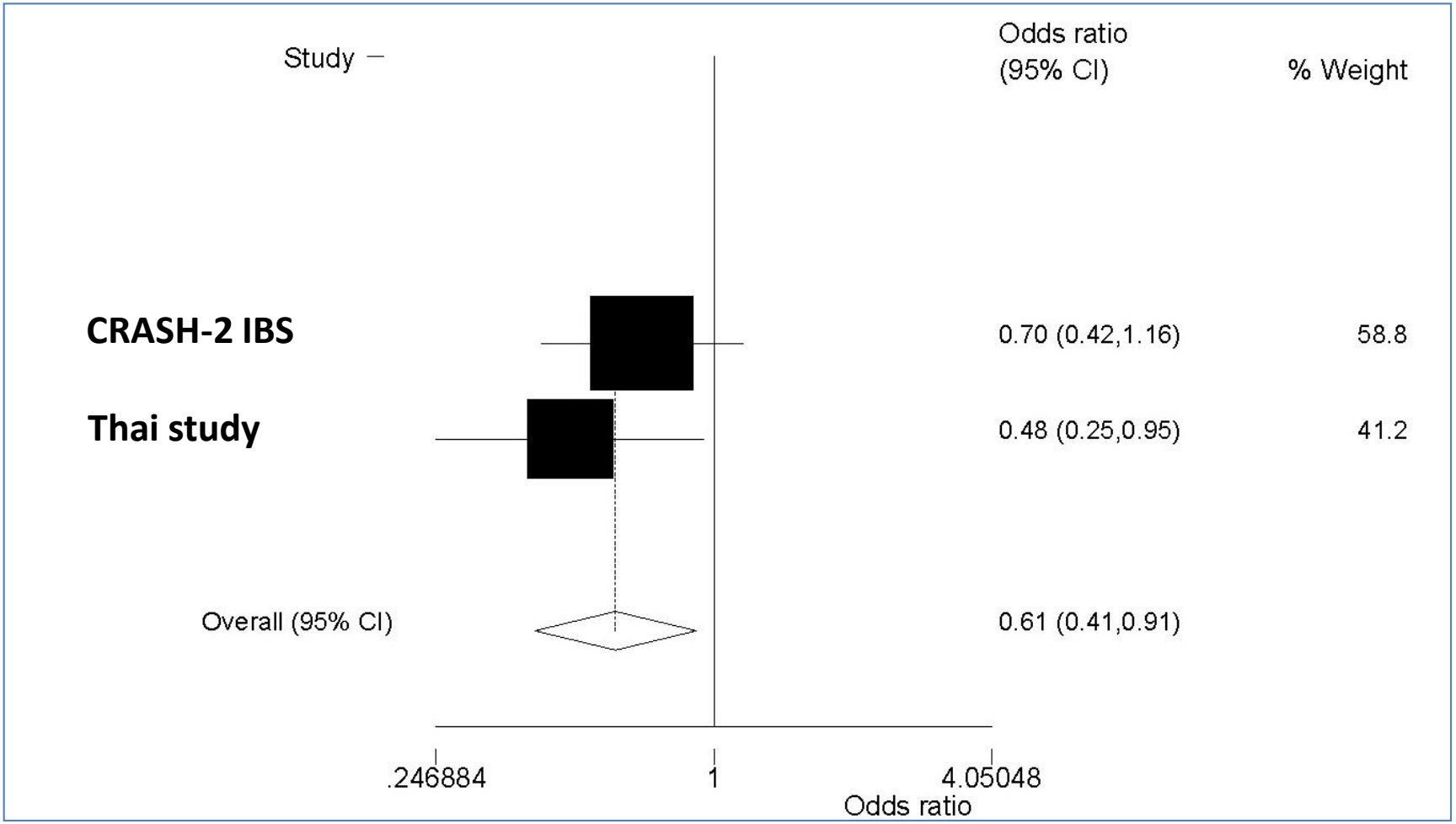
240 patients with isolated TBI

	RR (95% CI)
Haemorrhage growth	0.56 (0.32–0.96)
Mortality	0.67 (0.34–1.32)

- *Yutthakasemsunt S, et al. Tranexamic Acid for preventing progressive intracranial hemorrage in adults with traumatic brain injury; a preliminary report presented at the National Neurotrauma Symposium 2010.*
- *Available from http://www.neurotrauma.org/2010/abstracts.htm*

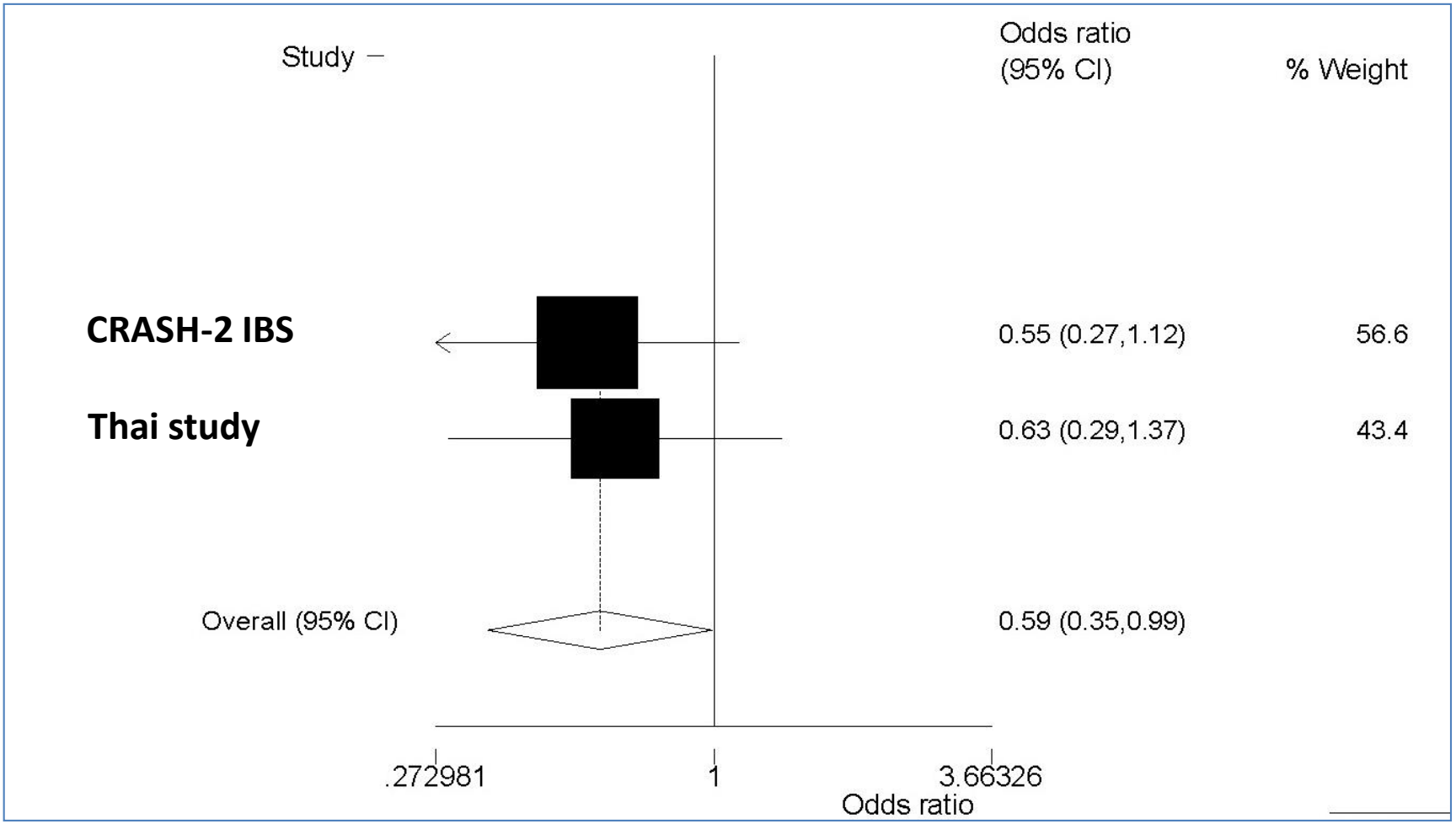
Meta-analysis

Significant Haemorrhage growth



Meta-analysis

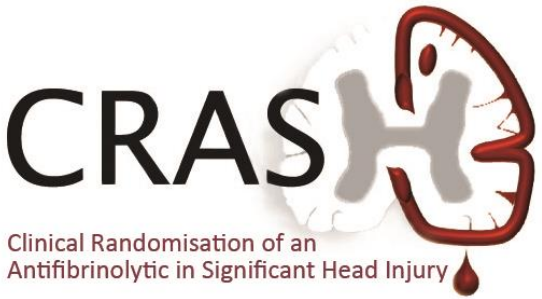
Mortality



CRASH-3 trial

The CRASH-3 trial will provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with TBI.

The effect of TXA on the risk of vascular occlusive events and seizures will also be assessed.



Sample size

13,000 TBI patients

- 90% power (two sided alpha=1%)
- 15% relative reduction in all-cause mortality

Before the trial starts

- A completed Hospital & Principal Investigator CV Form
- GCP training certificate(s)
- Approval of your hospital (if required)
- Ethics Approval (local and/or national)
- Ministry of Public Health approval (if applicable)
- A signed Principal Investigator Agreement
- A copy of the approved Patient Information Sheet & Consent form (if different from the protocol sent to you)

Good Clinical Practice (GCP)

Good Clinical Practice (GCP): is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

- Free online training via our website
- All staff should complete prior to the study starting at your hospital

Create a trial team

Provide information and training to all team members

Identify people to be responsible for specific trial processes – they must be interested in the trial

Nominate someone to be responsible in your absence

Roles may include:
- Principal Investigator
- Sub-investigator
- Data collection
- Study coordinator

Every specialty should be represented:
- neurosurgeons
- traumatologists
- nurses
- intensivists
- general surgeons
- clerical staff
- pharmacy
- managers
- administrators

Overview

ELIGIBILITY

- adult
- with traumatic brain injury
- within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury)
- any intracranial bleeding on CT scan OR GCS ≤12
- no significant extracranial haemorrhage (requiring immediate transfusion)
- where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in a patient

Appropriate **CONSENT PROCESS** for patient
eg prior representative agreement or waiver

RANDOMISE (tranexamic acid or placebo)
Entry form completed

Give **loading dose** over 10 minutes

Give **maintenance dose** over 8 hours

Complete **outcome form** at prior discharge, death, or day 28

All clinically indicated treatment is given in addition to trial enrolment

Adverse events are reported up to day 28

If prior consent waiver used, consent from patient or relative required after emergency is over

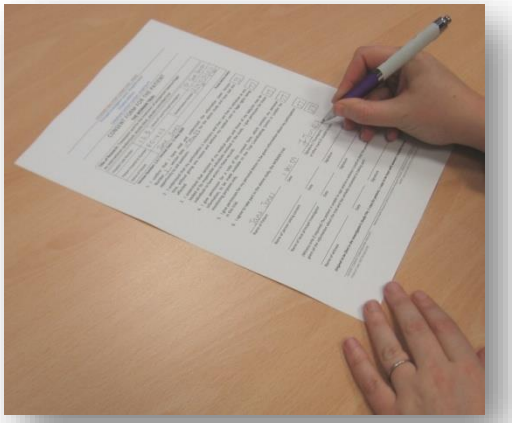
Consent – at trial entry

- **If representative is available:** Bear in mind the distressing nature of the situation and lack of time. Provide them with brief information and if agreement, continue to randomise. Full consent to be obtained after emergency situation is over.
- **If no representative:** Two clinicians (one independent of the trial) will consider the eligibility criteria and any known views of the patient about trial participation. Together they will decide whether or not to enrol the patient into the trial (i.e. a waiver)

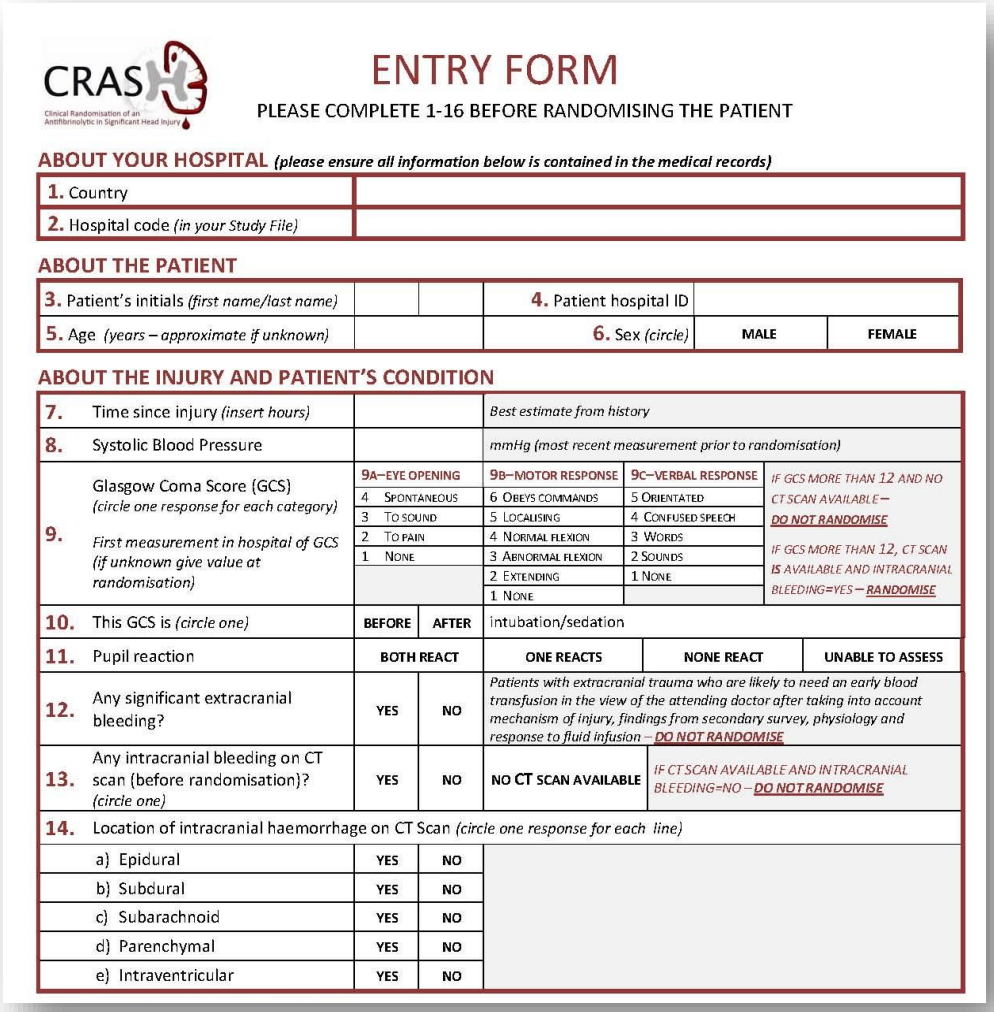
Consent – after emergency is over

Full informed written consent for continuation to be obtained from either:

- patient (if capacity returns)
- relative (if they become known and patient unable)
- other representative (if patient unable and if no relative)



Entry Form



CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

ENTRY FORM

PLEASE COMPLETE 1-16 BEFORE RANDOMISING THE PATIENT

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

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

ABOUT THE PATIENT

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

ABOUT THE INJURY AND PATIENT'S CONDITION

7.	Time since injury *(insert hours)*		*Best estimate from history*		
8.	Systolic Blood Pressure		*mmHg (most recent measurement prior to randomisation)*		
9.	Glasgow Coma Score (GCS) *(circle one response for each category)* *First measurement in hospital of GCS (if unknown give value at randomisation)*	9A–EYE OPENING	9B–MOTOR RESPONSE	9C–VERBAL RESPONSE	*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*
		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		
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			

One page only

- Complete questions 1–14 to assess eligibility
- If eligible, follow appropriate consent process
  – complete 15–16
- **RANDOMISE:**
  Use next lowest available pack number
  – STRICT NUMERICAL ORDER

Randomisation

- Use next lowest available pack number
- Record on Randomisation log
- Record pack used on Drug Accountability Log

Entry form and Randomisation

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**		
17. Insert treatment pack number here			**BOX**			**PACK**		
18. Date of randomisation	*day*	*month*	*year*	**19.** Time of randomisation *(24-hour clock)*		*hours*	*minutes*	
20. Name of person randomising				**21.** Signature				

- Use next lowest available pack number
- Record on Randomisation log
- Record pack used on Drug Accountability Log

Dose

Treatment	Dose TXA or placebo
Loading	1 gram / 10 minutes (IV infusion)
Maintenance	1 gram / 8 hours (IV infusion)

How to give the trial treatment

ALL AMPOULES ARE IDENTICAL AND CONTAIN 500mg OF EITHER TRANEXAMIC ACID OR PLACEBO

LOADING DOSE

2 ampoules over 10 minutes

Give immediately after randomisation

PRESCRIBE: *"CRASH-3 Trial (1 gram of tranexamic acid/placebo) over 10 minutes"*

Draw up 10mL (2 ampoules of tranexamic acid / placebo) and add to 100mL bag of Sodium Chloride 0.9% (provided) and infuse over 10 minutes.

MAINTENANCE DOSE

2 ampoules over 8 hours

Start immediately after completion of loading dose

PRESCRIBE: *"CRASH-3 Trial (1 gram of tranexamic acid / placebo). Infuse at 60 mL/hour"*

Draw up 10mL (2 ampoules of tranexamic acid / placebo) and add to 500mL bag of any isotonic intravenous solution and infuse over about 8 hours.

Outcomes

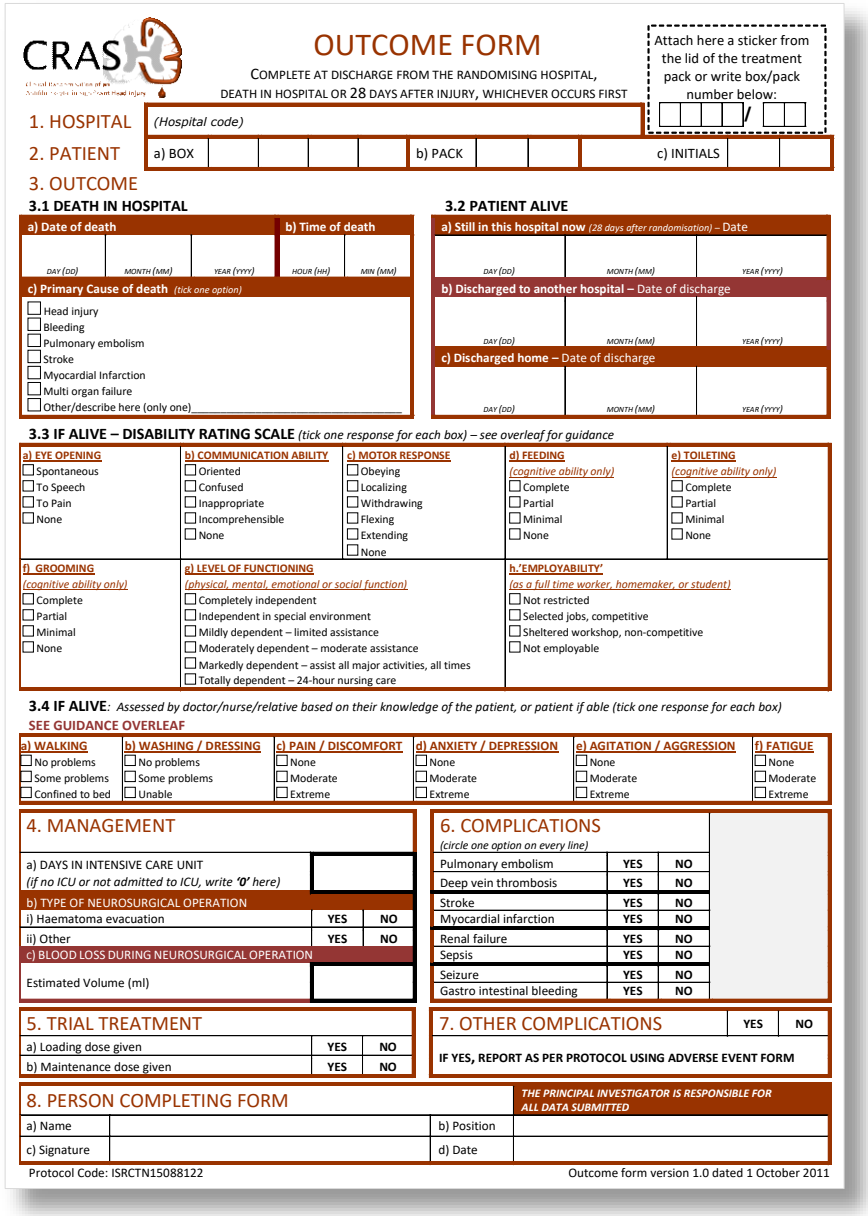
Primary outcome

- Death in hospital within four weeks of injury among patients randomised within 3 hours of injury
- Cause-specific mortality will also be recorded

Secondary outcomes

- Vascular occlusive events
- Disability
- Seizures
- Neurosurgical intervention
- Days in intensive care
- Other adverse events will be described

Outcome form



CRASH

OUTCOME FORM

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

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

1. HOSPITAL (Hospital code)

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

3. OUTCOME

3.1 DEATH IN HOSPITAL

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

c) Primary Cause of death (tick one option)
- Head injury
- Bleeding
- Pulmonary embolism
- Stroke
- Myocardial Infarction
- Multi organ failure
- Other/describe here (only one)

3.2 PATIENT ALIVE

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

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

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

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

a) EYE OPENING
- Spontaneous
- To Speech
- To Pain
- None

b) COMMUNICATION ABILITY
- Oriented
- Confused
- Inappropriate
- Incomprehensible
- None

c) MOTOR RESPONSE
- Obeying
- Localizing
- Withdrawing
- Flexing
- Extending
- None

d) FEEDING (cognitive ability only)
- Complete
- Partial
- Minimal
- None

e) TOILETING (cognitive ability only)
- Complete
- Partial
- Minimal
- None

f) GROOMING (cognitive ability only)
- Complete
- Partial
- Minimal
- None

g) LEVEL OF FUNCTIONING (physical, mental, emotional or social function)
- Completely independent
- Independent in special environment
- Mildly dependent – limited assistance
- Moderately dependent – moderate assistance
- Markedly dependent – assist all major activities, all times
- Totally dependent – 24-hour nursing care

h.'EMPLOYABILITY' (as a full time worker, homemaker, or student)
- Not restricted
- Selected jobs, competitive
- Sheltered workshop, non-competitive
- Not employable

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

SEE GUIDANCE OVERLEAF

a) WALKING
- No problems
- Some problems
- Confined to bed

b) WASHING / DRESSING
- No problems
- Some problems
- Unable

c) PAIN / DISCOMFORT
- None
- Moderate
- Extreme

d) ANXIETY / DEPRESSION
- None
- Moderate
- Extreme

e) AGITATION / AGGRESSION
- None
- Moderate
- Extreme

f) FATIGUE
- None
- Moderate
- Extreme

4. MANAGEMENT

a) DAYS IN INTENSIVE CARE UNIT (if no ICU or not admitted to ICU, write '0' here)

b) TYPE OF NEUROSURGICAL OPERATION

	YES	NO
i) Haematoma evacuation	YES	NO
ii) Other	YES	NO

c) BLOOD LOSS DURING NEUROSURGICAL OPERATION

Estimated Volume (ml)

6. COMPLICATIONS (circle one option on every line)

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

5. TRIAL TREATMENT

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

7. OTHER COMPLICATIONS YES NO

IF YES, REPORT AS PER PROTOCOL USING ADVERSE EVENT FORM

8. PERSON COMPLETING FORM THE PRINCIPAL INVESTIGATOR IS RESPONSIBLE FOR ALL DATA SUBMITTED

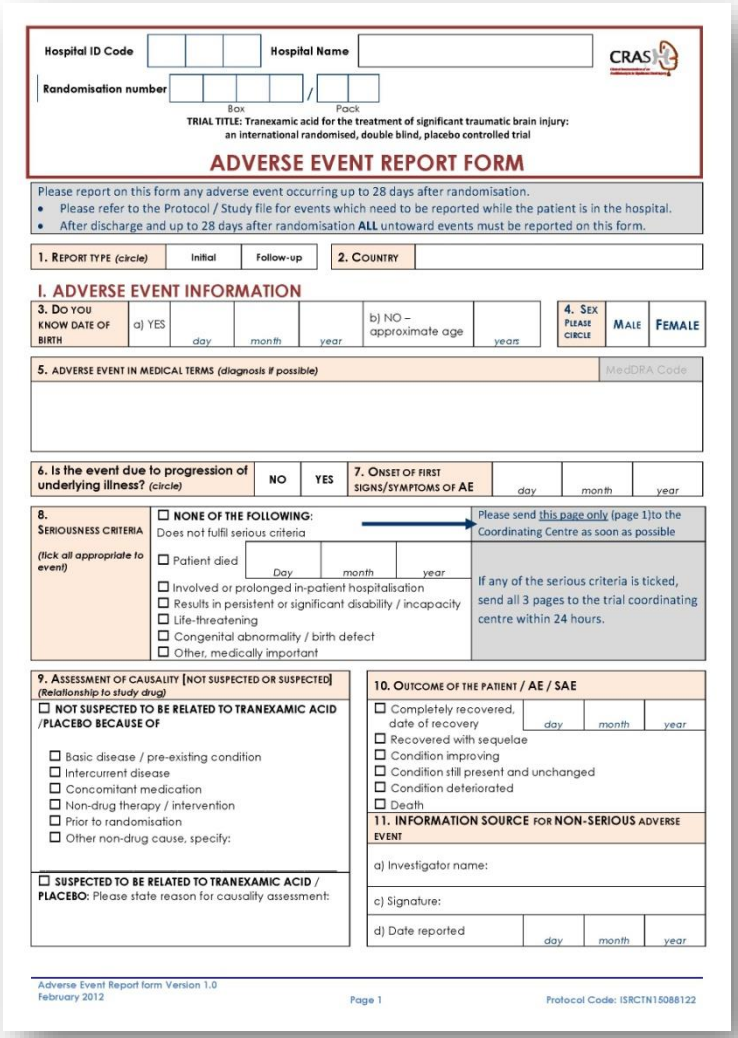
a) Name b) Position

c) Signature d) Date

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

- No extra tests required – a short single page Outcome form completed 4 weeks (28 days) after randomisation, at discharge, or at death (whichever occurs first)
- Outcome to be collected even if the trial treatment is interrupted or is not actually given
- Form to be sent to the TCC as soon as possible

Adverse Event



Hospital ID Code | Hospital Name | CRASH

Randomisation number: Box / Pack

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

ADVERSE EVENT REPORT FORM

Please report on this form any adverse event occurring up to 28 days after randomisation.
- Please refer to the Protocol / Study file for events which need to be reported while the patient is in the hospital.
- After discharge and up to 28 days after randomisation **ALL** untoward events must be reported on this form.

1. REPORT TYPE (circle) | Initial | Follow-up | 2. COUNTRY

I. ADVERSE EVENT INFORMATION

3. DO YOU KNOW DATE OF BIRTH | a) YES | day | month | year | b) NO – approximate age | years | 4. SEX PLEASE CIRCLE | MALE | FEMALE

5. ADVERSE EVENT IN MEDICAL TERMS (diagnosis if possible) | MedDRA Code

6. Is the event due to progression of underlying illness? (circle) | NO | YES | 7. ONSET OF FIRST SIGNS/SYMPTOMS OF AE | day | month | year

8. SERIOUSNESS CRITERIA (tick all appropriate to event)
- ☐ NONE OF THE FOLLOWING: Does not fulfil serious criteria
- ☐ Patient died | Day | month | year
- ☐ Involved or prolonged in-patient hospitalisation
- ☐ Results in persistent or significant disability / incapacity
- ☐ Life-threatening
- ☐ Congenital abnormality / birth defect
- ☐ Other, medically important

Please send this page only (page 1)to the Coordinating Centre as soon as possible

If any of the serious criteria is ticked, send all 3 pages to the trial coordinating centre within 24 hours.

9. ASSESSMENT OF CAUSALITY [NOT SUSPECTED OR SUSPECTED] (Relationship to study drug)

☐ NOT SUSPECTED TO BE RELATED TO TRANEXAMIC ACID /PLACEBO BECAUSE OF
- ☐ Basic disease / pre-existing condition
- ☐ Intercurrent disease
- ☐ Concomitant medication
- ☐ Non-drug therapy / intervention
- ☐ Prior to randomisation
- ☐ Other non-drug cause, specify:

☐ SUSPECTED TO BE RELATED TO TRANEXAMIC ACID / PLACEBO: Please state reason for causality assessment:

10. OUTCOME OF THE PATIENT / AE / SAE
- ☐ Completely recovered, date of recovery | day | month | year
- ☐ Recovered with sequelae
- ☐ Condition improving
- ☐ Condition still present and unchanged
- ☐ Condition deteriorated
- ☐ Death

11. INFORMATION SOURCE FOR NON-SERIOUS ADVERSE EVENT
- a) Investigator name:
- c) Signature:
- d) Date reported | day | month | year

Adverse Event Report form Version 1.0 February 2012 | Page 1 | Protocol Code: ISRCTN15088122

- Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes.
- Adverse events will be limited to serious events that are NOT already listed as primary or secondary outcomes, yet, which might reasonably occur as a consequence of the study drug.
- Events that are part of the natural history of the primary event, or expected complications of critical medical events, should not be reported as serious adverse events e.g. low blood pressure, increased intracranial pressure and reduced urine output associated with TBI.

After discharge and up to Day 28
all untoward medical occurrences should be reported

Sending your data

Internet: Primary data collection is to be done via internet

A username and password to use this site will be sent to you by email before you start the trial.

Email: as scanned documents

Trial Materials

BEFORE YOU START THE TRIAL YOU WILL RECEIVE:

- a study file compiled specifically for your hospital, containing contact details, further information, guidance, spare forms and filing space for completed data forms
- training CD with PowerPoint presentations
- training DVD of the trial procedures and a protocol presentation
- randomisation posters with step by step guidance
- brief information leaflets and wall posters for the families

PROTOCOLS

- protocol summaries
- pocket cards

TREATMENT PACKS

- Initially one box of 8 patient packs
- Stock level is monitored by patient entries received at the TCC
- We will send new boxes when you reach your minimum stock level, which is dependent on your randomisation rate
- With each box you will receive a document pack containing your hospital specific patient information sheets, consent forms, alert cards and brief information leaflets

TRAINING AND PRESENTATIONS

Please contact the TCC if

- you need more training materials for staff sessions
- you are presenting the trial at meetings or conferences

Trial Materials

UKCRC Registered Clinical Trials Units

CRASH-3

Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

If a simple and widely practicable treatment was shown to improve outcomes in patients with TBI, it could save many thousands of lives

Join us now at crash3.Lshtm.ac.uk

Trial Coordinating Centre

London School of Hygiene & Tropical Medicine

Room 180, Keppel Street, London WC1E 7HT

Tel +44(0)20 7299 4684 | Fax +44(0)20 7299 4663

crash@Lshtm.ac.uk