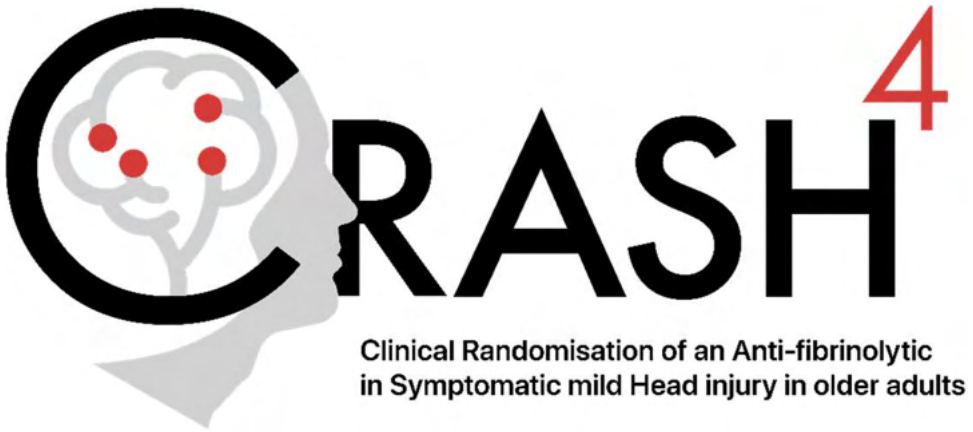


Intramuscular tranexamic acid for the treatment of symptomatic mild traumatic brain injury in older adults: a randomised, double-blind, placebo-controlled trial

TRIAL OVERVIEW

CRASH-4 Trial Overview_Version 2.0, 26 November 2021
EudraCT number: 2020-003391-40, Clinicaltrials.gov ID: NCT04521881

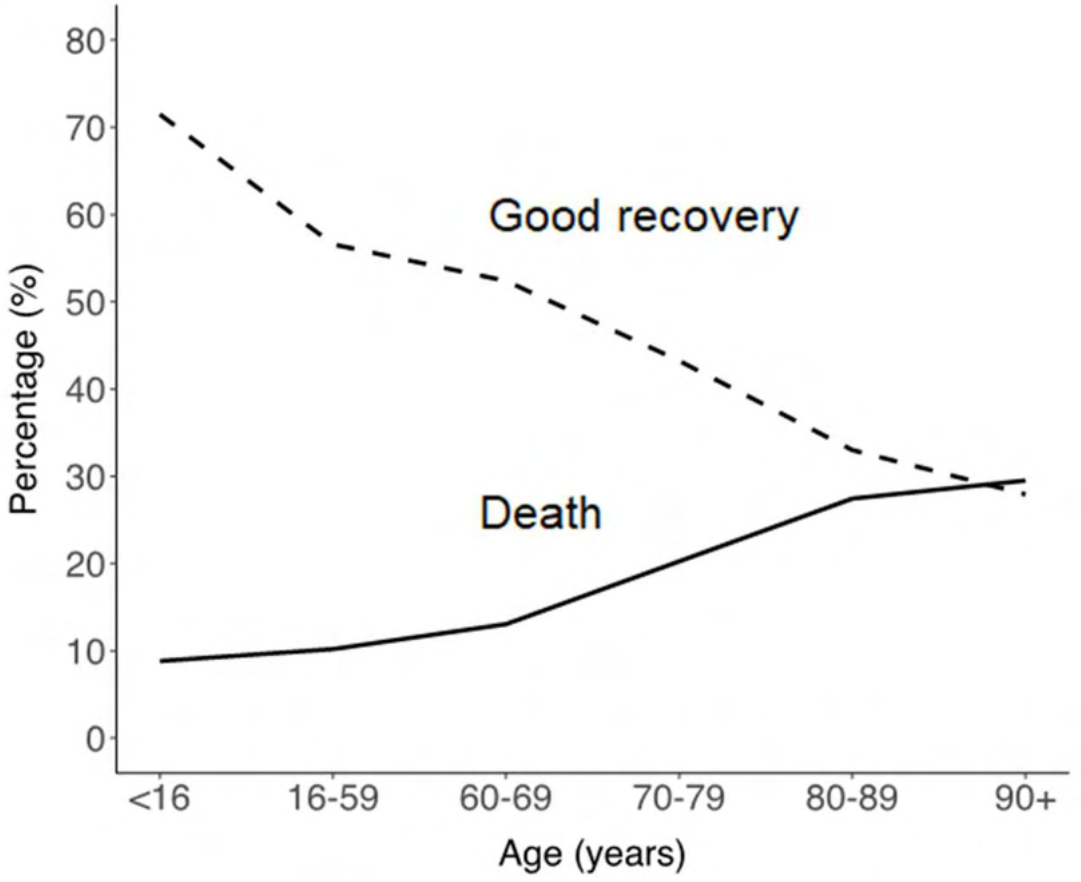
BACKGROUND

- Every year in England & Wales, about 1.4 million patients attend UK Emergency Departments (ED) with a Traumatic Brain Injury (TBI)
- Most are categorised as mild (Glasgow Coma Scale (GCS) score 13-15)
- The term ‘mild’ is misleading in older adults who have higher death rates and worse neurological outcomes than younger adults
- TBI is a strong risk factor for dementia, particularly in older adults
- Even mild TBI without loss of consciousness doubles dementia risk

BACKGROUND

Older adults have worse outcomes after TBI

(more older adults die and fewer have a full recovery)



Source UK TARN 2017

BACKGROUND

TBI patients have microbleeds not visible on CT scan, which early TXA treatment may prevent

doi:10.1093/brain/awz290 BRAIN 2019: 142; 3550–3564 | 3550

BRAIN
A JOURNAL OF NEUROLOGY

Traumatic microbleeds suggest vascular injury and predict disability in traumatic brain injury

Allison D. Griffin,[1,2] L. Christine Turtzo,[2] Gunjan Y. Parikh,[3,4] Alexander Tolpygo,[5] Zachary Lodato,[1,5] Anita D. Moses,[1,2] Govind Nair,[6] Daniel P. Perl,[1,7] Nancy A. Edwards,[8] Bernard J. Dardzinski,[1,7] Regina C. Armstrong,[1,7] Abhik Ray-Chaudhury,[8] Partha P. Mitra[5] and Lawrence L. Latour[1,2]

BACKGROUND

- The CRASH-3 trial showed that:
  - early (within 3 hours of injury) tranexamic acid (TXA) treatment improves outcome in patients with mild head injuries who have bleeding on a CT scan
  - with no evidence of adverse effects or complications

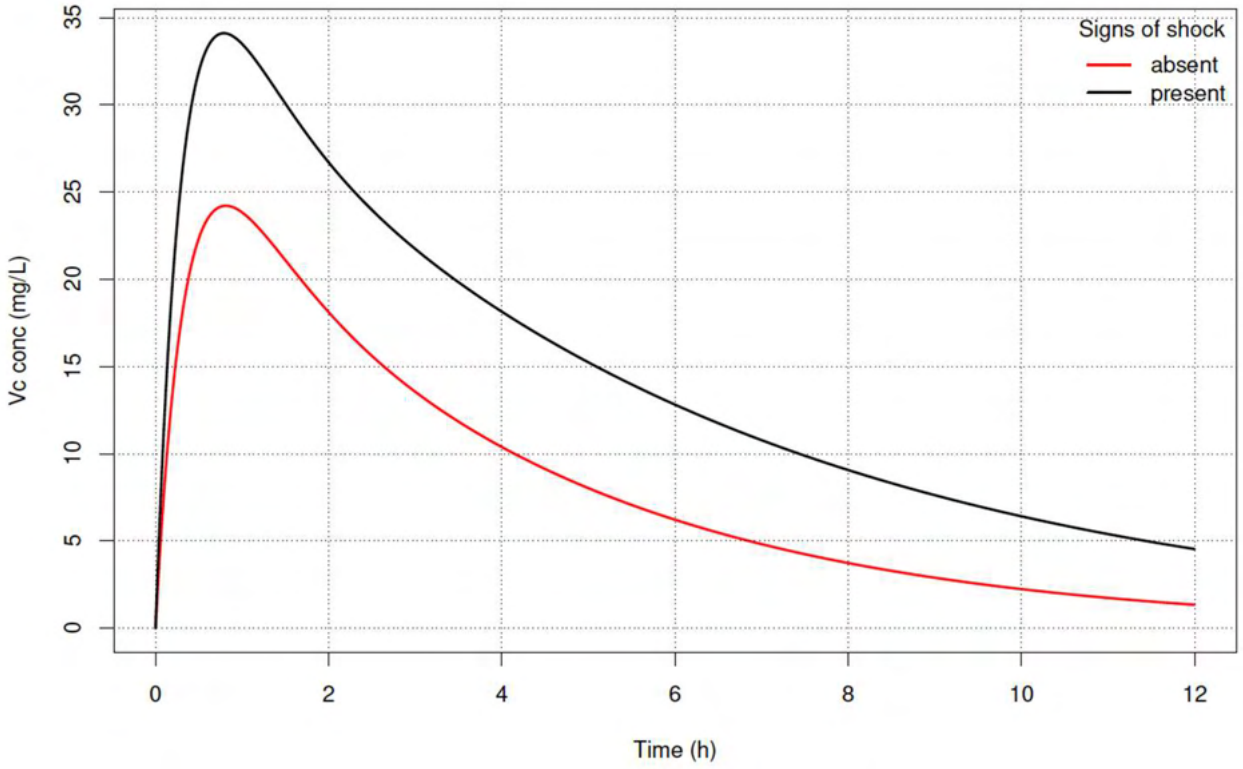
- CRASH-3 only included patients with GCS 12-15 if bleeding was present on CT scan.

- But many of these patients are scanned too late to benefit from treatment

- Earlier TXA treatment may prevent intracranial bleeding and increase the number of patient who can benefit

BACKGROUND

Intramuscular TXA is well tolerated and rapidly absorbed reaching therapeutic blood levels within 11 minutes of injection



Therapeutic concentrations reached after 1 gram TXA:

- 5 mg/L = ≅ 4 minutes
- 10 mg/L ≅ 11 minutes

TRAUMA-INTACT Trial: ClinicalTrials.gov Identifier: NCT03875937

AIM

To assess the effectiveness and safety of early intramuscular TXA administration in older adults with symptomatic mild head injury

To provide reliable evidence about the effects of early intramuscular TXA on intracranial haemorrhage, disability, death, and dementia

TRIAL DESIGN

- Randomised, double blind, placebo-controlled trial
- 10,000 older adults
- Symptomatic mild head injury
- Patients randomly allocated to receive intramuscular TXA (500mg) or matching placebo (0.9% NaCl)
- The trial will be conducted by ambulance services and in emergency departments of trauma centres and trauma units in the UK

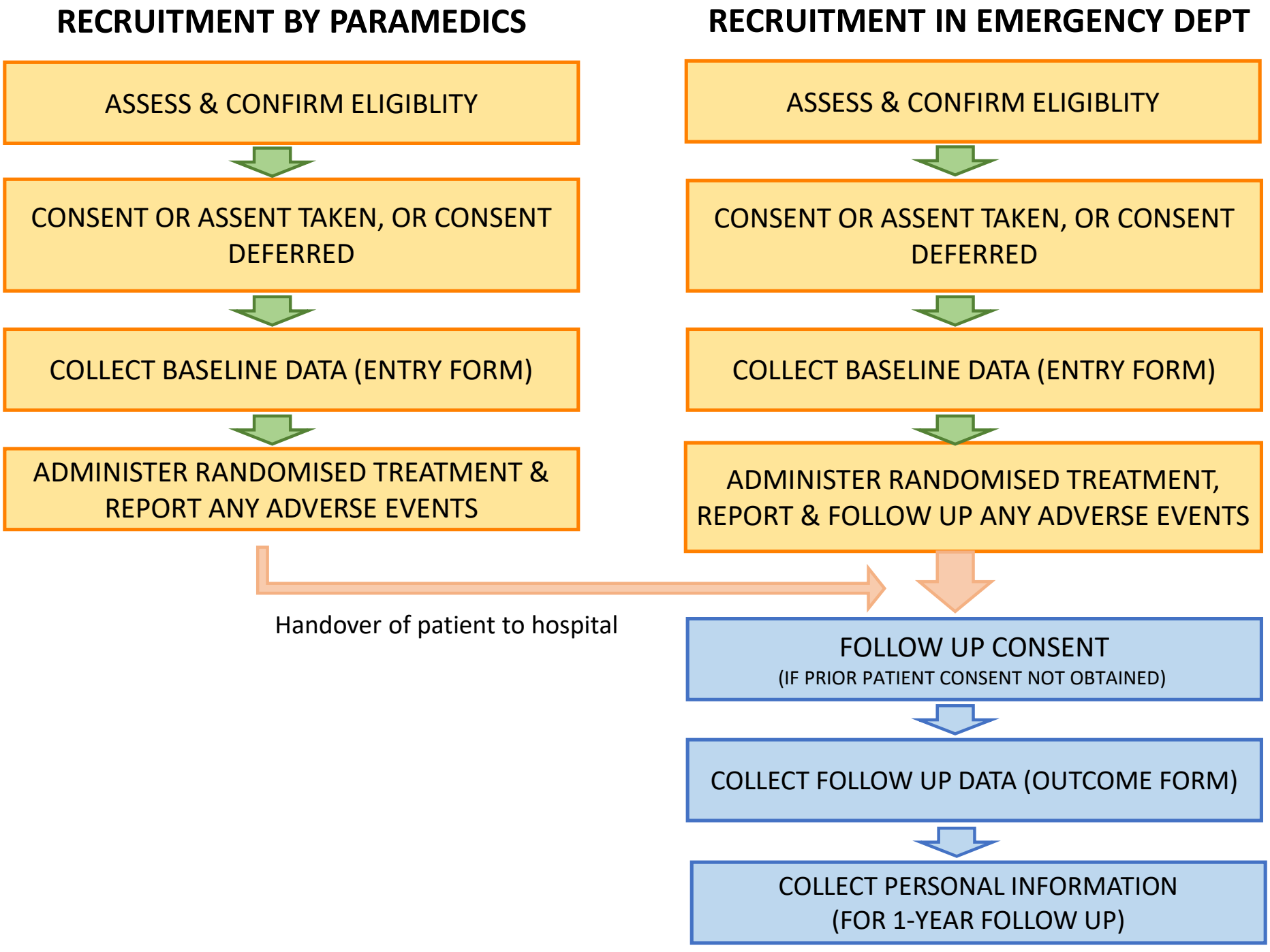
PILOT PHASE

A pilot phase is planned due to the current SARS-CoV-2 pandemic

The pilot phase will allow us to:

- assess the potential impact on recruitment rate
- determine whether the trial procedures are fit for purpose

TRIAL OVERVIEW



ELIGIBLITY CRITERIA

- Appears 50 years or more
- Signs of head injury (e.g. laceration, bruise, swelling, pain in head or face) and has/had impaired consciousness (loss of consciousness, amnesia, confusion) or nausea or vomiting
- GCS ≥ 13
- Within 3 hours of injury (do not include if interval cannot be estimated)
- Not living in nursing home, mental health institution, prison
- TXA is not indicated (e.g. major bleeding) or contraindicated (e.g. known allergy or suspected acute arterial or venous thrombosis)
- Patient will be taken to a participating hospital

ASSESSMENT OF CAPACITY TO CONSENT

- Eligible patients may not have the capacity to consent - they have sustained a symptomatic head injury and may have impaired consciousness.

- Capacity to consent needs to be assessed by the person responsible for the patient's care.

- Does the patient possess sufficient mental capability to:
  - understand the information provided, including the risks and benefits
  - appreciates how it is relevant to their circumstances
  - make a reasoned decision about whether or not to participate
  - to communicate that choice

- Relatives/friends might not be available, or if available, their capacity to give informed consent might be impaired due to shock and the short time available

CONSENT OPTIONS (1)

Where a patient has full capacity:

- Obtain written consent from patient

Where a patient does not have full capacity:

- Give information to level of capacity and obtain verbal assent – Note: this is not consent.
- Respect decision if assent not given

If patient is unable to give assent and a personal representative (relative/friend) is available and willing and able to make a decision on behalf of the patient:

- Obtain written consent from personal representative or
- Obtain verbal assent

CONSENT OPTIONS (2)

Where neither the patient or personal representative can consent or assent:

- Get consent from the Professional Legal Representative (an independent doctor working with the patient or a person nominated by the healthcare provider) if available in the emergency (unlikely to be used where patients are recruited at pre-hospital) OR
- Defer consent

FOLLOW UP CONSENT

Where deferred consent, or assent has been used:

- Obtain consent for continuation in the trial

Situations where no/missed opportunity to obtain consent:

- Patient discharged directly from ED without admission to hospital: post information sheet and consent form to patient (max 3 times)

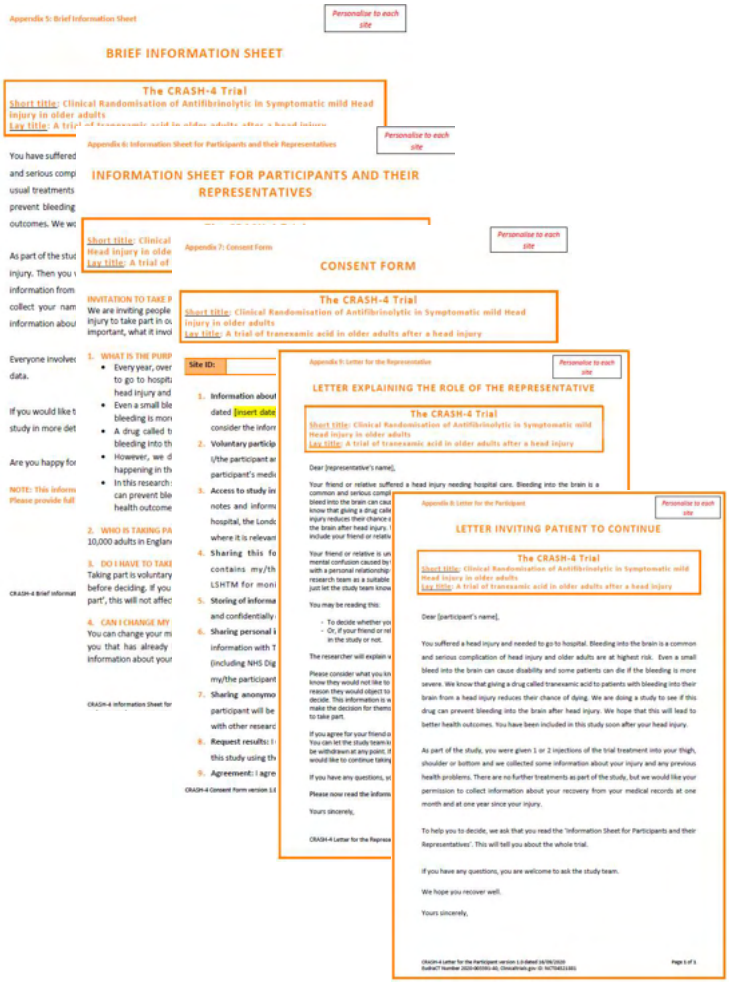
- Patient dies: the most appropriate healthcare professional should notify the relative/friend of the research involvement. Where it has been determined that obtaining informed consent from relative/friend is not appropriate, informed consent will be obtained from a PrLR

CONSENT DOCUMENTATION

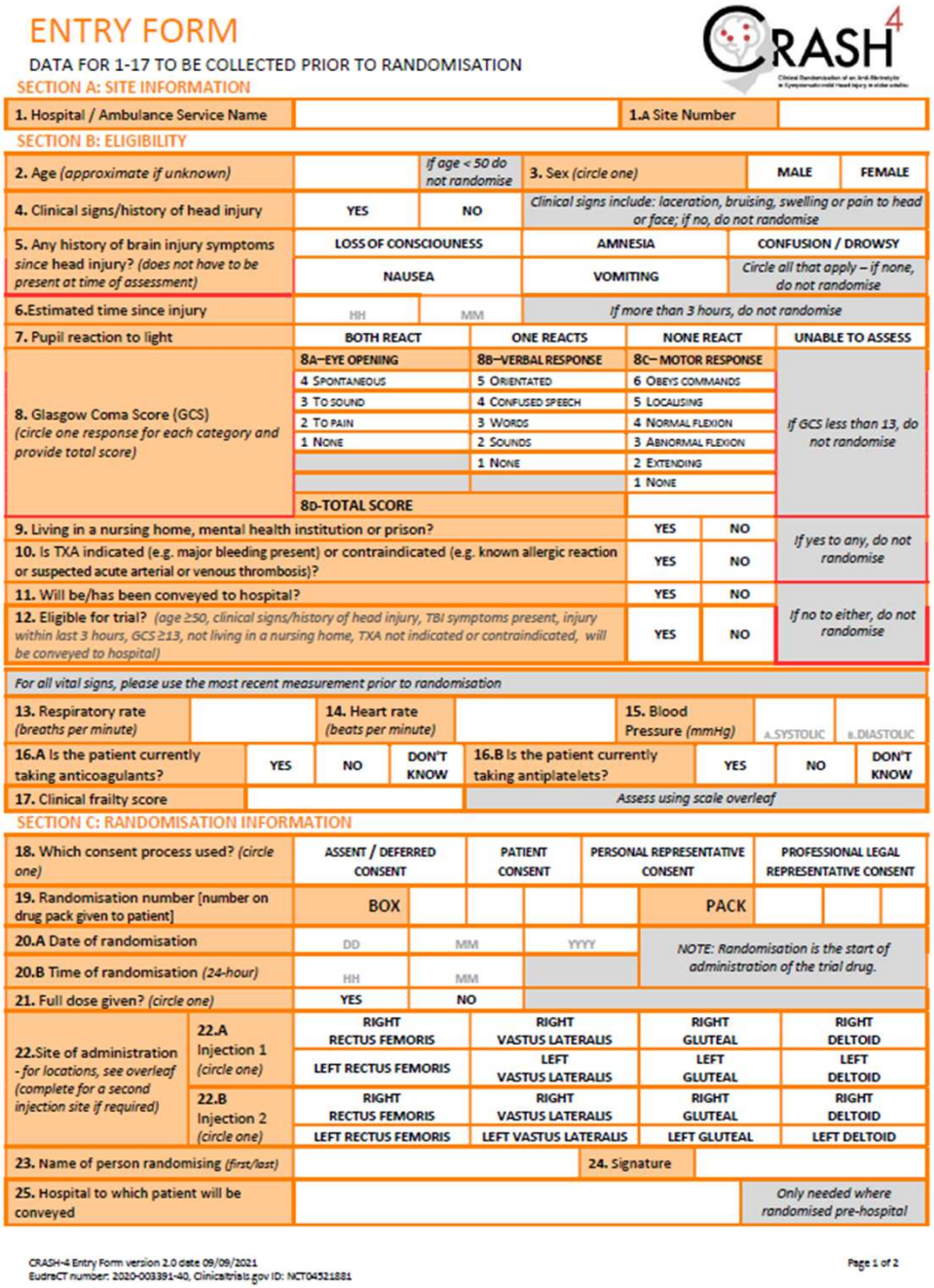
Electronic consent / paper consent

Consent documents provided:

- brief information sheet
- information sheet
- consent form
- invitation letter to the participant
- invitation letter to the representative



BASELINE DATA



ENTRY FORM

DATA FOR 1-17 TO BE COLLECTED PRIOR TO RANDOMISATION

CRASH 4

SECTION A: SITE INFORMATION

1. Hospital / Ambulance Service Name		1.A Site Number	

SECTION B: ELIGIBILITY

2. Age *(approximate if unknown)*		*If age < 50 do not randomise*	3. Sex *(circle one)*		MALE	FEMALE
4. Clinical signs/history of head injury	YES	NO	*Clinical signs include: laceration, bruising, swelling or pain to head or face; if no, do not randomise*			
5. Any history of brain injury symptoms *since* head injury? *(does not have to be present at time of assessment)*	LOSS OF CONSCIOUNESS		AMNESIA		CONFUSION / DROWSY	
	NAUSEA		VOMITING		*Circle all that apply – if none, do not randomise*	
6.Estimated time since injury	HH	MM	*If more than 3 hours, do not randomise*			
7. Pupil reaction to light	BOTH REACT		ONE REACTS		NONE REACT	UNABLE TO ASSESS

8. Glasgow Coma Score (GCS) *(circle one response for each category and provide total score)*	8A–EYE OPENING	8B–VERBAL RESPONSE	8C– MOTOR RESPONSE	*If GCS less than 13, do not randomise*
	4 SPONTANEOUS	5 ORIENTATED	6 OBEYS COMMANDS	
	3 TO SOUND	4 CONFUSED SPEECH	5 LOCALISING	
	2 TO PAIN	3 WORDS	4 NORMAL FLEXION	
	1 NONE	2 SOUNDS	3 ABNORMAL FLEXION	
		1 NONE	2 EXTENDING	
			1 NONE	
	8D-TOTAL SCORE			

9. Living in a nursing home, mental health institution or prison?	YES	NO	*If yes to any, do not randomise*
10. Is TXA indicated (e.g. major bleeding present) or contraindicated (e.g. known allergic reaction or suspected acute arterial or venous thrombosis)?	YES	NO	
11. Will be/has been conveyed to hospital?	YES	NO	
12. Eligible for trial? *(age ≥50, clinical signs/history of head injury, TBI symptoms present, injury within last 3 hours, GCS ≥13, not living in a nursing home, TXA not indicated or contraindicated, will be conveyed to hospital)*	YES	NO	*If no to either, do not randomise*

For all vital signs, please use the most recent measurement prior to randomisation

13. Respiratory rate *(breaths per minute)*		14. Heart rate *(beats per minute)*		15. Blood Pressure *(mmHg)*	A.SYSTOLIC / B.DIASTOLIC

16.A Is the patient currently taking anticoagulants?	YES	NO	DON'T KNOW	16.B Is the patient currently taking antiplatelets?	YES	NO	DON'T KNOW
17. Clinical frailty score				*Assess using scale overleaf*			

SECTION C: RANDOMISATION INFORMATION

18. Which consent process used? *(circle one)*	ASSENT / DEFERRED CONSENT		PATIENT CONSENT		PERSONAL REPRESENTATIVE CONSENT		PROFESSIONAL LEGAL REPRESENTATIVE CONSENT
19. Randomisation number [number on drug pack given to patient]	BOX					PACK	
20.A Date of randomisation	DD	MM	YYYY		*NOTE: Randomisation is the start of administration of the trial drug.*		
20.B Time of randomisation *(24-hour)*	HH	MM					
21. Full dose given? *(circle one)*	YES	NO					

22.Site of administration - *for locations, see overleaf (complete for a second injection site if required)*					
	22.A Injection 1 *(circle one)*	RIGHT RECTUS FEMORIS	RIGHT VASTUS LATERALIS	RIGHT GLUTEAL	RIGHT DELTOID
		LEFT RECTUS FEMORIS	LEFT VASTUS LATERALIS	LEFT GLUTEAL	LEFT DELTOID
	22.B Injection 2 *(circle one)*	RIGHT RECTUS FEMORIS	RIGHT VASTUS LATERALIS	RIGHT GLUTEAL	RIGHT DELTOID
		LEFT RECTUS FEMORIS	LEFT VASTUS LATERALIS	LEFT GLUTEAL	LEFT DELTOID

23. Name of person randomising *(first/last)*		24. Signature	
25. Hospital to which patient will be conveyed			*Only needed where randomised pre-hospital*

CRASH-4 Entry Form version 2.0 date 09/09/2021
EudraCT number: 2020-003391-40, ClinicalTrials.gov ID: NCT04521881

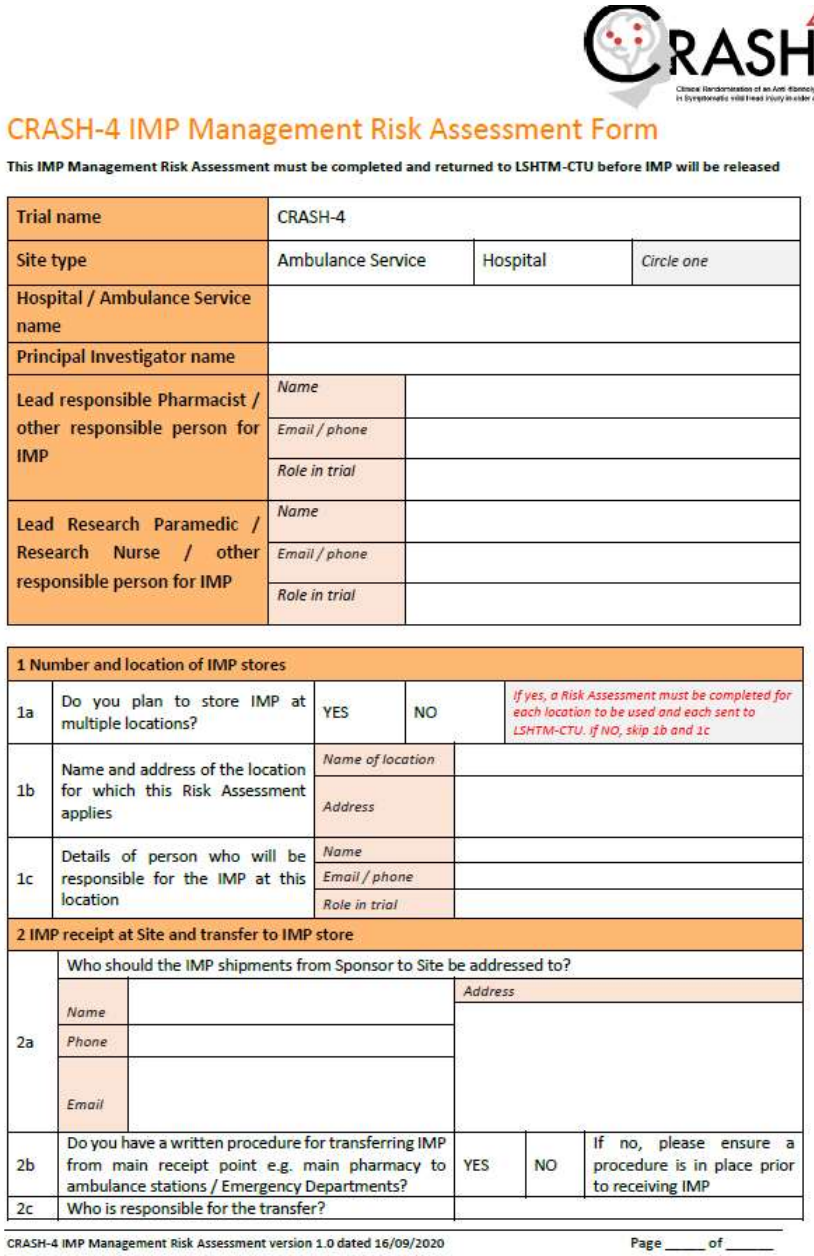
Page 1 of 2

- Complete as soon as possible
- Mostly routine clinical information
- Direct database entry or paper
- For direct database entry, have all information needed before logging in

RANDOMISATION

- The trial drug is packed according to a randomisation list
- Each drug box has 8 uniquely numbered treatment packs (number format xxxx/xxx)
- Select the lowest numbered treatment pack available and to randomise a patient
- Document who prescribed the treatment and when
- Time of randomisation is the start of the first injection
- Trial drug must be available where patients are recruited (with paramedics or Emergency Department)
- There is no need to restrict any clinically indicated treatments

INVESTIGATIONAL MEDICINAL PRODUCT (IMP) MANAGEMENT



CRASH-4 IMP Management Risk Assessment Form

This IMP Management Risk Assessment must be completed and returned to LSHTM-CTU before IMP will be released

Trial name	CRASH-4		
Site type	Ambulance Service	Hospital	*Circle one*
Hospital / Ambulance Service name			
Principal Investigator name			
Lead responsible Pharmacist / other responsible person for IMP	*Name*		
	Email / phone		
	Role in trial		
Lead Research Paramedic / Research Nurse / other responsible person for IMP	*Name*		
	Email / phone		
	Role in trial		

1 Number and location of IMP stores				
1a	Do you plan to store IMP at multiple locations?	YES	NO	*If yes, a Risk Assessment must be completed for each location to be used and each sent to LSHTM-CTU. If NO, skip 1b and 1c*
1b	Name and address of the location for which this Risk Assessment applies	*Name of location*		
		Address		
1c	Details of person who will be responsible for the IMP at this location	*Name*		
		Email / phone		
		Role in trial		
2 IMP receipt at Site and transfer to IMP store				
2a	Who should the IMP shipments from Sponsor to Site be addressed to?			
	Name		*Address*	
	Phone			
	Email			
2b	Do you have a written procedure for transferring IMP from main receipt point e.g. main pharmacy to ambulance stations / Emergency Departments?	YES	NO	If no, please ensure a procedure is in place prior to receiving IMP
2c	Who is responsible for the transfer?			

CRASH-4 IMP Management Risk Assessment version 1.0 dated 16/09/2020 Page _____ of _____

Oversight of IMP and local procedures required for security and accountability

IMP management risk assessment to be completed before trial can be started at a site

Key points:

- How will drug be made available where it is needed (ambulance or Emergency Department)?
- How will drug be accounted for when given to paramedics?
- Who will be responsible for accountability at ambulance stations/Emergency Department?

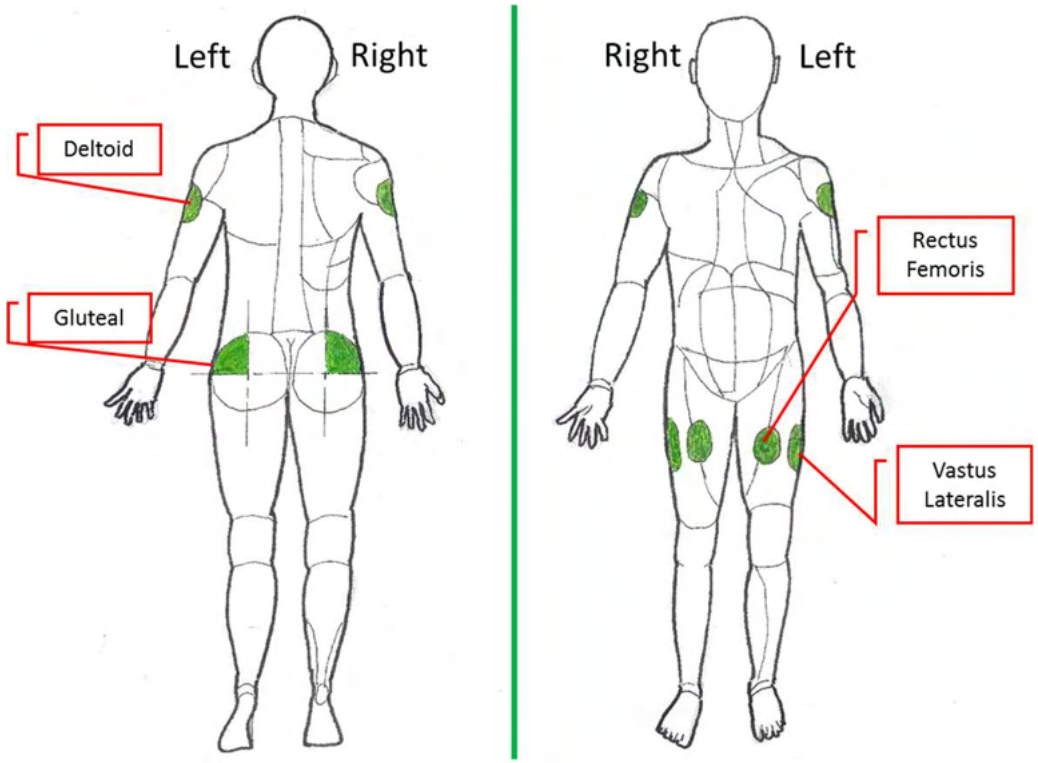
HOW TO GIVE THE TRIAL TREATMENT

- Assess the patients muscle mass; the dose (500mg TXA or placebo) can be given as either:
  - a single 5 mL intramuscular (IM) injection of 100 mg/ml or
  - two 2.5mL intramuscular injections if the muscle mass cannot accommodate a 5mL injection

- Use the most appropriate needle size for IM administration from your stock (usually 1" between 19 - 25 G and from 1 ½ inches up to 3" for large adults)

- Select injection site(s): deltoid, thigh or buttocks depending on muscle mass

- Use the Z-track method to administer to seal the medication in the muscle



SAFE HANDOVER OF PATIENTS AT HOSPITAL

Hospital staff need to know the patient has been recruited to CRASH-4 and have all the information to care for the patient and complete follow up procedures:

- place a trial wristband on the patient immediately after giving the trial drug stating 'Randomised to the CRASH-4 trial', 'Randomisation number', 'Received tranexamic acid 500mg/placebo', 'Date', 'Time (24hrs)'
- record randomisation number, the fact that the CRASH-4 trial treatment was given, by who and what time it was given on the ambulance Patient Report Form
- handover a copy of ambulance Patient Report Form to be added to the patient's medical record to ensure this information is available to the hospital team
- verbally inform the receiving Emergency Department team of the patient's recruitment in the trial

OUTCOMES

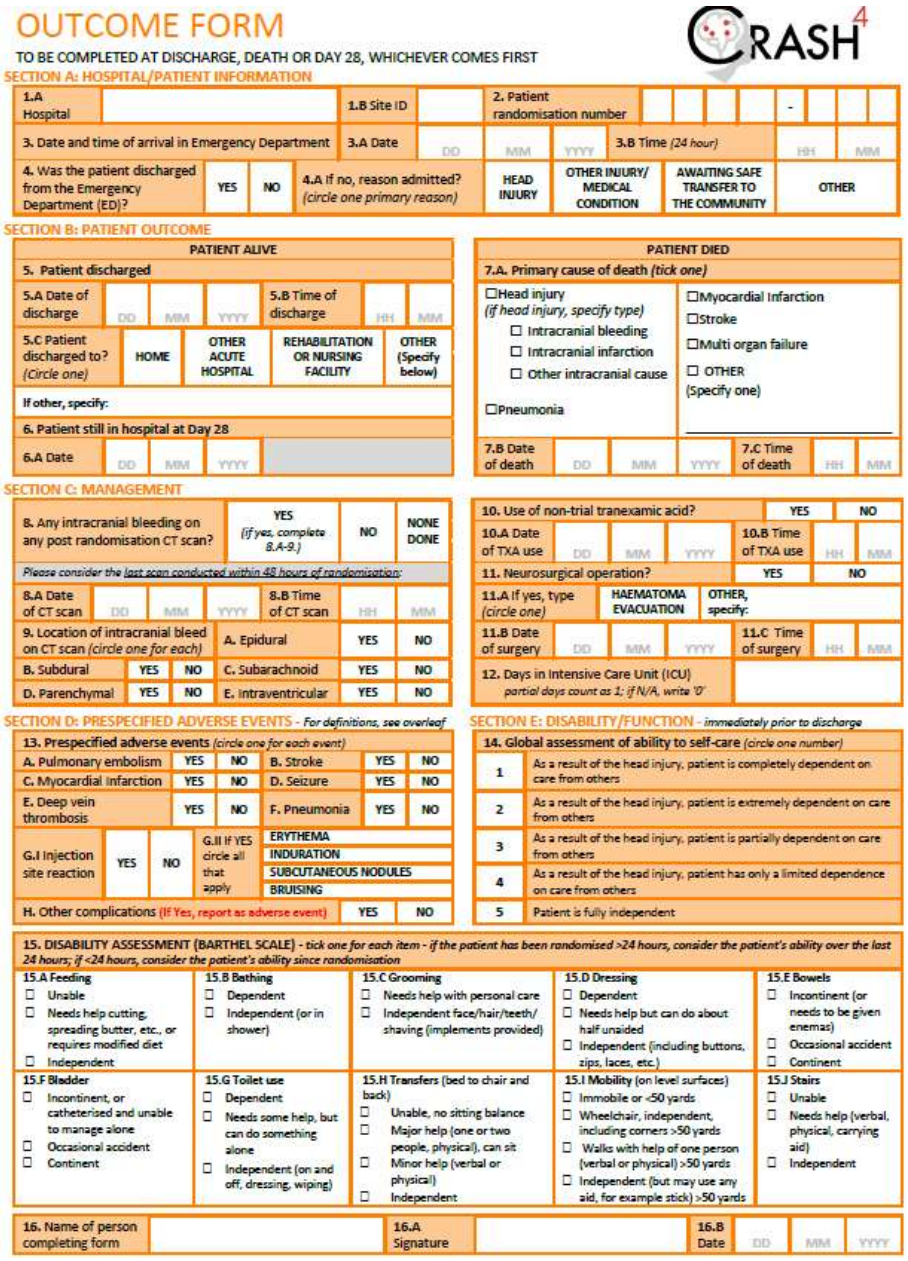
Primary Outcome:

- Discharge from the emergency department within 24 hours of arrival

Secondary Outcomes:

- Intracranial bleeding on CT scan
- Death (intracranial bleeding-related, other causes)
- Disability (Barthel scale)
- Global assessment of ability to self-care
- Patient management (neurosurgery, days in ICU, days in hospital)
- Vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis, stroke)
- Seizures
- Pneumonia
- Injection site reaction
- Other adverse events
- Re-admission to hospital (within 28 days)
- Dementia diagnosis at 1 year

OUTCOMES



OUTCOME FORM

TO BE COMPLETED AT DISCHARGE, DEATH OR DAY 28, WHICHEVER COMES FIRST

CRASH 4

SECTION A: HOSPITAL/PATIENT INFORMATION

1.A Hospital | 1.B Site ID | 2. Patient randomisation number

3. Date and time of arrival in Emergency Department | 3.A Date DD MM YYYY | 3.B Time (24 hour) HH MM

4. Was the patient discharged from the Emergency Department (ED)? YES NO | 4.A If no, reason admitted? (circle one primary reason) HEAD INJURY | OTHER INJURY/ MEDICAL CONDITION | AWAITING SAFE TRANSFER TO THE COMMUNITY | OTHER

SECTION B: PATIENT OUTCOME

PATIENT ALIVE

5. Patient discharged

5.A Date of discharge DD MM YYYY | 5.B Time of discharge HH MM

5.C Patient discharged to? (Circle one) HOME | OTHER ACUTE HOSPITAL | REHABILITATION OR NURSING FACILITY | OTHER (Specify below)

If other, specify:

6. Patient still in hospital at Day 28

6.A Date DD MM YYYY

PATIENT DIED

7.A. Primary cause of death (tick one)

☐Head injury (if head injury, specify type)
☐ Intracranial bleeding
☐ Intracranial infarction
☐ Other intracranial cause
☐Pneumonia
☐Myocardial Infarction
☐Stroke
☐Multi organ failure
☐ OTHER (Specify one)

7.B Date of death DD MM YYYY | 7.C Time of death HH MM

SECTION C: MANAGEMENT

8. Any intracranial bleeding on any post randomisation CT scan? YES (If yes, complete 8.A-9.) NO NONE DONE

Please consider the last scan conducted within 48 hours of randomisation:

8.A Date of CT scan DD MM YYYY | 8.B Time of CT scan HH MM

9. Location of intracranial bleed on CT scan (circle one for each)

A. Epidural			YES	NO
B. Subdural	YES	NO	C. Subarachnoid	YES NO
D. Parenchymal	YES	NO	E. Intraventricular	YES NO

10. Use of non-trial tranexamic acid? YES NO

10.A Date of TXA use DD MM YYYY | 10.B Time of TXA use HH MM

11. Neurosurgical operation? YES NO

11.A If yes, type (circle one) HAEMATOMA EVACUATION | OTHER, specify:

11.B Date of surgery DD MM YYYY | 11.C Time of surgery HH MM

12. Days in Intensive Care Unit (ICU) partial days count as 1; if N/A, write '0'

SECTION D: PRESPECIFIED ADVERSE EVENTS - For definitions, see overleaf

13. Prespecified adverse events (circle one for each event)

A. Pulmonary embolism	YES	NO	B. Stroke	YES	NO
C. Myocardial infarction	YES	NO	D. Seizure	YES	NO
E. Deep vein thrombosis	YES	NO	F. Pneumonia	YES	NO
G.I Injection site reaction	YES	NO	G.II If YES circle all that apply	ERYTHEMA / INDURATION / SUBCUTANEOUS NODULES / BRUISING		
H. Other complications (If Yes, report as adverse event)				YES	NO

SECTION E: DISABILITY/FUNCTION - immediately prior to discharge

14. Global assessment of ability to self-care (circle one number)

1	As a result of the head injury, patient is completely dependent on care from others
2	As a result of the head injury, patient is extremely dependent on care from others
3	As a result of the head injury, patient is partially dependent on care from others
4	As a result of the head injury, patient has only a limited dependence on care from others
5	Patient is fully independent

15. DISABILITY ASSESSMENT (BARTHEL SCALE) - tick one for each item - if the patient has been randomised >24 hours, consider the patient's ability over the last 24 hours; if <24 hours, consider the patient's ability since randomisation

15.A Feeding ☐ Unable ☐ Needs help cutting, spreading butter, etc., or requires modified diet ☐ Independent	15.B Bathing ☐ Dependent ☐ Independent (or in shower)	15.C Grooming ☐ Needs help with personal care ☐ Independent face/hair/teeth/ shaving (implements provided)	15.D Dressing ☐ Dependent ☐ Needs help but can do about half unaided ☐ Independent (including buttons, zips, laces, etc.)	15.E Bowels ☐ Incontinent (or needs to be given enemas) ☐ Occasional accident ☐ Continent
15.F Bladder ☐ Incontinent, or catheterised and unable to manage alone ☐ Occasional accident ☐ Continent	15.G Toilet use ☐ Dependent ☐ Needs some help, but can do something alone ☐ Independent (on and off, dressing, wiping)	15.H Transfers (bed to chair and back) ☐ Unable, no sitting balance ☐ Major help (one or two people, physical), can sit ☐ Minor help (verbal or physical) ☐ Independent	15.I Mobility (on level surfaces) ☐ Immobile or <50 yards ☐ Wheelchair, independent, including corners >50 yards ☐ Walks with help of one person (verbal or physical) >50 yards ☐ Independent (but may use any aid, for example stick) >50 yards	15.J Stairs ☐ Unable ☐ Needs help (verbal, physical, carrying aid) ☐ Independent

16. Name of person completing form | 16.A Signature | 16.B Date DD MM YYYY

- **Primary Outcome: Discharge from the emergency department within 24 hours of arrival**
- Outcome form to be completed at discharge, death, or Day 28 (whichever is sooner)
- Complete electronically (via database) or paper (then upload)
- Complete from medical records (so all information on the form has to be recorded there)
- If patient discharged from ED, need local procedures in place to collect disability data Q14 and Q15

ADVERSE EVENT (AE) REPORTING

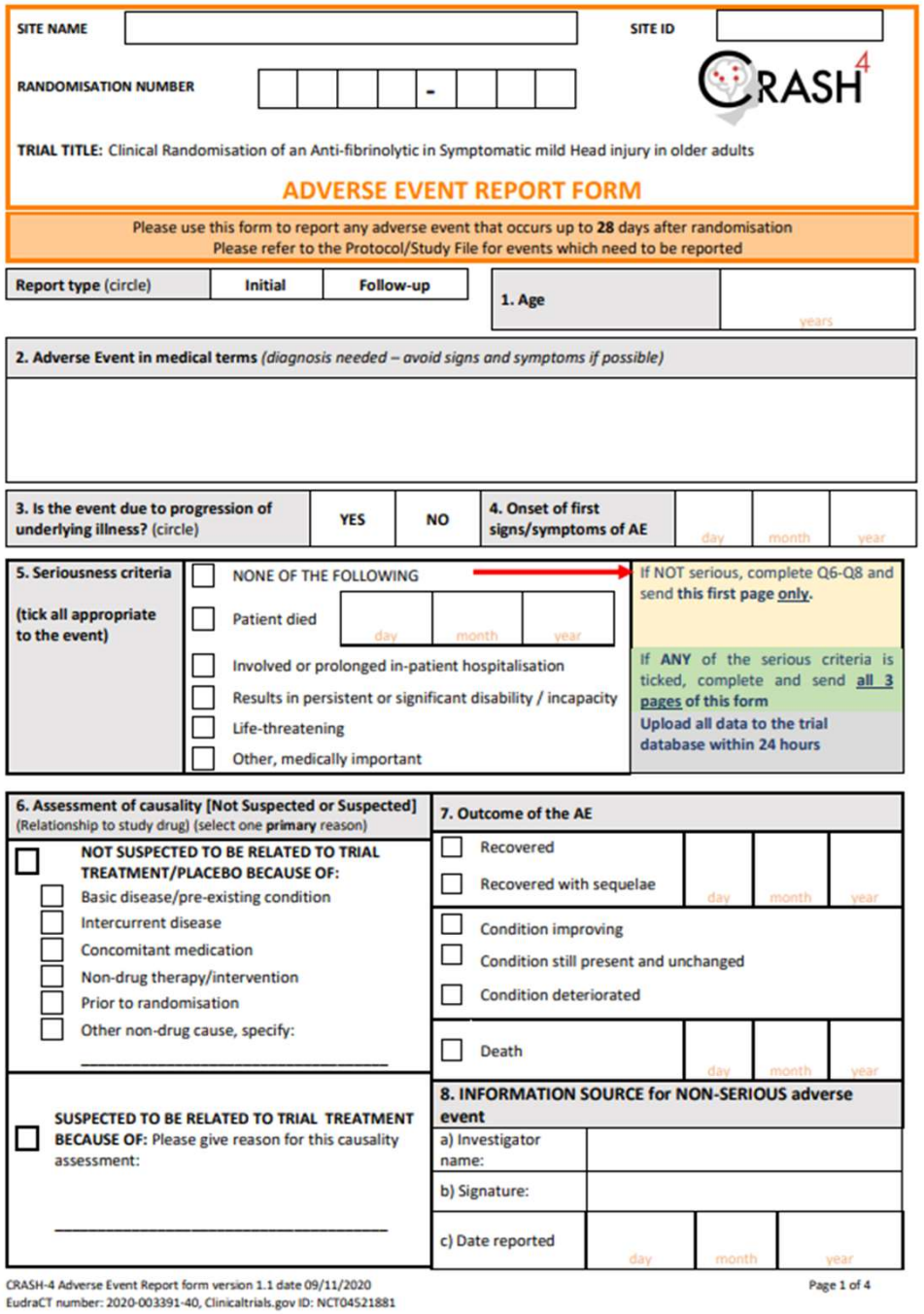
AEs to be reported (up to 28 days after randomisation):
Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product

Do not report:
Events already listed as outcomes, or those that relate to a pre-existing condition (including the patient's head injury) or any planned hospitalisations for elective treatment of a pre-existing condition

If a patient is discharged before 28 days:
AEs reported after discharge will include all pre-specified adverse outcome events

- See protocol page 21 for further information
- If you need advice on AE reporting, call emergency helpline
- Give patient an alert card if discharged before 28 days

HOW TO REPORT AN ADVERSE EVENT



SITE NAME | SITE ID | RANDOMISATION NUMBER | CRASH-4

TRIAL TITLE: Clinical Randomisation of an Anti-fibrinolytic in Symptomatic mild Head injury in older adults

ADVERSE EVENT REPORT FORM

Please use this form to report any adverse event that occurs up to **28** days after randomisation
Please refer to the Protocol/Study File for events which need to be reported

Report type (circle): Initial | Follow-up

1. Age ____ years

2. Adverse Event in medical terms *(diagnosis needed – avoid signs and symptoms if possible)*

3. Is the event due to progression of underlying illness? (circle): YES | NO

4. Onset of first signs/symptoms of AE: day / month / year

5. Seriousness criteria (tick all appropriate to the event)

- ☐ NONE OF THE FOLLOWING → If NOT serious, complete Q6-Q8 and send **this first page only**.
- ☐ Patient died (day / month / year)
- ☐ Involved or prolonged in-patient hospitalisation
- ☐ Results in persistent or significant disability / incapacity
- ☐ Life-threatening
- ☐ Other, medically important

If **ANY** of the serious criteria is ticked, complete and send **all 3 pages of this form**
Upload all data to the trial database within 24 hours

6. Assessment of causality [Not Suspected or Suspected] (Relationship to study drug) (select one **primary** reason)

☐ **NOT SUSPECTED TO BE RELATED TO TRIAL TREATMENT/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 TRIAL TREATMENT BECAUSE OF:** Please give reason for this causality assessment: _____

7. Outcome of the AE

- ☐ Recovered
- ☐ Recovered with sequelae (day / month / year)
- ☐ Condition improving
- ☐ Condition still present and unchanged
- ☐ Condition deteriorated
- ☐ Death (day / month / year)

8. INFORMATION SOURCE for NON-SERIOUS adverse event

a) Investigator name:
b) Signature:
c) Date reported (day / month / year)

CRASH-4 Adverse Event Report form version 1.1 date 09/11/2020
EudraCT number: 2020-003391-40, Clinicaltrials.gov ID: NCT04521881

Page 1 of 4

- Use Adverse Event Report Form
- Complete electronically (via database) or paper (and upload)
- If event is **serious**, report to LSHTM-CTU within 24 hours of becoming aware of the event
- Complete form as fully as possible
- Submit follow up report as soon as additional information known (but no later than five working days of becoming aware of the event)
- Event must be reported with assessment of seriousness, causality, and expectedness.

UNBLINDING

If an investigator wishes to give additional TXA, they can do so without the need to unblind (only receive ½ gram in the trial)

Can unblind a patient if clinical management depends importantly upon knowledge of whether the patients received TXA or placebo

Contact the emergency 24-hour unblinding service at:

+44(0)7768 707500

If some contraindication to TXA develops after randomisation, the usual standard care should be given

Complete unblinding request form within 24 hours

1 YEAR OUTCOME

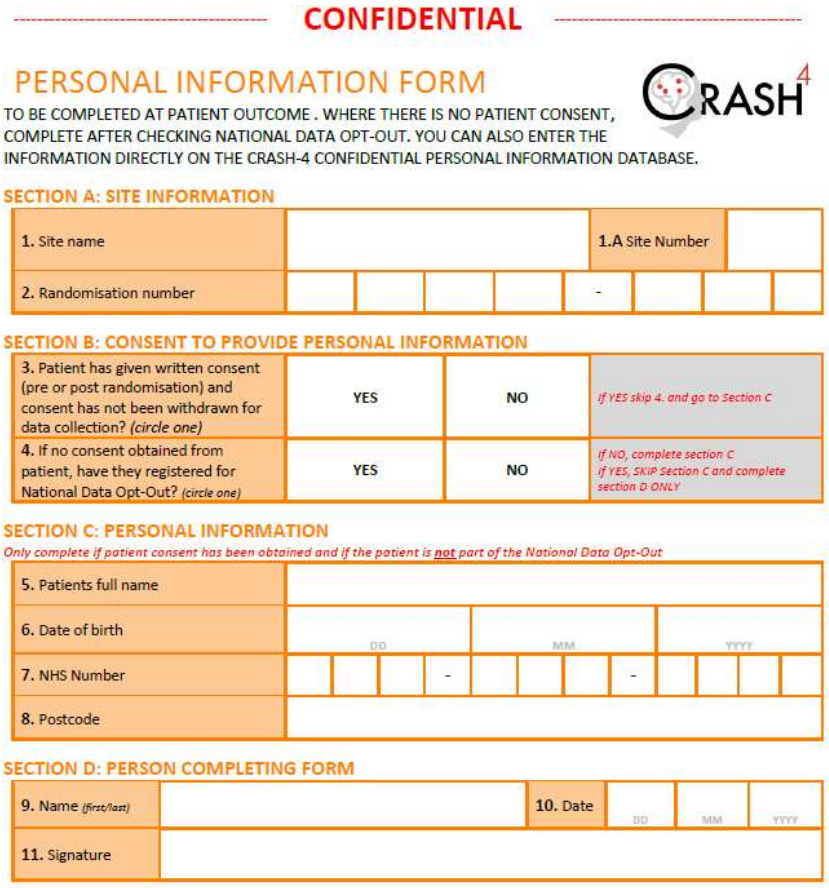
- 1-year outcome data for incidence of dementia to be provided by NHS digital/NHS Wales Informatics Service

- Confidential Personal Information (CPI) needed to link to HES data

- Personal Information Form sent after:
  1. patient has consented OR
  2. confirming the patient is not part of the National Data Opt-Out scheme

- Personal Information Form can be uploaded directly onto the personal information database – no need to complete a paper form

- CPI will be held in a separate database to trial data



CONFIDENTIAL

PERSONAL INFORMATION FORM

CRASH-4

TO BE COMPLETED AT PATIENT OUTCOME . WHERE THERE IS NO PATIENT CONSENT, COMPLETE AFTER CHECKING NATIONAL DATA OPT-OUT. YOU CAN ALSO ENTER THE INFORMATION DIRECTLY ON THE CRASH-4 CONFIDENTIAL PERSONAL INFORMATION DATABASE.

SECTION A: SITE INFORMATION

1. Site name		1.A Site Number	
2. Randomisation number		-	

SECTION B: CONSENT TO PROVIDE PERSONAL INFORMATION

3. Patient has given written consent (pre or post randomisation) and consent has not been withdrawn for data collection? *(circle one)*	YES	NO	*if YES skip 4. and go to Section C*
4. If no consent obtained from patient, have they registered for National Data Opt-Out? *(circle one)*	YES	NO	*if NO, complete section C if YES, SKIP Section C and complete section D ONLY*

SECTION C: PERSONAL INFORMATION

Only complete if patient consent has been obtained and if the patient is not part of the National Data Opt-Out

5. Patients full name			
6. Date of birth	DD	MM	YYYY
7. NHS Number	-	-	
8. Postcode			

SECTION D: PERSON COMPLETING FORM

9. Name *(first/last)*		10. Date	DD	MM YYYY
11. Signature				

POST DISCHARGE REQUIREMENTS

- Give patient an alert card if discharged before 28 days
- **If a patient is discharged before 28 days and readmitted:** AEs include all pre-specified adverse outcome events
- Re-admission to hospital (within 28 days) is a secondary outcome: need local procedure in place to flag patients

TRIAL TRAINING

Paramedic

- Self-directed online training package online
- Local procedures training: contact Research Paramedic for access details
- Evidence of completion provided. End test pass rate of 90% needed.

Principal Investigator, Research Paramedics, Research Nurses, Pharmacists

- Training materials available online
- Site initiation training webinar held with LSHTM-CTU
- Once relevant training has been completed, staff must log training on the training log available in the investigator site file
- All staff must complete training relevant to their role in the trial
- Remote training using videoconference or teleconference can be provided by the LSHTM-CTU as needed

LOCAL PROCEDURES – AMBULANCE SERVICE

- How will the Principal Investigator and Research Paramedic know when a patient is randomised?
- Who will complete the Drug Accountability Log and Randomisation Log?
- How will you ensure the treatment packs get signed back in at the end of each shift and not left in kit bags (especially at Make Ready centres)
- Who will handle data queries?

How will the paramedics know:

- Where to collect and return drugs
- How and where to sign drugs in and out at each station i.e. paper or electronic documentation
- What to do with broken/damaged drug pack - do they return to the station or destroy
- What to do with a used pack – do they return the empty box to the station, or destroy
- Who to contact if they lose a pack
- What to do if their system goes off-line and so they can’t enter data or they need urgent advice?

LOCAL PROCEDURES – IN-HOSPITAL

- How will everyone be informed of the trial?
- Where patient is recruited pre-hospital 'out of hours' who will be responsible for handover of patients to ED and ensuring follow up by research team?
- For those patients not recruited pre-hospital, how will potentially eligible patients be identified?
- Who will obtain consent and complete entry data? Will this be done electronically?
- What is the process for ensuring that the trial drug is secure but accessible in the emergency setting? Who will monitor the trial drug?
- How will you know if a patient is due for discharge or has died?
- How will you track randomised patients to make sure follow-up is done on time?
- How will you ensure that the QoL measure is routinely done for all patients?
- How will adverse events be monitored and reported as per the protocol?

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

CLINICAL TRIALS UNIT

CRASH 4

Clinical Randomisation of an Anti-fibrinolytic in Symptomatic mild Head injury in older adults

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