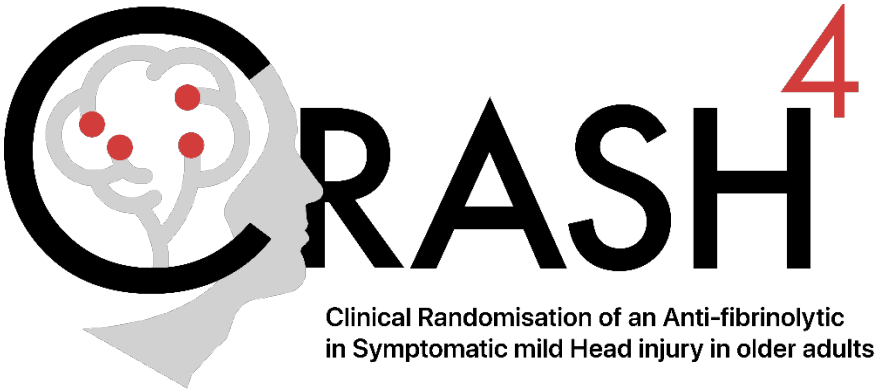

STUDY PROTOCOL

FULL TITLE	**Intramuscular tranexamic acid for the treatment of symptomatic mild traumatic brain injury in older adults: a randomised, double-blind, placebo-controlled trial**
SHORT TITLE	**Clinical Randomisation of an Anti-fibrinolytic in Symptomatic mild Head injury in older adults**
ACRONYM	**CRASH-4**

IRAS Number	283157
EudraCT Number	2020-003391-40
Clinicaltrials.gov Number:	NCT04521881
Sponsor's ID Number:	2020-KEP-456

NUMBER	DATE
V1.3	15/06/2021

[This protocol has regard for the HRA guidance]

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PROTOCOL SUMMARY

FULL TITLE OF STUDY	Intramuscular tranexamic acid for the treatment of symptomatic mild traumatic brain injury in older adults: a randomised, double-blind, placebo-controlled trial		
SHORT TITLE	Clinical Randomisation of Antifibrinolytic in Symptomatic mild Head injury in older adults		
TRIAL ACRONYM	CRASH-4		
SPONSOR'S ID NUMBER	2020-KEP-456		
EUDRACT NUMBER	2020-003391-40	**CLINICALTRIALS.GOV ID:**	NCT04521881

BACKGROUND: A fall from standing height in older adults is the commonest cause of major trauma in the UK. Traumatic brain injury (TBI) accounts for half of trauma admissions in older adults and is a leading cause of death and disability. Because the population aged over 70 years is increasing, the number of older adults with TBI will continue to rise. Most (90%) of the 1.4 million TBI patients seen each year in emergency departments in England and Wales have mild (Glasgow Coma Scale (GCS) score 13-15) head injury, but the term 'mild' is misleading in older adults who have higher death rates and worse outcomes than younger patients. Due to increased use of anticoagulant and antiplatelet drugs, older adults are more likely to suffer intracranial bleeding after mild TBI. TBI is also a strong risk factor for dementia in older adults.

Tranexamic acid (TXA) reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. Results from randomised trials (CRASH-3 and NCT01990768) show that early treatment with TXA reduces head injury deaths (pooled RR 0.89, 95% CI 0.80-0.99). In the CRASH-3 trial, the reduction in head injury deaths with TXA was largest in patients with mild and moderate head injuries, particularly if patients were treated soon after injury. However, the CRASH-3 trial included mild TBI patients only if they had intracranial bleeding on CT scan. It is uncertain whether the results apply to mild TBI patients more generally.

Intracranial bleeding occurs soon after injury and early treatment is most effective. We have shown that TXA is rapidly absorbed after intramuscular injection in trauma patients without local side effects. This means that paramedics can give intramuscular TXA before transport to hospital, and for those who do not travel by ambulance, intramuscular TXA can be given immediately on hospital arrival. If early intramuscular TXA treatment reduces death and disability in older adults with mild TBI this would be a major medical advance that would improve the care of many millions of patients in the UK and world-wide.

AIM: The CRASH-4 trial aims to provide reliable evidence about the effects of early intramuscular TXA on intracranial haemorrhage, disability, death, and dementia in older adults with symptomatic mild head injury.

OBJECTIVES: To assess the effectiveness and safety of early intramuscular TXA administration in older adults with mild head injury. Outcomes include the proportion of patients discharged from the emergency department within 24 hours of arrival, intracranial bleeding on CT scan, neurosurgery, death due to intracranial bleeding and the risk of dementia at 1 year. Key safety outcomes include vascular occlusive events, seizures, and pneumonia. The pilot phase will test all trial procedures and will also establish the impact of the SARS-CoV-2 pandemic on the trial. This will allow us to modify the procedures for recruitment and data collection for the main trial.

TRIAL DESIGN: A randomised, double blind, placebo-controlled trial in symptomatic mild TBI in about 10,000 older adults. The pilot phase will include about 500 patients.

ELIGIBILITY CRITERIA:

- 70 years or older (actual or estimated)
- History or evidence of head injury (e.g. laceration, bruise, swelling or pain in head or face)
- GCS ≥ 13
- Has one or more of the following symptoms:
  - has or had any impaired consciousness (loss of consciousness, amnesia, or confusion)
  - nausea or vomiting
- Within 3 hours of injury (do not include if interval cannot be estimated e.g. patient unable to confirm time of fall or patient found on floor after an unwitnessed fall and home alone)
- Not living in a nursing home, mental health institution or prison
- Patient will be conveyed to or is admitted to a participating hospital
- TXA not clearly indicated (e.g. major bleeding) or contraindicated (e.g. known allergic reaction or suspected acute arterial or venous thrombosis)
- Not known to have a diagnosis of dementia

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: Patients will be randomised to receive either 500mg TXA or matching placebo (a single 5mL IM injection of 100mg/ml or two x 2.5mL IM injections) as soon as possible after injury but no later than 3 hours, into the thigh (rectus femoris or vastus lateralis), buttocks (gluteal muscles) or arm (deltoid muscle) depending on muscle mass.

DURATION OF TREATMENT AND PARTICIPATION: A dose of 500mg TXA will be given intramuscularly as soon as possible after injury. Outcome will be assessed in-hospital at discharge, death, or 28 days after randomisation, whichever occurs first. Where patients are discharged before day 28, readmission to hospital will be collected until day 28. Dementia diagnosis will be collected 1 year after randomisation from the HES dataset via NHS Digital / NHS Wales Informatics Service (NWIS). For recruited patients, the trial ends at death or 12 months after randomisation.

PRIMARY OUTCOME: The primary outcome is discharge from the emergency department within 24 hours of arrival.

SECONDARY OUTCOMES:

a. Intracranial bleeding on CT scan
b. Death (intracranial bleeding-related, other causes)
c. Disability (Barthel scale)
d. Global assessment of ability to selfcare functioning
e. Vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis, stroke)
f. Seizures
g. Pneumonia
h. Injection site reaction
i. Other adverse events
j. Patient management (neurosurgery, days in ICU, days in hospital)
k. Re-admission to hospital within 28 days
l. Dementia diagnosis at 1 year

SETTING: This trial will be conducted in ambulance services and emergency departments in the UK and coordinated from the Clinical Trials Unit, London School of Hygiene & Tropical Medicine.

CRITERIA FOR EVALUATION: All patients randomly assigned to one of the treatments will be analysed together, regardless of whether they completed or received that treatment or not, on an intention to treat basis.

CLINICAL PHASE	3		
PLANNED TRIAL START	01 June 2020	**PLANNED RECRUITMENT START**	01 November 2020
PLANNED DATE OF LAST PATIENT ENROLMENT	31 January 2025	**PLANNED DATE OF LAST OUTCOME**	28 February 2026

1 BACKGROUND AND RATIONALE

1.1 BACKGROUND

A fall from standing height in older adults is now the commonest cause of major trauma in the UK.[1] Traumatic brain injury (TBI) accounts for half of trauma admissions in older adults and is the leading cause of trauma death and disability. Because the population aged over 70 years is increasing, the burden of TBI in older adults will continue to rise. Although older adults' equal right to care is enshrined in the NHS constitution, services are not configured to their needs. Injury severity is frequently underappreciated in older adults so they are more likely to be transferred to a local trauma unit rather than a major trauma centre, be seen by a junior doctor and wait longer for investigation and treatment.[1–3]

Most (90%) of the more than one million TBI cases seen in UK emergency departments is categorised as mild (Glasgow Coma Scale (GCS) score 13-15),[4] but the term 'mild' is misleading in older adults who have higher death rates and worse neurological outcomes than younger adults.[5–7] TBI is a strong risk factor for dementia, particularly in older adults.[8–10] Even mild TBI without loss of consciousness doubles dementia risk.[9] Due to increased use of anticoagulant and antiplatelet drugs, older adults are more likely to suffer intracranial bleeding after mild TBI. However, because they can have significant bleeding despite being fully conscious (GCS score of 15), CT scanning and neurosurgery are often delayed compared to younger patients.[1,11,12] Intracranial bleeding is a strong risk factor for dementia.[13] MRI studies show that one quarter of patients with mild TBI have microbleeds that are not seen on CT scan.[14,15] Traumatic microvascular damage causes leakage of red cells and the resulting inflammatory response to blood in the brain tissue leads to brain cell loss.[16] Cohort studies show microbleeds increase the risk of cognitive decline.[17,18]

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine binding sites on plasminogen. TXA reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fibrinolysis).[19] Plasminogen produced by the liver is converted into the fibrinolytic enzyme plasmin by the tissue plasminogen activator (tPA). Plasminogen and tPA bind to lysine residues on fibrin leading to localised plasmin formation and fibrin cleavage.[20] TXA is a molecular analogue of lysine that inhibits fibrinolysis by competing with fibrin for the lysine binding sites in plasminogen. TXA inhibits the capacity of plasminogen and plasmin to bind to fibrin, hence preserving blood clots from plasmin-mediated lysis.[19]

The CRASH-3 trial showed that early TXA treatment reduces head injury deaths.[21] Because the trial only included patients with mild TBI if they had evidence of intracranial bleeding on CT scan, the results are not readily generalizable to all mild TBI patients. This group represents a large patient population for which it remains unclear whether TXA treatment is warranted. The CRASH-4 trial

will investigate the safety and efficacy of TXA for the treatment of mild TBI (GCS score 13-15) in older adults.

We conducted a systematic review of trials of TXA in November 2019, searching Ovid MEDLINE, Embase, Cochrane Controlled Register of Trials (CENTRAL), clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). We identified eight trials of TXA for TBI. One study was an open-label trial with inadequate randomisation and allocation concealment resulting in a high risk of bias.[22] Five small randomised controlled trials provided some evidence to suggest TXA may reduce mortality in TBI, although the estimates were imprecise and the quality of evidence was low to moderate.[23–26] There was also evidence of a reduction in intracranial bleeding and no increase in vascular occlusive events with TXA. These studies were summarised in a recent systematic review and meta-analysis.[27] Since then, two large randomised controlled trials (CRASH-3 and NCT01990768) have provided high quality evidence of a reduction in death from TBI with TXA (pooled RR 0.89, 95% CI 0.80-0.99).[21,28]

Although the pharmacokinetics of TXA after intravenous (IV) administration has been well studied, there have been fewer studies of intramuscular (IM) use of TXA. We conducted a systematic review of pharmacokinetic (PK) studies of TXA administered by IM injection and found two studies in healthy volunteers.[29,30] These showed that the bioavailability of TXA after IM injection is over 95% with therapeutic TXA levels (>10 mg/L)[31] achieved within about 30 minutes from the administration. There were no adverse effects. The meta-analysis and pharmacokinetic modelling based on data from these studied showed that TXA therapeutic level would be reached in less than 30 minutes in both healthy volunteers and trauma patients,[32] but larger studies were needed in relevant patient populations. The Trauma-INTACT trial (ClinicalTrials.gov: NCT03875937) assessed the PK of TXA administered intramuscularly in bleeding trauma patients, and the PharmacoTXA trial (ClinicalTrials.gov: NCT03777488) is assessing the PK of TXA administered intramuscularly or orally in healthy volunteers. Data from the Trauma-INTACT trial of the IM administration of TXA in 30 bleeding trauma patients show that IM TXA is well tolerated with only mild and transient reactions at the injection site. Furthermore, TXA is rapidly absorbed reaching therapeutic levels within 11 minutes.

1.2 Rationale

The CRASH-3 trial showed that early TXA treatment reduces head injury deaths.[21] The trial recruited 9,202 adult TBI patients within 3 hours of injury, who had a GCS score of 12 or less or GCS 13-15 and intracranial bleeding on CT scan. Early treatment of patients with 'complicated' mild (GCS 13–15 and intracranial bleeding on CT scan) and moderate TBI (GCS 9-12) conferred the greatest survival benefit. Because bleeding occurs soon after injury, rapid treatment is critical. There is a 10% reduction in the survival benefit with TXA for every 20-minute treatment delay.

Severe TBI patients have less to gain from TXA because they have extensive bleeding before treatment and have other intracranial pathologies that are unaffected by TXA. These results raise the possibility that early treatment of older adults with mild TBI could prevent intracranial bleeding and reduce the risks of dementia, disability, and death. There was no increase in thrombotic adverse events with TXA.[21]

The CRASH-3 trial changed the way that TBI patients are treated in the NHS. Patients with a GCS score of 12 or less, or any intracranial bleeding on CT scan will get IV TXA at the scene of the injury or after CT scanning in hospital. However, older adults with mild TBI (GCS 13 to 15) will not receive pre-hospital TXA and by the time they have been scanned and assessed in hospital, for most patients, it will be too late to receive TXA, or too late to achieve the full benefits of early treatment.[1,33] Older TBI patients also tend to have more intracranial bleeding and worse neurological outcomes.

The CRASH-4 trial will test early IM TXA treatment in older adults with mild TBI. PK research has shown that TXA is rapidly absorbed after IM injection in trauma patients, without local side effects. This means that paramedics can give IM TXA before transport to hospital, and for those who do not travel by ambulance, IM TXA can be given immediately on hospital arrival (without waiting for IV cannula insertion). Although absorption from muscle involves a short delay compared with IV treatment, our PK data show that immediate IM treatment can achieve therapeutic levels much sooner than with a delayed IV injection.

Because TXA has an excellent safety profile in trauma patients and prevents life threatening intra-cranial and extra-cranial bleeding, it is best considered a preventive intervention, more akin to vaccination, than as a treatment for bleeding. If early IM TXA treatment improves outcomes in high risk older adults and is shown to be safe, this would radically change how TXA is used in the NHS.

While mild head injury remains an important public health problem, the SARS-CoV-2 pandemic currently presents a huge challenge to the NHS. As well as having worse outcomes in mild head injury, older adults have an increased risk of death from COVID-19 infection and are being strongly advised to follow social distancing measures. A safe and effective treatment for mild head injury that can be easily administered at home would avoid the need for older adults to be admitted to hospital, reducing the strain on NHS resources and allowing older adults to return home as soon as possible to maintain social distancing and shielding thereby reducing their risk of contracting COVID-19.

The CRASH-4 trial will recruit 10,000 patients with symptomatic mild head injury. We will conduct a pilot phase in the first 500 participants primarily because the trial is focused on older adults who are an at-risk population in the current SARS-CoV-2 pandemic. The UK government's strong recommendation on social distancing measures for adults aged ≥70 years may impact their willingness to access care, call an ambulance, or attend an emergency department. It may also

influence the willingness of medical staff to convey or admit patients presenting with mild head injury to hospital given the balance of risks and benefits in the face of COVID-19 infection. The pilot phase will allow us to assess the potential impact of the SARS-CoV-2 pandemic on recruitment rates and determine whether the trial procedures are fit for purpose mid-pandemic or need adapting.

2 AIM AND OBJECTIVES

The CRASH-4 trial will provide reliable evidence about the effects of early IM TXA on intracranial haemorrhage, disability, death, and dementia in older adults with symptomatic mild head injury.

The main trial will assess the effectiveness of early IM TXA for intracranial haemorrhage in mild head injury by measuring the proportion of patients discharged from the emergency department within 24 hours of arrival, the frequency of intracranial bleeding on CT scan, incidence of in-hospital head injury-related death within 48 hours of injury, and incidence of dementia at 1 year.

We will assess the safety of early IM TXA for mild head injury in older adults by measuring the frequency of adverse events including vascular occlusive events, seizures, pneumonia, and other events in the TXA and placebo groups. Cause-specific mortality at 28 days will also be recorded.

The pilot phase will establish if the SARS-CoV-2 pandemic impacts recruitment and whether alternative procedures are necessary for effective recruitment and data collection. The pilot will also test the trial procedures and establish event rates.

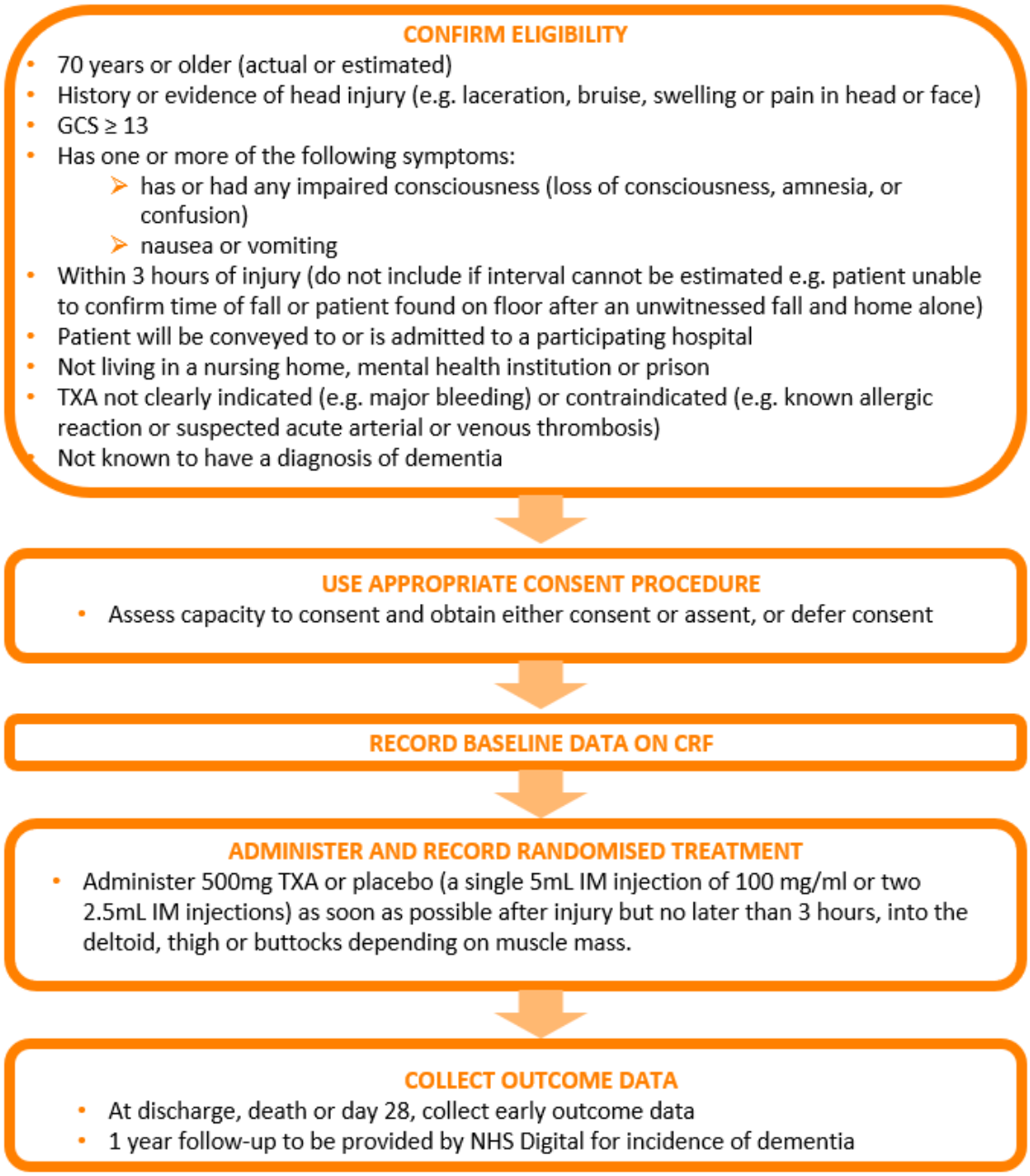
3 TRIAL DESIGN AND PROCEDURES

3.1 TRIAL DESIGN

The CRASH-4 trial is a, randomised, double-blind, placebo-controlled trial to test the safety and efficacy of TXA for symptomatic mild head injury in 10,000 older adults. Patients nor the researchers or clinical team caring for the patients will know which study group the patients are in.

The trial will be conducted by ambulance services and in emergency departments of trauma centres and trauma units in the UK.

3.2 TRIAL OVERVIEW



3.3 TRIAL SETTING

This is a multicentre trial. Patients will be screened by clinicians authorised to diagnose and consent patients for their clinical care (paramedics, nurses and medical doctors) and, if eligible, consent or assent will be taken or consent will be deferred, baseline data will be collected and the trial treatment administered. Follow up of patients will occur in-hospital for early outcomes and via NHS Digital / NHS Wales Informatics Service (NWIS) at 1 year after randomisation. Patients may be recruited on scene by ambulance services or after presenting to emergency departments of both trauma centres and trauma units. The pilot phase will include 500 patients to allow us to assess the potential impact of the SARS-CoV-2 pandemic on recruitment rates and determine whether the trial procedures are fit for purpose mid-pandemic or need adapting.

3.4 RECRUITMENT OF TRIAL SITES

All NHS Ambulance Trusts, major trauma centres and trauma units in England and Wales will be invited to take part. Site suitability will be assessed on interest in the trial, the number of potentially eligible patients they look after and their willingness to put in place facilities to ensure the trial can be conducted in their setting. A risk assessment for Investigational Medicinal Product (IMP) handling and storage will be made for each site before a site can be accepted. Before any site can enrol patients into the study, the London School of Hygiene and Tropical Medicine (LSHTM) Clinical Trials Unit (CTU) will ensure that appropriate approvals from participating organisations, relevant regulatory and ethics approvals are in place and the site principal investigator has agreed to conduct the trial according to the Protocol, ICH-Good Clinical Practice guidelines, data protection and all relevant regulations.

3.5 ELIGIBILITY OF PARTICIPANTS

INCLUSION CRITERIA

- 70 years or older (actual or estimated)
- History or evidence of head injury (e.g. laceration, bruise, swelling or pain in head or face)
- GCS ≥ 13
- Has one or more of the following symptoms:
  - has or had any impaired consciousness (loss of consciousness, amnesia, or confusion)
  - nausea or vomiting
- Within 3 hours of injury (do not include if interval cannot be estimated e.g. patient unable to confirm time of fall or patient found on floor after an unwitnessed fall and home alone)
- Patient will be conveyed or is admitted to a participating hospital

- Not living in a nursing home, mental health institution or prison
- TXA not clearly indicated (e.g. major bleeding) or contraindicated (e.g. known allergic reaction or suspected acute arterial or venous thrombosis)
- Not known to have a diagnosis of dementia

3.6 INFORMATION GIVING AND CONSENT PROCEDURE

Potential trial participants will have experienced a TBI and may have impaired consciousness and therefore may be unable to provide informed consent to participate in the trial. Additionally, 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. Where relatives are available but are self-isolating or self-shielding because of COVID-19, witnessed verbal consent or assent can be obtained by phone/video. Eligibility for inclusion in this trial will need to be assessed immediately and trial procedures started as soon as possible. An overview of the consent procedure is provided in Appendix 10.

3.6.1 ASSENT / CONSENT PROCEDURE FOR ENROLMENT

Patient: Patients will be given verbal information appropriate to the level of their capacity bearing in mind their clinical condition. Specifically, the trial will be explained verbally, supported by use of a written brief information sheet if needed (Appendix 5), and verbal assent will be obtained. If the patient objects to inclusion, their views will be respected. If the patient is competent to give fully informed consent, full information about the trial will be given (Appendix 6) and s/he can sign the informed consent form (Appendix 7).

Relative/friend assent/consent: If a patient cannot give assent or consent, a relative or friend may act as a Personal Legal Representative (PeLR). If a relative or a friend is immediately available (in person or by phone/video) and bearing in mind their level of shock and time available, they will be provided with a letter explaining their role as a representative (Appendix 9) and given written information about the trial. If they are willing and able to act as a PeLR then their consent will be obtained. If the PeLR is on the phone/video, the information will be read to them in the presence of a witness. If there is insufficient time due to the nature of the patient's condition, then brief information will be given either verbally (in person or by phone/video) or using the brief information sheet. Investigators can use the exact wording or can add further information verbally to support the needs of the relative/friend in their decision making. They will then be asked to give their assent for their relative/friend to be included in the trial. If the PeLR is on the phone/video, they will be asked to assent in the presence of a witness. If the relative/friend objects to the patient's inclusion, their views will be respected.

Professional Legal Representative (PrLRs) consent: If a patient or PeLR cannot give assent or consent, an independent healthcare professional identified by the healthcare provider may act as a Professional Legal Representative (PrLR). It is unlikely that a PrLR will be available when a patient is being considered for randomisation at home or in an ambulance. In this case, if a patient is unable to consent/assent and no relatives/friends are available or willing or able to consent/assent, then the consent process will be deferred. Each participating hospital will identify individuals independent of this trial who can act as a PrLR. A list of PrLRs will be maintained in the Investigator Site File (ISF). If a PrLR is immediately available, and a patient cannot provide assent/consent for her/himself and a relative/friend is either unable, unwilling to act as a PeLR or not available to provide assent/consent, consent can be obtained in hospital from a PrLR.

Deferring consent: In the event the patient cannot give assent/consent, no relative or friend is present (or is unable/unwilling to make a decision), and a PrLR is not immediately available, informed consent will be deferred. In this case the treating healthcare professional will consider the patient's eligibility, any known views of the patient about trial participation and will decide whether or not to randomise the patient into the trial.

3.6.2 Information giving and consent procedure after randomisation

As soon as the emergency is over and the patient regains capacity, the patient will be given a letter explaining they have been enrolled in the trial (Appendix 8) and the information sheet. The patient will be asked to consent to their continuation in the study. If after the emergency is over and the patient does not regain capacity, but a relative/friend becomes available (in person or by phone/video if self-isolating/self-shielding because of COVID-19) and is willing and able to act as a PeLR, they will be given a letter explaining their role as a representative and the information sheet. If the PeLR is on the phone/video, the information will be read to them in the presence of a witness. The PeLR will be asked to consent to the patients' continuation in the trial. If the PeLR is on the phone/video, they will be asked to give their verbal consent in the presence of a witness and the witness will be responsible for signing the consent form. If consent was deferred and the patient does not regain capacity and no relative/friend becomes available during hospitalisation, the PrLR should provide written consent.

It is likely that some patients will be discharged directly from the emergency department without admission to hospital and the opportunity to obtain consent in hospital might be missed. In these cases, the research team can post the information sheet and consent form to the patient for their consideration up to a maximum of 3 times.

3.6.3 Patient dies before consent and relatives/friends become available

It is anticipated that approximately 10% of patients will die. When a participant dies before consent has been sought, the site investigators should obtain information from colleagues to establish the most appropriate health care professional to notify the PeLR of the research involvement. Written informed consent can be sought from PeLRs following the death of their relative/friend and prior to their departure from the hospital. However, it is at the discretion of the site staff to determine if this is appropriate for each individual situation. Where it has been determined that obtaining PeLR informed consent is not appropriate, informed consent will be obtained from a PrLR.

3.6.4 Documenting the consent process

The method of initial consent will be recorded on the Entry Form. Where consent was not initially obtained from the patient, subsequent attempts made to obtain consent from the patient or other representatives should be recorded in the participant's medical notes or a log stored in the ISF. The site investigators should retain the original signed and dated consent form and a copy should be given to the person providing consent. Sites may choose to use an electronic method to obtain consent to minimise the risk of cross-infection from COVID-19. In this case, the approved information sheet and consent forms will be uploaded to a secure RedCap system which will be housed on the LSHTM secure server. The forms can then be signed and will be stored as a .pdf document in the Site electronic Investigator's Site File. Copies can then be printed or emailed securely via RedCap secure transfer to the consent giver. Alternatively, trial Sites may host their own electronic consent system which must comply with General Data Protection Regulation (GDPR) and regulatory requirements.

3.6.5 Consent procedure for collecting confidential personal information for follow-up

As TBI is a strong risk factor for dementia in older adults, data on dementia diagnosis will be collected at 1 year after randomisation using data linkage from the UK NHS Hospital Episode Statistics (HES) dataset via NHS Digital/NWIS. To link to the HES dataset we will need to collect Confidential Personal Information (CPI). Consent will be obtained from participants where possible.

As there may be instances where consent cannot be obtained from the patient themselves (for example if consent was deferred prior to randomisation and the patient did not regain capacity to consent) we will apply for Section 251 support from the HRA Confidential Advisory Group (CAG) to collect CPI in the absence of participant consent.

3.7 BASELINE DATA

The entry form (Appendix 2) will be completed by the recruiting healthcare professional prior to randomisation to confirm eligibility and collect baseline data, which include the following:

- Site details (name and ID number)
- Patient characteristics (age, sex)
- Eligibility criteria and prognostic factors (clinical signs of head injury, brain injury symptoms, estimated time since injury, pupil reaction to light, GCS, respiratory rate, heart rate, blood pressure)
- Concomitant medication (anticoagulants and antiplatelets)
- Randomisation details (consent process used, randomisation number, name of person randomising)
- Trial drug administration details (date, time, site of administration and if full dose given)

3.8 RANDOMISATION AND BLINDING

3.8.1 RANDOMISATION

Block randomisation will be used to increase the probability that each arm will contain a similar number of individuals. A randomisation list will be generated by an IT specialist not involved in the trial using Stata's random-number generation and seed function. The randomisation codes will be given to clinical trial supply company by the IT Specialist in a secure way so that blinded treatment packs can be prepared. Patients will be randomised by selecting and administering the dose from a uniquely numbered treatment pack from a box of blinded packs (identical apart from the pack number) held by participating site. Time of randomisation will be when administration of the first injection starts. Patients, their caregivers, and all trial staff will be masked to treatment allocation.

3.8.2 BLINDING

Treatment and placebo ampoules will be identical in appearance. A designated clinical trial supply company approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) will carry out the blinding process in line with EU GMP Annex 13. In summary, the original manufacturer's labels will be completely removed and replaced with the clinical trial label bearing a randomisation number used to identify the treatment pack. The label will clearly state that the contents is for IM injection only. All other packaging will be identical for both TXA and placebo.

The first stage Qualified Person release will also be done by the designated clinical trial supply company. They will maintain the Product Specification File until final database lock and after unblinding of the trial data and will be responsible for archiving it. Second stage release will be done by appropriately qualified personnel from LSHTM-CTU.

3.9 TRIAL TREATMENTS

Patients will receive a 500mg dose of TXA or placebo by IM injection within 3 hours of injury. The dose can be given as a single 5 mL injection or divided into two injections of 2.5 mL each into the thigh (rectus femoris or vastus lateralis), buttocks (gluteal muscles) or arm (deltoid muscle), depending on a clinical assessment of muscle mass. The injections will be given using the most appropriate needle size for IM administration from the sites stock (1" between 19 - 25 G and from 1 ½ inches up to 3" for large adults) using the Z-track method to seal the medication in the muscle.[34]

3.10 OUTCOME MEASURES

The Outcome Form (Appendix 3) will be used to collect short term (in-hospital) outcomes at discharge, death, or 28 days after randomisation, whichever occurs first. Long term outcomes on dementia incidence will be collected one year after randomisation by data linkage using the UK NHS Hospital Episodes Statistics (HES) / via NWIS. Recent studies in pre-hospital care (e.g. AIRWAYS-2 and PARAMEDIC-2) have shown that it is feasible to track patients from the pre-hospital setting through to hospital admission with a high degree of success.[35, 36]

3.11 PRIMARY OUTCOME

The primary outcome is discharge from the emergency department within 24 hours of arrival. Patients will be assessed for discharge by a registered healthcare professional. If a patient is discharged from the emergency department without admission to hospital, their head injury is of minimal concern to the treating clinician and the patient is considered to have a good outcome. Patients will be admitted for further observation if they have clinically significant abnormalities on head CT, their GCS does not return to 15 after imaging, they have continuing worrying signs, or have indications for CT scanning but it cannot be done at that time.[37] Additionally, admissions may be unrelated to the head injury e.g. for other injuries or medical conditions, drug or alcohol intoxication, or if safe transfer to the community or suitable supervision at home is not possible at that time. If the patient is admitted, we will record the reason for admission (head injury, other injury, or medical condition, awaiting safe transfer to community, other). Date and time of discharge will be recorded. Patients still in hospital at 28 days will be classified as such and the reason they remain in hospital will be recorded (head injury, other).

In older patients with mild TBI, death is important but relatively uncommon, limiting its use as a primary outcome measure. About half of older patients admitted to hospital for a mild TBI are discharged to rehabilitation, nursing or care facilities due to their cognitive, physical, and behavioural impairments,[38–41] however, discharge destination is influenced by provision of institutional care and ability of family members to provide care. Early discharge from the

emergency department is an objective outcome measure that should be influenced only by the extent of brain injury. It is important to patients and the NHS, and most importantly, has the potential to be affected by pre-hospital TXA treatment.

3.12 SECONDARY OUTCOMES:

Secondary outcomes are as follows:

- **Intracranial bleeding on CT scan:** Among patients who undergo a head CT scan within 48 hours of randomisation, evidence of intracranial bleeding and location of bleeding will be recorded.
- **Death:** In-hospital head injury-related death within 48 hours of injury, and all-cause and cause-specific mortality within 28 days.
- **Disability:** The Barthel Scale will be used to assess functional disability at the point of discharge, or at 28 days if the patient is still in hospital. In the COVID-19 pandemic situation, priority will be given to discharging patients from hospital as quickly as possible. If the Barthel Scale is not completed prior to discharge, the research team may contact the patient / relative via telephone to obtain this information as soon as possible, and no later than 1 week after discharge.
- **Global assessment of ability to self-care:** Patients' ability to self-care at discharge/day 28 will be recorded (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 to a great extent 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 is only to a limited extent dependent on care from others; 5. As a result of the head injury, patient fully independent). In the COVID-19 pandemic situation, priority will be given to discharging patients from hospital as quickly as possible. If the global assessment of ability to self-care is not completed prior to discharge, the research team may contact the patient / relative via telephone to obtain this information as soon as possible, and no later than 1 week after discharge.
- **Patient management:** Neurosurgery (type of surgery and time to surgery), days in the intensive care unit and days in hospital up to discharge, death or 28 days will be recorded.
- **Re-admission to hospital:** Re-admissions up to 28 days after randomisation will be identified through the adverse event reporting procedure.
- **Pre-specified adverse events:** Vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis and stroke), seizures, injection site reaction and pneumonia up to 28 days will be recorded.
- **Other adverse events:** As defined in Section 4 of the protocol up to 28 days.
- **Dementia:** The occurrence of all-cause dementia will be determined 12 months after randomisation. Dementia will be identified through linkage to routinely collected health-care

data from NHS Digital / NWIS. Two recent systematic reviews showed that the accuracy of dementia diagnosis in these routinely collected datasets is generally high.[42, 43] Dementia will be defined according to ICD-10 codes. Studies of the accuracy of dementia diagnoses in HES dataset (using data from a large mental health care database as gold standard) show that the specificity of dementia recording is high (92%).[44] Although the sensitivity of diagnosis was 78%, when assessing outcome measures in clinical trials, provided there are few false positives (high specificity), estimates of the relative risk are unbiased even when sensitivity is imperfect.

3.13 WITHDRAWAL CRITERIA

A patient can leave the trial at any time. If withdrawal from the trial is requested by a patient or their representative, they may provide the site investigators with the reason(s) for leaving the study, but this not mandatory and their wishes will be respected. If a patient withdraws, the site investigators should inform the LSHTM-CTU. If the patient or their representative wishes to discontinue the trial treatment but allows on-going data collection, the treatment will be discontinued, and all outcome data will be collected. The patient's data will be handled as per section 5.5.2 (Data handling and record keeping).

3.14 UNBLINDING

Unblinding should only be done when the treating clinician believes that clinical management depends importantly upon knowledge of whether the patients received TXA or placebo. A 24-hour unblinding telephone service will be available. The caller will be sent an email detailing which treatment the patient received. An unblinding report form should be completed by the investigator and sent to the LSHTM-CTU within one working day. If some contraindication to TXA develops after randomisation, the usual standard care should be given. If an investigator wishes to give additional TXA, they can do so without the need to unblind.

3.15 END OF TRIAL

All patients will be followed up in-hospital until discharge, death, or 28 days after randomisation, whichever occurs first. Dementia diagnosis will be collected 1 year after randomisation from the HES dataset via NHS Digital / NWIS. The trial ends for a participant at death or 1 year after randomisation. The trial may be terminated early by the Sponsor on the advice of the Trial Steering Committee (TSC). The independent Data Monitoring Committee (DMC) may give advice to the TSC for the early termination of the trial but the TSC and Sponsor are responsible for the final decision.

The trial will end when NHS Digital / NWIS provide the 1-year follow-up data for the final randomised patient.

4 PHARMACOVIGILANCE

4.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	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. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP).
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death; • is life-threatening; • requires inpatient hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability/incapacity • other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the in the Investigator's Brochure (IB).

4.2 ADVERSE EVENTS

Events recorded on the Outcome Form (Appendix 3) up to discharge, death, or day 28 (whichever occurs first) will not be included in the definitions detailed in Section 4. These pre-specified adverse outcome events include vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis and stroke), seizures, pneumonia, injection site reactions, intracranial bleeding on CT scan and causes of death. The LSHTM-CTU will present data on these pre-specified adverse outcome events to the independent DMC for regular review. These events will not be reported using the Adverse Events reporting procedure.

However, all other medical events fulfilling the Adverse Event definition (including ARs, SAEs, SARs and SUSARs), will be reported up to 28 days after administration of the trial treatment. In the event a patient is discharged before 28 days, adverse events reported after discharge will also include all pre-specified adverse outcome events.

At discharge, participants will be given an 'alert card' that identifies them as a CRASH-4 participant, and asked to present this card to anyone providing medical care after discharge, or to use the information to report any medical problems they may be experiencing to the trial team up to day 28. Adverse Events (AE) considered related to the trial medication as judged by a site investigator or the LSHTM-CTU should be followed either until resolution, or the event is considered stable.

Events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition will not be reported as AEs.

4.3 Reporting procedures

The reporting procedure is summarised as a flowchart in Appendix 11.

Adverse Events (AEs)/Adverse Reactions (ARs): AEs and ARs should be reported using an Adverse Event Reporting Form. Events which fulfill the serious criteria must be reported to the LSHTM-CTU within 24 hours of the Principal Investigator (PI) or delegate becoming aware of the event. The form must be completed and submitted to the LSHTM-CTU with as much detail of the event that is available at that time. If awaiting further details, a follow up report must be submitted promptly upon receipt of any additional information (but no later than five working days of becoming aware of the event). The site PI or medical delegate must record the event with an assessment of seriousness, causality, and expectedness.

The causality of Serious Adverse Eventss (SAEs) (i.e. relationship to trial treatment) will be assessed by the investigator(s) using the following:	
Relationship	**Description**
Suspected to be related	There is evidence to suggest a causal relationship with administration of the trial treatment and the influence of other factors is unlikely.
Not suspected to be related	There is little or no evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

In the case of an SAE/Serious Adverse Reaction (SAR), the staff at the site should:

- Contact the LSHTM-CTU immediately by phone or email to obtain guidance on the reporting procedure if needed. Emergency contact information can be found in the ISF.
- Submit an Adverse Event Report, completed with all available information (within 24 hours, together with anonymised copies of all relevant clinical investigations).

- Submit any additional information promptly upon request.

Adverse Event Reporting Forms can be submitted in the following ways:

- Directly via the trial database (see ISF for full details)
- Scanned copies of paper forms by email: crash4data@lshtm.ac.uk

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS): All SAEs assigned by the Site PI or medical delegate as suspected to be related to the trial treatment will be assessed for expectedness against the Reference Safety Information (RSI) (Tranexamic Acid 500mg/5ml Solution for Injection Summary of Product Characteristics (SmPC) produced by Focus Pharmaceuticals Limited, date of revision 05 July 2018) by LSHTMCTU. Events, which are unexpected, will be classified as SUSARs and reported to the Sponsor who will then report to the MHRA and Ethics Committee as follows:

- Fatal or life threatening SUSARs within 7 days. Any additional relevant information will be reported within eight calendar days of the initial report.
- All other SUSARs within 15 days.

Treatment codes will be unblinded for specific participants if required. Site PIs, relevant regulatory agencies and ethics committees will be informed of all SUSARs for all studies using TXA sponsored by LSHTM, whether or not the event occurred in the CRASH-4 trial.

ANNUAL SAFETY REPORTING: The Sponsor will prepare an annual Development Safety Update Report (DSUR) which includes, in particular:

- an analysis of safety data concerning trial participants
- a description of the participants included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial.

The DSUR will be submitted to the MHRA no later than 60 calendar days from the DSUR data lock point which will be set based as the date of the first clinical trial authorisation approval of the IMP and each year until final closeout (currently 6 November).

REPORTING URGENT SAFETY MEASURES: Any urgent safety measures taken by the Chief Investigator (CI)/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, will be reported in writing to the MHRA and the relevant Research Ethics Committee (REC) of the measures taken and the circumstances giving rise to those measures.

4.4 Data Monitoring Committee (DMC)

To provide protection for study participants, an independent DMC has been appointed for this trial to oversee the safety monitoring. The DMC will review on a regular basis accumulating data from the ongoing trial and advise the TSC regarding the continuing safety of current participants and those yet to be recruited, as well as reviewing the validity and scientific merit of the trial.

The DMC composition, name, title and address of the chairman and of each member, will be given in the DMC Charter, stored in the Trial Master File (TMF), which will be in line with that proposed by the DAMOCLES Study Group (DAMOCLES Study Group 2005). Membership includes expertise in the relevant field of study, statistics, and clinical trials. An independent statistician will be appointed to provide the unblinded analysis required by the DMC.

The DMC Charter includes, but is not limited to, defining:

- the schedule and format of the DMC meetings
- the format for presentation of data
- the method and timing of providing interim reports
- stopping rules

The DMC 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 TSC. The DMC Charter states that they will do this if, and only if, the following 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, participants in terms of the major outcome; and (2) the results, if revealed, would be expected to substantially change the prescribing patterns of clinicians 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. The DMC Charter is in agreement with the Peto-Haybittle stopping rule whereby an interim analysis of a major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure (Haybittle 1971; Peto 1977). 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 require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgment.

4.5 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one ‘lay’ representative. The TSC will have an independent Chairperson. 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, post, or teleconferencing. The TSC 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 DMC
- informing and advising the Trial Management Group (TMG) on all aspects of the trial

A TSC Charter will be agreed at the first meeting and will detail the composition of the committee and how the committee will conduct its business. The TSC Charter will be stored in the TMF.

When outcome data are available for 500 trial participants, the TSC will review the rate of recruitment into the trial and the overall event rates. The TSC will consider the extent to which the rate of recruitment and the event rates correspond to those anticipated before the trial and will take whatever action is needed in light of this information. Final decisions regarding changes to the Protocol resides with the Sponsor.

5 DATA MANAGEMENT AND ANALYSIS

5.1 SAMPLE SIZE

The sample size depends on the control group event rate and the size of the treatment effect. In a US cohort study of 1,316 adults presenting to the emergency department in 11 trauma centres from 2014-16 with symptomatic mild head injury and a head CT scan indicated, approximately 35% were discharged from the emergency deparment.[45] The admission rate might be higher in older adults, who comprised only a tenth of this cohort. In CENTER-TBI Core study, a European cohort study of TBI patients, 17% of 1,254 adults ≥65 years were discharged from the emergency department, although the study included mild, moderate and severe head injury.[46] Because TXA is inexpensive and widely practicable, even a modest increase in the proportion of patients discharged early would be worthwhile. Assuming pre-hospital IM TXA treatment could increase the proportion of older adults discharged from the emergency department from 25% to 29% (RR=1.15) then a study of 10,000 patients would have 95% power at the 0.01 level of significance.

5.2 STATISTICS AND DATA ANALYSIS

The main analyses will compare all those allocated TXA versus those allocated placebo, on an 'intention to treat' basis, irrespective of whether they received the allocated treatment or not. Results will be presented as appropriate effect estimates (relative risks and absolute risks) with a measure of precision (95% confidence intervals). There is strong evidence that TXA will be most effective when given soon after injury. We will examine this hypothesis by conducting a sub-group analysis of the effect of TXA according to the time interval between injury and TXA treatment (≤1, >1-2, >2-3). Other subgroup analyses for the primary outcome will also include the age, severity of TBI (GCS, pupil reaction to light), anticoagulant/antiplatelet use, and baseline risk. Interaction tests will be used to test whether the effect of treatment (if any) differs across these subgroups. Between-sites heterogeneity in effectiveness will also be explored. A secondary analysis will be conducted in which the primary outcome will be adjusted by age, anticoagulant/antiplatelet use, pupil reaction to light, blood pressure and GCS. All analyses will be conducted in Stata 16. A detailed Statistical Analysis Plan setting out full details of the proposed analyses will be finalised before the trial database is locked for final analysis.

5.3 PROCEDURE(S) TO ACCOUNT FOR MISSING OR SPURIOUS DATA

Missing data will be recorded and presented as such, not imputed.

5.4 ECONOMIC EVALUATION

If IM TXA is found to be a safe and effective treatment for mild head injury in older adults, we will undertake an economic evaluation of the intervention.

5.5 DATA MANAGEMENT

5.5.1 CASE REPORT FORMS AND SOURCE DATA

Data will be collected at each site (ambulance service or hospital) by local investigators and sent to the LSHTM-CTU. Data outlined on the entry, outcome and adverse event forms will be collected, as well as data on dementia at 1 year after randomisation.

The **entry form** (Appendix 2) will be used before randomisation to confirm eligibility and collect baseline data. Source data for information collected on the entry form will include ambulance record card, ambulance electronic data, hospital admission records and the patient's medical and nursing records. Clinical observations (e.g. GCS, Blood pressure, heart rate) and type of consent used may be recorded directly on the case report forms (CRF).

The **outcome form** (Appendix 3) will be completed 28 days after randomisation or at death or hospital discharge. These data will be collected from the patient's routine medical records and no special tests will be required. Therefore, all source data should be available in the patient's medical records. In the COVID-19 pandemic situation, priority will be given to discharging patients from hospital as quickly as possible. If the Barthel Scale and global assessment of ability to self-care are not recorded in the patient's medical records prior to discharge, the research team may contact the patient / relative via telephone to obtain this information as soon as possible, and no later than 1 week after discharge. Where data is obtained from the patient or relative by telephone, the outcome CRF will be considered the source data.

The **personal information form** (Appendix 4) will be used to collect personal information (name, date of birth, NHS number and postcode). This information will be collected after confirming that the patient has consented for the trial or, if no patient consent is available, that they have not previously opted-out of sharing their personal information (as part of the National Data Opt-Out scheme). This information will be collected from the patient's medical records. This information will only be kept until 1-year follow-up data has been completed.

Data used for **Adverse Event report forms** must be available in the patient's medical records.

5.5.2 DATA HANDLING AND RECORD KEEPING

The data controller for the trial is the CI and the data processor is the LSHTM-CTU.

Site investigators will collect data on paper or directly onto electronic CRFs, whichever is most suitable for each trial site. Original paper CRFs will remain at each trial site. Entry, Outcome, and

Adverse Event Data will be transmitted to LSHTM-CTU by data entry into the trial database by authorised site investigators. Where data has been entered directly onto the trial database, sites should download / print a copy for their ISF.

Personal information will be collected for 1-year follow-up using the HES dataset via NHS Digital / NWIS. Site investigators will ensure that patient consent is obtained for this information to be sent to LSHTM-CTU where possible and for onward transmission to NHS Digital / NWIS. If a patient is unable to provide consent, then their personal information will be sent to LSHTM-CTU only if a representative consent has been obtained and Message Exchange for Social Care and Health (MESH) has been used to check that the patient has not previously opted out of sharing their personal information. If a patient does not provide consent and had previously opted-out of sharing their personal information, then no personal information will be sent.

If a patient or their representative withdraws a previously given informed consent, or refuses to consent for continuation in the trial, the patient's data will be handled as follows:

- Pseudonymised trial data collected up to the point of withdrawal will be used in an intention to treat analysis;
- All data on adverse events, including those routinely collected as outcomes, will be collected and reported as required by the MHRA.

Personal information will be deleted from LSHTM-CTU electronic systems immediately after 1-year follow-data has been completed and no later than at final hard-lock of the trial database. A patient can request removal of their personal information at any time.

6 ETHICAL, REGULATORY AND OPERATIONAL CONSIDERATIONS

6.1 ETHICS COMMITTEE AND REGULATORY AGENCY REVIEW

Approval will be obtained from an NHS REC, the Health Research Authority (HRA), the MHRA and relevant R&Ds and Pharmacy Departments. Additionally, to comply with the Sponsor's requirement, we will obtain approval from LSHTM's REC.

As TBI is a strong risk factor for dementia in older adults we plan to collect dementia diagnosis at 1 year after randomisation. We will collect this by data linkage using the UK NHS HES dataset via NHS Digital / NWIS. To link to the HES dataset we will collect personal information. We sought Section 251 approval from the HRA CAG to collect personal information in instances where consent is not obtained from the participant (for example if consent was deferred prior to randomisation and the participant does not regain capacity to consent) for the following purposes:

- to allow sites to share personal information with LSHTM-CTU for 1-year follow-up via NHS Digital / NWIS
- to allow personal information to be shared by LSHTM-CTU to link to HES dataset via NHS Digital / NWIS, and for de-identified data to be returned to LSHTM-CTU
- to allow access to medical records by those outside the direct healthcare team (e.g. LSHTM as Sponsor, LSHTM-CTU and other regulatory bodies)

CAG has confirmed that their approval is not needed, and that CPI can be collected under the following circumstances: consent has been obtained from the patient, or if no patient consent is available the patient has not opted-out from the use of their data for research and consent has been obtained from a PeLR or PrLR. Where a patient has not provided their own consent, sites must check the secure MESH system to see if a patient has opted out before sharing any CPI.

ANNUAL REPORTING: Annual progress reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. An End of Trial Declaration will be submitted to the Authorities (REC/MHRA) within 3 months of the end of the trial (whether planned or premature). A final report will be submitted to the Authorities with the trial results within one year of the end of the trial.

6.2 PROTOCOL AND REGULATORY COMPLIANCE

The trial will be conducted in conformance with the principles of the Declaration of Helsinki and to International Conference on Harmonisation Good Clinical Practice (GCP) guidelines. It will also comply with the Medicines for Human Use (Clinical Trials) Act 2004, subsequent amendments and

LSHTM'S Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the EU GDPR and the UK Data Protection Act (DPA) 2018.

SERIOUS BREACHES: Notification of serious breaches to GCP and/or trial protocol.

A "serious breach" is a breach which is likely to effect to a significant degree:

1. the safety or physical or mental integrity of the participants of the trial; or
2. the scientific value of the trial

Trial Sites should inform LSHTM-CTU of any serious breaches immediately and no longer than 24 hours of becoming aware of the breach. The LSHTM-CTU will inform the Sponsor immediately and no longer than 24 hours of any case where the above definition applies during the trial conduct phase. Furthermore, the sponsor will notify the regulatory authority/Ethics Committee in writing of any serious breach of

1. the conditions and principles of GCP in connection with that trial; or
2. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

6.3 DATA PROTECTION AND PATIENT CONFIDENTIALITY

All data will be processed in accordance with the EU GDPR and the UK DPA. Authorised investigators will transmit baseline data, outcome data, personal information, and adverse event data to the LSHTM-CTU by data entry into the trial database. Investigators will be given a unique username, password, and PIN to access the database. Data stored on the trial database will be pseudonymised by linking to a unique participant ID number only. Only people authorised by the Trial Manager/CI will have access to the CRASH-4 trial database. The trial database will be accessed through a complex password system which includes a password ageing mechanism.

Personal information will stored separately to the research data, on LSHTMs secure server. Access to the electronic personal information will be restricted to LSHTM-CTU staff who are authorised by the CI to process the data request to NHS Digital / NWIS.

Once the 1-year data on dementia diagnosis has been received from NHS Digital / NWIS and added to the trial database, personal information for that participant will be deleted from LSHTMs secure server and Sites will be instructed to confidentially destroy any paper Personal Information Forms. Personal information will not be shared with any other organisations or used in any publication.

Totally anonymised data will be retained and shared for public use via our data sharing platform (freebird.lshtm.ac.uk).

Where consent has been given, Investigators will transmit an electronic image of the consent form to the LSHTM-CTU using Redcap secure transfer for central monitoring purposes. Consent forms will be deleted immediately after monitoring is completed.

Original copies of CRFs, consent forms and source data will be kept securely at each participating site. These must be archived securely for 10 years after the overall end of the trial.

6.4 INDEMNITY

LSHTM 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. The indemnity is renewed on an annual basis and LSHTM assures that it will continue renewal of the indemnity for the duration of this trial.

6.5 MONITORING, AUDIT AND INSPECTION

The CRASH-4 trial is a large, pragmatic, randomised double-blind placebo-controlled trial. The intervention (tranexamic acid) has marketing authorisation and has been in clinical use for decades. Its safety profile is well established, and no significant serious adverse events associated with its use have been identified. The trial will routinely collect data on adverse events, and these will be reviewed by the independent DMC. The trial procedures are based on routine clinical procedures and include (1) the IM administration of the trial drug; (2) collecting routine clinical information; and (3) informed consent. There are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each ambulance service and hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in this research study has been assessed as low in each of these categories. Based on the low risks associated with this trial, it has been categorised as a Type B (testing authorised medicinal products according to treatment regimens outside the marketing authorisation).

A detailed monitoring plan will be developed. In summary, monitoring will utilise central monitoring, site self-monitoring and onsite monitoring. Central data monitoring which will include review of AE reports across trial sites to assess where reporting is unexpectedly low or high, time to query resolution, statistical monitoring to identify unusual or extraordinary patterns in data such as sites that are outliers with respect to withdrawals and eligibility violations. Additionally, data collected will be examined for digit preference, distribution, and variance. The runs test will be used to examine whether a string of data is occurring randomly from a specific distribution.

Central monitoring will also utilise phone calls for status updates, central review of delegation logs, and monitoring of consent forms (where consent has been given to do so). Periodic self-monitoring of sites will be done with focus on sites where there has been no on-site monitoring.

Onsite monitoring will be carried out based on recruitment rate, findings on self-monitoring and central monitoring.

Investigators and sites are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial related and source documents must be kept for at least 10 years after the end of the trial and should only be destroyed on the written instruction of the Sponsor. The study may be subject to audit by the LSHTM under their remit as sponsor, the LSHTM-CTU and other regulatory bodies to ensure adherence to GCP.

7 SUPPLY OF TRIAL TREATMENTS

7.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

The active trial drug is TXA (500mg/5mL solution for injection) formulated for injection will be used in this trial. A commercially available brand manufactured by Focus Pharmaceuticals Limited for use in the UK will be used.

The placebo (sodium chloride 0.9% [5mL solution]) will be manufactured specially to match the TXA to GMP standards by Guy's and St Thomas's (GSTT) Pharmaceuticals, 13th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT.

TXA will not be used in its marketed presentation and packaging and trial specific labels and packaging will be applied to bind the treatment. The solution for Injection will be administered as an IM injection (500mg/a single 5mL IM injection of 100mg/ml, or two x 250mg/2.5mL IM injections) instead of intravenously.

Ampoules and packaging for both active trial treatment and placebo will be identical in appearance.

7.2 REGULATORY STATUS OF THE DRUG

TXA to be used in this trial is manufactured by Focus Pharmaceuticals Ltd under Marketing Authorisation Number PL 20046/0098. The marketing authorisation guarantees that the product has been manufactured and released in accordance with the European Union Commission Directive 2003/94/EC.

Placebo (sodium chloride 0.9%) will be manufactured specially to match the TXA by a GMP certified manufacturer [GSTT Pharmaceuticals].

GSTT Pharmaceuticals is responsible for ensuring the placebo is manufactured to GMP, the blinding, trial labelling and packaging processes and first stage Qualified Person (QP) release.

7.3 Product Characteristics

The Reference Safety Information (RSI) to be used in this trial is contained in Section 4.8 of the SmPC for Tranexamic Acid 500mg/5ml Solution for Injection (produced by Focus Pharmaceuticals Limited, date of revision 05 July 2018). The LSHTM-CTU will check for updates to the SmPC annually. Where there are significant updates to the SmPC the LSHTM-CTU will submit a substantial amendment to the MHRA. Following authorisation from the MHRA the LSHTM-CTU will circulate the updated SmPC to all investigators.

7.4 Preparation and labelling of Investigational Medicinal Product

A separate Investigational Medicinal Product Dossier (IMPD) will provide the detail of this process. In summary, blinding and the first stage Qualified Person release will be done by GSTT Pharmaceuticals. They will remove the original manufacturer's label and replace with the clinical trial label bearing the unique randomisation number which will be used as the pack identification. Other pack label text will be identical for both TXA and placebo treatments and will be in compliance with Annex 13 of Volume 4 GMP Guidelines. TXA and placebo will be packaged in an identical manner in small, durable cardboard and polystyrene containers to avoid breakage during transportation to sites or by the ambulance crew.

Accountability: The IMP will be sent to the named Pharmacist at each site. The site pharmacy should have overview of the drug accountability. Records of all IMP shipments and administration to a patient must be kept on the drug accountability log. If the IMP stock received from the Sponsor is unexpected, wrong, or damaged, the stock should be quarantined and LSHTM-CTU contacted for further actions.

Storage and supply: In advance of the trial start, the site pharmacist/delegate will carry out a risk assessment of suitable storage to ensure the trial drug is stored appropriately and available for use without delay. An initial stock will be provided by LSHTM-CTU at site activation and resupply will be triggered by participant enrolment.

Treatment packs held in central stock should be stored below 25°C. Individual treatment packs taken to the scene of an incident by paramedics do not require temperature monitoring.

7.5 Dosage schedules

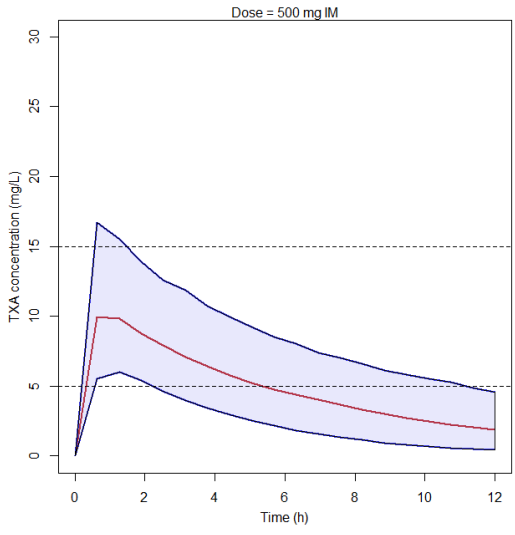
Each patient will be given 500mg of TXA or placebo (5mL ampoule) by IM injection into the thigh (rectus femoris or vastus lateralis), buttocks (gluteal muscles) or arm (deltoid), depending on a clinical assessment of muscle mass. If a patient's muscle mass is too small to accommodate a 5mL injection, the 500mg dose can be given as two 250mg (2.5mL) injections into different muscles. The injection(s) will be given using the most appropriate needle for the patient. Usually needle gauge will be 19-25 and needle length will be 1 to 1.5 inches but longer needles (up to 3 inches)

may be needed in obese adults. The Z-track injection method will be used to seal the medication in the muscle.[34]

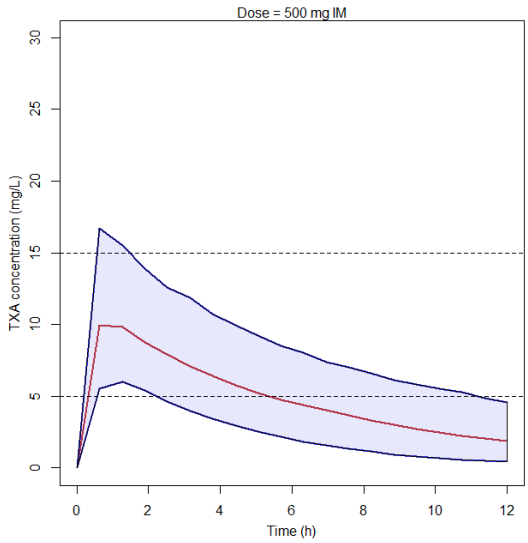
DOSE JUSTIFICATION: The estimated plasma TXA concentration needed to inhibit fibrinolysis in vitro is in the range 5 to 10 mg/L. Studies in healthy volunteers show that after IM injection of 500mg TXA, plasma TXA concentrations within this range are achieved within 30 minutes.[12,13] The Trauma-INTACT trial evaluated the pharmacokinetics of IM TXA injection in 30 bleeding trauma patients. IM TXA was well tolerated with only mild and transient reactions at the injection site. Because all patients in this study had received IV TXA prior to the IM injection, the plasma concentration-time profile after a single IM TXA dose were obtained by simulation. After a single IM injection of 500mg TXA, a plasma TXA concentration above 5 mg/L would be achieved in an average of 10 minutes, remaining above this level for 5.8 hours [*publication in press*]. Although the CRASH-2 and CRASH-3 trials of TXA in trauma patients used a larger TXA dose (1g IV bolus dose followed by a 1g IV maintenance dose over 8 hours), with no evidence of adverse effects, because patients included in the CRASH-4 trial are older and renal TXA clearance decreases with age, a single 500mg IM TXA dose should safely achieve the necessary therapeutic levels for the duration of the at-risk period.

Simulated TXA concentration-time profiles based on PK data from the TRAUMA-INTACT study

Aged 70 years



Aged 80 years



7.6 KNOWN DRUG REACTIONS AND INTERACTION WITH OTHER THERAPIES

The TXA solution for IM injection should not be mixed with other medicinal products (specifically blood for transfusion or with solutions containing penicillin).

7.7 TRIAL RESTRICTIONS AND THE USE OF CONCOMITANT MEDICATION

Patients should receive all clinically indicated treatments. There is no restriction on the use of concomitant medication. In the event that non-trial TXA is given after randomisation, this should be recorded on the CRF.

7.8 ASSESSMENT OF COMPLIANCE WITH TREATMENT

Site investigators will record the date and time of trial treatment administration. If the trial treatment is not administered this will be recorded in the CRF and the reason provided on the CRF. The following will not be considered non-compliance with the protocol: where a patient dies before receipt of the full dose of IMP or where a clinical reason is given for non-administration of the IM injection.

8 ROLES AND RESPONSIBILITIES

8.1 SPONSOR

The London School of Hygiene & Tropical Medicine (LSHTM) will act as the Sponsor for this trial. The trial will be coordinated from the LSHTM Clinical Trials Unit (LSHTM-CTU).

8.2 FUNDER

The JP Moulton Charitable Foundation are funding the pilot phase of this study. Funding for the main trial will be obtained after the start of the pilot phase. Participants will not be paid for taking part as there is no special travelling or time off work needed. Where a participant returns to hospital for any adverse event associated with the trial, travel costs will be reimbursed. Trial sites will be reimbursed for staff time and consumable costs associated with the conduct of the trial. A model Non-Commercial Agreement (mNCA) with each site will be in place prior to the start of the trial.

The funder will not have any role in trial design, conduct, data analysis and interpretation, manuscript writing of results. They may help with dissemination of trial results.

8.3 TRIAL MANAGEMENT GROUP (TMG)

A TMG will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be coordinated through the LSHTM-CTU. The TMG will consist of the key LSHTM-CTU staff including the Co-Chief Investigators, statistician, trial manager, data manager and trial administrator.

The LSHTM-CTU will act on behalf of the Sponsor and will be responsible to the TMG to ensure that all of the Sponsor's delegated responsibilities are carried out. The responsibilities include (but are not limited to):

- report to the Trial Steering Committee
- create and maintain the Trial Master File
- identify trial sites
- assess suitability of trial sites
- confirm all approvals are in place before enrolment of participants and release of the trial treatment
- provide training about the trial, including site initiation
- provide study materials
- data management
- 24-hour advice and un-blinding service

- give collaborators regular information about the progress of the study
- respond to any questions (e.g. from collaborators) about the trial
- monitoring of the trial
- ensure data security and quality and observe data protection laws
- safety reporting
- ensure trial is conducted in accordance with the ICH GCP;
- statistical analysis;
- publication of trial results

8.4 Site Principal Investigator

Coordination within each participating hospital will be through a site PI whose responsibilities will be detailed in an mNCA in advance of starting the trial and will include:

- personally supervise the study at site;
- before and if needed during the trial, obtain all appropriate approvals/favourable opinions
- delegate trial related responsibilities only to suitably trained and qualified personnel;
- document delegation of duties to appropriately qualified persons;
- train relevant medical, paramedic and nursing staff to ensure that they remain aware of the state of the current knowledge, the trial and its procedures (there are training materials provided in the Investigator's Site File and on the trial website to help with this);
- agree to comply with the final trial Protocol and any relevant amendments;
- ensure that all potentially eligible patients are considered promptly for the trial;
- ensure consent is obtained in line with approved procedures;
- ensure that the data are collected and completed and transmitted to the CTU in a timely manner;
- ensure all adverse events are reported promptly to the CTU;
- ensure the Investigator's Site File is up-to-date and complete;
- account for trial treatments at their site;
- ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements;
- allow access to source data, including participants' medical records for monitoring, audit and inspection;
- be responsible for archiving all original trial documents including medical records, Investigator's Site File, consent forms and data forms for at least ten years after the end of the trial.

8.5 Protocol Committee

The Protocol Committee are responsible for the development of, and agreeing to, the final protocol. Subsequent changes to the final Protocol will require the agreement of the TSC. The membership list is maintained in the TMF.

8.6 Public and Patient Involvement (PPI)

We have previously carried out a qualitative focus group study to gain insights into lay perspectives on involvement in the design and management of emergency clinical trials and to identify an appropriate consent procedure for entering trauma patients into emergency clinical trials [CRASH-3 trial, NIHR-HTA report in press]. This focus group included a group of older men belonging to a social club and group of older women who were involved in a continuing education project and crafts-based activities. The consent procedure to be used for the CRASH-4 trial is based on the results of this focus group and was previously utilised successfully in the CRASH-3 and HALT-IT trials. [21, 47]

Specific PPI involvement in the CRASH-4 trial include input to:

(1) the brief lay title of the trial to be used on trial documents

(2) the procedure for consent and recruitment of older people by paramedics at home, the brief information sheet, deciding on the number and content of the information sheet and consent forms

(3) the personal information to collect and the procedure for collecting, handling, storing and sharing of personal information in the trial

(4) the outcome measures to be used in the trial, specifically primary outcome and disability measures

(5) trial oversight as members of the TSC

(6) drafting of the dissemination strategy as the trial is ongoing

(7) interpreting of the trial results when available

(8) reporting of the trial results

The PPI advisory group in place for the CRASH-4 trial consists of a member of RoadPeace (the national charity for road crash victims in the UK). RoadPeace supports survivors and their families and works to prevent serious injury and deaths from road crashes. A second PPI representative is a lay member of the Clinical Audit and Research Steering Group of the London Ambulance Service and a member of the Patient Advisory Group and the Early Detection and Awareness groups of the Transforming Cancer Services for London. The third PPI representative is a patient who was

included in the CRASH-3 trial after suffering a TBI. She has experience of being included in an emergency care trial, has suffered and is still suffering the consequences of a TBI.

9. PUBLICATION POLICY

All efforts will be made to ensure that the trial protocol, statistical analysis plan and results arising from the CRASH-4 trial are published in an established peer-reviewed journal. At least one publication of the main trial results will be made. All publications will follow relevant external guidance such as the *'Uniform Requirements for Submission of Manuscripts to Biomedical Journals'* issued by the International Committee of Medical Journal Editors (ICMJE) (2008 update) and the CONSORT statement (Moher 2001). Links to the publication will be provided in all applicable trial registers. Dissemination of results to patients will take place via the media, trial website (http://crash4.Lshtm.ac.uk) and relevant patient organisations. In addition, participants and their families will be sent a copy of trial results if requested. Sites will be asked to maintain a list of all patients/families who requested a copy of the results. Collaborating investigators will play a vital role in disseminating the results to colleagues and patients. The success of the trial will be dependent entirely upon the collaboration of the paramedics, nurses, doctors and other health professionals in the participating ambulance services and hospitals and those who hold key responsibility for the trial. Hence, the credit for the trial will be assigned to the key collaborator(s) from each participating site, as it is crucial that those taking credit for the work have actually carried it out. The results of the trial will be reported first to trial collaborators. As a large number of sites will contribute to this trial, individual sites cannot restrict the publication of the manuscript relating to the outcomes of this trial. Anonymised data for this trial will be made available for free use at http://freebird.lshtm.ac.uk.

10. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CAG	Confidential Advisory Group
CENTRAL	Cochrane Controlled Register of Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPI	Confidential Personal Information
CRASH-2	Clinical Randomisation of an Anti-fibrinolytic in Significant Haemorrhage
CRASH-3	Clinical Randomisation of an Anti-fibrinolytic in Significant Head injury
CRASH-4	Clinical Randomisation of an Anti-fibrinolytic in Symptomatic mild Head injury in older adults
CRF	Case Report Form
CRO	Contract Research Organisation
CT scan	Computerised Tomography scan
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DAMOCLES	Data Monitoring Committee: Lessons, Ethics, Statistics
DMC	Data Monitoring Committee
DPA	Data Protection Act
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GSTT	Guy's and St Thomas's
HALT-IT	Haemorrhage ALleviation with Tranexamic acid – InTestinal System
HES	Hospital Episode Statistic
HRA	Health Research Authority
IB	Investigator Brochure
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive Care Unit
ID	Identification

IM	Intramuscular
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System
ISF	Investigator Site File (this forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
IT	Information Technology
IV	Intravenous
LSHTM	London School of Hygiene & Tropical Medicine
LSHTM-CTU	London School of Hygiene & Tropical Medicine Clinical Trials Unit
MA	Marketing Authorisation
MESH	Message Exchange for Social Care and Health
mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
mL	Milliliters
mNCA	Model Non-Commercial Agreement
MRI	Magnetic Resonance Imaging
MS	Member State
NHS	National Health Service
NHS Digital	National Health Service Digital
NHS R&D	National Health Service Research & Development
NIHR-HTA	National Institute for Health Research Health Technology Assessment
NIMP	Non-Investigational Medicinal Product
NWIS	NHS Wales Informatics Service
PeLR	Personal Legal Representative
PharmacoTXA	Pharmacokinetics and pharmacodynamics of tranexamic acid
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PK	Pharmacokinetic
PPI	Public and Patient Involvement
PrLR	Professional Legal Representative
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic Brain Injury
TMF	Trial Master File
TMG	Trial Management Group
tPA	Tissue Plasminogen Activator

Trauma-INTACT	The trauma-INtramuscular Tranexamic Acid Clinical Trial
TSC	Trial Steering Committee
TXA	Tranexamic Acid
UK	United Kingdom
WHO	World Health Organisation

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12 LIST OF APPENDICIES

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Appendix 1: Key Trial Contacts

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Emergency Telephone Contact *To be used only if urgent unblinding of the trial treatment or advice for reporting an SAE is needed (24 hour)*	+44(0)7768 707500

Appendix 14: Amendment History

Amendment no.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made	Rationale
1	1.1	04/11/20	Lauren Frimley	Update to eligibility criteria (page 5), trial overview (page 12), inclusion criteria (page 14), adverse events (page 23)	As requested during MHRA initial review
2	1.2	19/01/21	Lauren Frimley	Update to secondary outcomes (page 19) and data management (page 27)	To allow post discharge disability assessment