PROTOCOL

FULL TITLE	Pharmacokinetics of intramuscular tranexamic acid in trauma patients: a clinical trial
SHORT TITLE	The trauma INtramuscular Tranexamic Acid Clinical Trial
ACRONYM	Trauma-INTACT

IRAS Number	262119
EudraCT Number	2019-000898-23

	NUMBER	DATE
FINAL VERSION	1.1	05 July 2019

[This protocol has regard for the HRA guidance]

REFERENCE NUMBERS

IRAS Number:	262119
EudraCT Number:	2019-000898-23
Clinicaltrials.gov Number:	NCT03875937
Sponsor's Number:	2019/KEP/218

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:
..... **Date:** ...../...../.....

Name (please print): Patricia Henley

Position: Head of Integrity and Research Governance and Sponsor's Legal Representative

Chief Investigator:

Signature: **Date:** ...../...../.....
.....

Name: (please print): Ian Roberts

Co-Chief Investigator:

Signature: **Date:** ...../...../.....
.....

Name: (please print): Haleema Shakur-Still

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i. LIST OF CONTENTS

ii LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CHMP	Committee for Medicinal Products for Human Use
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ED	Emergency Department
EMEA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EWP	Efficacy Working Party
g	gram
GCP	Good Clinical Practice
HILIC	Hydrophilic Interaction LIquid Chromatography
IB	Investigator Brochure
ICF	Informed Consent Form
i.d.	internal diameter
IM	Intramuscular
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PK	Pharmacokinetics
PeLR	Personal Legal Representative
PrLR	Professional Legal Representative
PPH	Post-Partum Haemorrhage
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TXA	Tranexamic Acid

iii. TRIAL SUMMARY

Trial Title	Pharmacokinetics of intramuscular tranexamic acid in trauma patients: a clinical trial.	
Acronym	Trauma INTACT	
Clinical Phase	Exploratory study	
Trial Design	Prospective, open-label, multi-centre pharmacokinetic study.	
Trial Participants	Trauma patients	
Planned Sample Size	30 patients with at least 2 post treatment pharmacokinetic blood samples	
Treatment duration	Once only administration of 1 gram intramuscular tranexamic acid	
Follow up duration	7 days	
Planned Trial Period	18 months	
Primary	**Objectives**	**Outcome Measures**
	Pharmacokinetic parameters	Serum TXA concentrations over time
Secondary	Local reactions at injection site and adverse events	Local reactions at injection site and adverse events.
Investigational Medicinal Product(s)	Tranexamic acid	
Formulation, Dose, Route of Administration	Tranexamic Acid (100mg/ml Solution for Injection) 1 gram divided in 2 x 0.5 gram/5 mL injections Intramuscular injection	

iv. FUNDING AND SUPPORT IN KIND

This trial is funded by a grant provided by JP Moulton Charitable Foundation. Funding to support data management is provided by the London School of Hygiene & Tropical Medicine (LSHTM).

v. ROLE OF TRIAL SPONSOR AND FUNDER

The funders (see above) did not play a role in the design of the trial and will not play a role in its conduct, data collection, analysis, and interpretation, manuscript preparation, review, and approval, and dissemination of the results. The Sponsor is responsible for the approval of any substantial amendment which may be needed to the protocol. After approval is given, the Sponsor must obtain, prior to implementing the amendment, approval from the relevant Research Ethics Committees (REC) and Regulatory Authority (MHRA). The Sponsor is responsible for reporting all serious breaches to the MHRA and REC.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUPS & INDIVIDUALS

Protocol Development Committee: This includes the chief investigators (CIs), site principal investigators (PIs) and participating clinicians and study staff. Its role is to ensure that the study protocol is scientifically appropriate and that all ethical, regulatory and scientific aspects of the trial have been considered. If the protocol requires amending, this committee will review and recommend any changes. The final decision for any amendment to the protocol resides with the Sponsor.

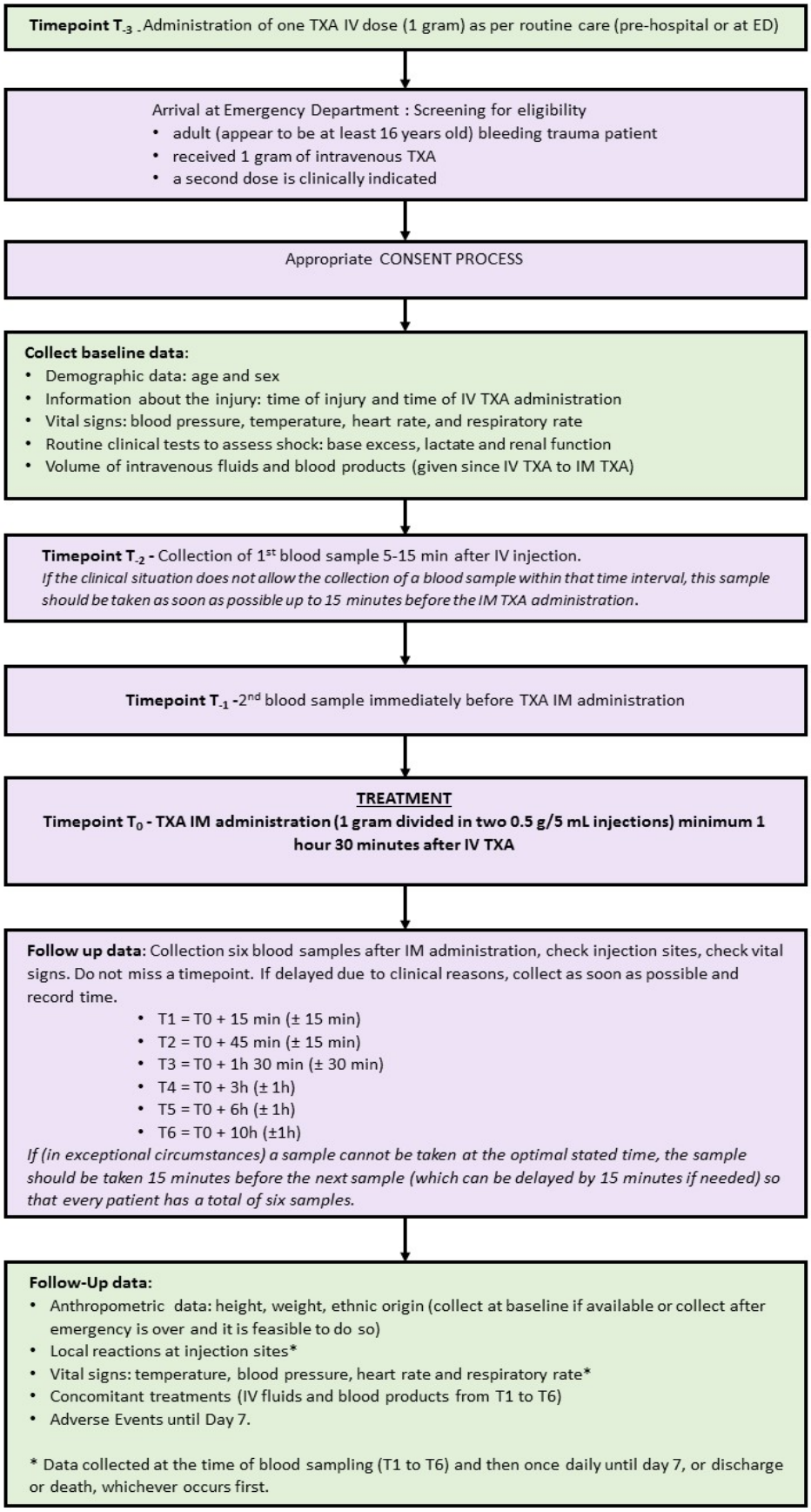
Members of the Protocol Development Committee:

- Ian Roberts: Study design, drafting the protocol
- Haleema Shakur-Still: Study design, drafting the protocol
- Stanislas Grassin Delyle: Pharmacokinetic methods and analysis
- Jason Pott: Drafting the protocol
- Nigel Tai: Drafting the protocol
- Phil Moss: Drafting the protocol
- Heather Jarman: Drafting the protocol
- Harvey J Pynn: Drafting the protocol
- Roberto Picetti: Study design and drafting the protocol

Data Monitoring Committee: A Data Monitoring Committee is not required in this trial. Tranexamic acid (TXA) is a marketed product with robust safety and efficacy data. Although there is less data on intramuscular use, we do not anticipate any safety issues. Only patients in whom TXA is clinically indicated will be included in this trial. The trial includes only 30 participants and will be completed within a short timeframe.

Trial Management Group: The Trial Management Group will comprise the CIs, research fellow, trial manager, data manager and statistician. They will meet regularly to ensure that the trial is progressing according to the protocol.

vii. TRIAL FLOW CHART



1 BACKGROUND

1.1 Summary

The anti-fibrinolytic TXA has been licensed for over 30 years for use in the prevention and treatment of haemorrhage. More recently, large clinical trials have shown that TXA reduces death from bleeding after trauma and post-partum haemorrhage (PPH).[1-3] Urgent treatment is essential. Most haemorrhage deaths occur soon after bleeding onset and treatment delay reduces the survival benefit.[4] Every fifteen minutes treatment delay reduces the survival benefit by about 10% until around three 1 after which there is no benefit.[4] To reduce treatment delay, UK patients with serious injury are often given an intravenous (IV) injection of TXA in the ambulance, before they get to hospital. Nevertheless, there are times when giving an IV injection is difficult, such as in patients trapped in crashed vehicles or soldiers in combat situations with no medics available. If TXA could be given by intramuscular (IM) injection, rapid administration would be possible even in difficult situations. Studies in healthy volunteers show that therapeutic plasma TXA levels (plasma TXA >10 mg/L) are reached rapidly (within 30 minutes) after IM injection.[5,6] If absorption was similarly rapid in trauma patients, this would strongly suggest the IM route as a potential alternative to IV use. In this study we will assess the population pharmacokinetics of IM TXA in trauma patients. Based on the results of the CRASH-2 trial, trauma patients are usually given a loading dose of 1 gram TXA by IV injection followed by an IV maintenance infusion of 1 gram over 8 hours. In this study all patients will receive the initial 1g IV loading dose but the second TXA dose will be given intramuscularly rather than intravenously. Bearing in mind that the maintenance infusion is often interrupted while the patient undergoes diagnostic tests (e.g. CT scanning) or surgery and is sometimes omitted completely, giving the second dose of TXA by IM injection should not involve any risk. IM injection may cause some pain and redness at the injection site. However, these symptoms are unlikely to be significant in trauma patients who routinely receive strong analgesia. The study involves additional blood samples but we will take the smallest possible volume of blood which will allow us to carry out the analysis. Blood will be taken from a cannula to avoid multiple venepuncture.

1.2 Existing knowledge relating to the condition under investigation

TXA reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fibrinolysis).[7] Plasminogen produced by the liver is converted into the fibrinolytic enzyme plasmin by tissue plasminogen activator (tPA). Plasminogen and tPA bind to lysine residues on fibrin leading to localised plasmin formation and fibrin cleavage.[8] 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.[7]

IV administration of TXA safely reduces death due to bleeding in patients with trauma and PPH.[1-3] In both situations, most deaths occur soon after bleeding onset and treatment delay reduces the survival benefit.[4] One of the main barriers to rapid treatment is the need for an IV injection. Paramedics and other first line responders who are trained to insert IV lines are not always available and even when they are, securing IV access can be difficult in shocked patients with collapsed veins. Although TXA is available for oral (tablet or oral solution) and IV use, there has been little research into alternative routes of administration. IM injection would be easier and faster to administer and would require less training than IV use. Because TXA has a wide therapeutic index, an initial IV injection could be followed by an IM TXA.

1.3 Summary of relevant pre-clinical and clinical trials

Although the pharmacokinetics of TXA after IV administration has been well studied, there have been fewer studies of IM use. A systematic review identified two pharmacokinetic studies of IM TXA in healthy volunteers.[5,6] These showed that the bioavailability of TXA after IM injection is over 95% with therapeutic TXA levels (>10 mg/L) achieved within about 30 minutes of administration. There were no adverse effects. Nevertheless, larger studies are needed in patient populations before IM TXA can be recommended as an alternative to IV use. We will study the pharmacokinetics of TXA after IM injection.

TXA has been used to prevent and treat bleeding for over 40 years. The evidence is summarised below:

Obstetric haemorrhage

Treatment of postpartum haemorrhage: A systematic review identified two trials involving 20,212 women and showed that 1 gram of IV TXA (plus an additional 1 gram if bleeding continued up to 24 hours) reduces the risk of death due to bleeding after PPH compared to placebo. There was no evidence of any increase in thromboembolic events, seizures or other side effects with TXA.[9] Based on this evidence, the WHO recommends the early use of IV TXA (within 3 hours of birth) in women with PPH.[10] The WHO also states that "research on other routes of TXA administration is a priority."

Prevention of postpartum haemorrhage: A systematic review including 26 randomised trial of TXA for the prevention of PPH found that most trials are small and unreliable.[11] One exception is the placebo-controlled TRAAP trial which enrolled 4079 women who were giving birth vaginally in French hospitals.[12] There was no statistically significant difference in the primary outcome of blood loss ≥500 mL. Fewer woman in the TXA group received additional uterotonics and fewer experienced clinically significant PPH according to care provider. The rates of nausea and vomiting were higher in the TXA group compared to the placebo group.

Traumatic haemorrhage

The CRASH-2 trial involving 20,211 trauma patients found that early administration of TXA reduces death due to bleeding by about one third. There was no evidence for an increase in risk of thromboembolic events, seizures or any other side effects associated with TXA.[2]

Gastrointestinal bleeding

A systematic review including eight randomised trials found fewer deaths among patients with acute upper gastrointestinal bleeding with TXA.[13] However, the quality of the trials was poor. Two trials have assessed the effect of oral TXA in patients with lower gastrointestinal bleeding. In one trial the proportion of stools containing visible blood was lower when patients received TXA.[14] However, in the second trial there were no statistically significant differences between the TXA and placebo groups for any of the outcomes assessed.[15]

Surgical haemorrhage

A systematic review of 129 randomised trials found that TXA reduced the risk of receiving a blood transfusion by 38% and the amount of blood loss by 34% in patients undergoing surgery. The effect of TXA on risk of thromboembolic events was uncertain.[16]

Intracranial haemorrhage

Spontaneous intracerebral haemorrhage: A systematic review including nine randomised controlled trials suggest that TXA reduces re-bleeding. However, long term use of TXA may increase the risk of

cerebral ischaemia in these patients. There is some evidence that shorter treatment might reduce re-bleeding without an increase in the risk of ischaemia.[17]

A trial of TXA in patients with spontaneous intracerebral haemorrhage found no statistically significant differences in functional status or death at day 90. There were fewer deaths at day 7 in the TXA group.[18]

Traumatic brain injury: The results of two randomised trials in patients with traumatic brain injury showed that TXA reduced intracranial haemorrhage growth compared to placebo. The effect of TXA on risk of death and other patient outcomes is uncertain.[19-21]

Pulmonary haemorrhage

A systematic review including two small randomised trials found that TXA reduced the amount and duration of blood loss in patients with haemoptysis.[22] Another recent trial also suggests that using inhaled TXA can be safe and effective to control bleeding in patients with non-massive hemoptysis.[23]

Menorrhagia

Randomised trials of oral TXA show that it reduces blood loss in women with menorrhagia.[24]

Ocular haemorrhage

Randomised trials of oral TXA show that it reduces secondary haemorrhage in patients with hyphema.[25]

2 RATIONALE

2.1 Hypothesis for the trial

IM TXA will be well absorbed in trauma patients. Based on pharmacokinetic (PK) modelling we predict that a 1g IM injection of TXA will provide therapeutic TXA levels within about 30 minutes.[26]

2.2 Description of trial population and justification of choice of participants

Thirty trauma patients who have received 1 gram of TXA by IV injection and a second 1 gram dose of TXA is clinically indicated will be included. This study population will provide information on the pharmacokinetics of TXA after IM administration in the population in which IM TXA would be used. If TXA is well absorbed after IM injection it could be used in trauma patients in whom IV injection was not feasible (e.g. trauma patients trapped in vehicles or soldiers in combat, where securing IV access can be difficult in shocked patients with collapsed veins).

2.3 Name and description of the investigational medicinal product(s)

Patients will receive 1 gram tranexamic acid (100mg/ml solution for injection) split between two 5-mL IM injections.

2.4 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Based on the results of the CRASH-2 trial, bleeding trauma patients are usually given a loading dose of 1 gram TXA by IV injection followed by a maintenance infusion of 1 gram over 8 hours. The IV

loading dose must be given urgently since treatment delay reduces the survival benefit from TXA. Early activation of fibrinolysis is common after trauma and worsens bleeding. IV TXA treatment rapidly achieves the plasma levels of TXA needed to inhibit fibrinolysis and prevent excessive bleeding. Pharmacological research has shown that an IV loading dose of 1 gram TXA maintains therapeutic plasma levels for around 3 hours, the period when the risk of bleeding is greatest. The route of administration of the maintenance dose is less important. Indeed, no maintenance dose was given in the WOMAN trial of TXA after postpartum haemorrhage and the treatment benefit was identical to that seen in the CRASH-2 trial. Bearing in mind that the maintenance infusion is often interrupted while the patient undergoes surgery or diagnostic tests (e.g. CT scanning) and is sometimes omitted completely, giving the second dose of TXA by IM injection should not involve any risk. In this study all patients will receive the initial 1g IV loading dose but the second TXA dose will be given intramuscularly rather than intravenously. Studies of IM TXA in healthy volunteers report good absorption and no adverse effects. Patients will receive the second 1 gram dose by IM injection minimum 1.5 hours after the initial IV injection. The dose will be given as two 5 mL (0.5 gram each) injections into the thigh (rectus femoris or vastus lateralis), buttocks (gluteal muscles) or shoulder (deltoid) muscles, depending on the clinical situation (e.g. in the case of lower limb amputation). A large injection volume, i.e. 5 mL, in the deltoid muscle may be necessary if the other sites of injection are not available, and it has been done in healthy volunteers in a small pharmacokinetics study on TXA.[6] The 1 gram dose (10 mL) is divided to reduce the volume injected (5 mL is considered the upper limit).[27] See Section 6 for further information about administration of intramuscular TXA.

2.5 Potential benefits and risks for study participants

Since all patients in this study receive the recommended dose of TXA and only the route of administration of the second dose varies, the foreseeable risks relate to the IM route of administration. Intramuscular injection may cause pain and redness at the injection site However, these symptoms are unlikely to be significant in trauma patients who routinely receive strong analgesia. The study also involves additional blood samples. We will take the smallest possible volume of blood which will allow us to carry out the analysis. The total volume of blood taken (16 mL) should have no clinical impact on the patient.

This trial is categorised as:

Type B = Somewhat higher than the risk of standard medical care.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To assess the population pharmacokinetics of intramuscular TXA in trauma patients.

3.2 Primary endpoint

- Serum TXA concentrations over time.

3.3 Secondary endpoints

- Local reactions at injection sites

- Adverse events

4 TRIAL DESIGN

A prospective, open-label, multicentre, pharmacokinetic study conducted in the emergency departments of two UK hospitals. Potential eligible patients will have received a 1 gram IV dose of TXA at the scene of the injury or on arrival in hospital and a second dose is clinically indicated. Consent will be obtained as per section 7.2 below.

4.1 Trial intervention

Patients will receive a 1 gram dose of TXA by IM injection at least 1 hour and 30 minutes after their initial IV injection received at the scene or on arrival to hospital. The IM dose will be given as two 5mL (0.5 gram each) injections into the thigh (rectus femoris or vastus lateralis), gluteal or deltoid muscles, depending on the clinical scenario (e.g. taking into account the type of injury). Injections should be given in a non-injured muscle. The 1 gram dose (10 mL) is divided to reduce the volume injected into each muscle (5 mL is considered the upper limit).[27] 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.[27]

5 TRIAL SETTING

Patients will be recruited at the emergency departments at the following two UK hospitals:

- Royal London Hospital
  Barts Health NHS Trust
  Whitechapel Rd, Whitechapel
  London, E1 1BB

- St George's Hospital
  St George's University Hospitals NHS Foundation Trust
  Blackshaw Road, Tooting
  London, SW17 0QT

Recruitment, treatment and follow-up will be conducted at these hospitals.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Eligibility criteria

Adult (appear to be at least 16 years old) trauma patients who have received 1 gram of intravenous TXA for the management of haemorrhage in whom a second dose is clinically indicated are eligible.

7 TRIAL PROCEDURES

7.1 Screening

Patient eligibility will be assessed by a clinician/nurse in the emergency department (ED) of the participating hospitals as soon as possible after arrival.

7.2 Methods for informing and obtaining consent

Potential trial participants will have experienced a sudden, life threatening injury with significant bleeding. TXA 1 gram would be given by IV injection pre-hospital for their bleeding or soon after arrival to hospital. Eligibility for inclusion in this trial will need to be assessed immediately and trial procedures started as quickly as possible. The severity of injury and blood loss will impact participants' ability to give informed consent. Additionally, relatives/friends might not be available, or if available, their capacity to give informed consent might also be impaired due to shock and the short time available. We will use the consent procedure utilised in the CRASH-2, CRASH-3, HALT-IT and WOMAN trials.

The treating clinician will decide the best approach to obtain agreement or consent for participant's enrolment.

7.2.1 Prior information giving

Patient: Patients will be given verbal information appropriate to the level of their capacity bearing in mind their clinical condition and their level of shock. Specifically, the responsible doctor may explain verbally or with a written brief information sheet (Appendix 2) that they have received the usual emergency treatments for traumatic bleeding injury including a drug called tranexamic acid which has been shown to reduce bleeding. A second dose is needed and that we wish to enrol them in a study which is looking at an alternative way of giving tranexamic acid to patients. It will be explained that the study will see whether giving tranexamic acid into a muscle can be used as an alternative to giving it into a vein. We need to study this because injecting into a muscle is easier than infusing into a vein which in some circumstances would ensure that the drug is received. This would mean that the treatment could help many more patients with bleeding. If the patient objects to inclusion, their views will be respected. If the patient is capable to give consent, he/she can sign the informed consent (Appendix 3).

Relative/friend initial agreement: If a relative or a friend is immediately available and bearing in mind their level of shock and time available, they will be provided with brief verbal or written information about the trial. The brief information sheet (Appendix 4) outlines the information which can be provided. Researchers 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 if they are willing for their relative/friend to be included in the trial. The relative/friend can sign the brief information sheet if they wish but this is not mandatory. This is not a fully informed consent. If the relative/friend objects to the patient's inclusion, their views will be respected. If the relative or friend are willing to sign fully informed consent before enrolment, they may do so (Appendix 5).

Professional Legal Representative (PrLRs) consent: Each participating site 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 agreement for her/himself and a relative is either unable or not available to provide agreement, prior written informed consent can be obtained from a PrLR (Appendix 6).

Waiver: In the event the patient cannot provide agreement, no relative or friend is present (or is unable/unwilling to make a decision), and a PrLR is not immediately available, prior written informed consent will be waived. In this case the treating clinician will consider the patient's eligibility, any known views of the patient about trial participation and will decide whether or not to enrol the patient into the trial.

7.2.2 Information giving and written informed consent after enrolment.

As soon as the emergency is over and the patient regains capacity, fully informed written consent should be obtained from the patient for continuation of the study. The Patient's Invitation Letter (Appendix 7A) and the Information Sheet and Consent Form (Appendix 7B) should be used.

If after the emergency is over and the patient does not regain capacity, but a relative/friend becomes available and is willing to act as a Personal Legal representative (PeLR), fully informed written consent should be obtained from the relative/friend for the participant's continuation in the study. The PeLR Information Sheet and consent form should be used as per Appendix 8.

7.2.3 Patient dies before consent and relatives/friends become available

It is anticipated that approximately 20% of patients will die. When a participant dies before consent has been sought, the research team responsible for consent will obtain information from colleagues and bereavement counsellors to establish the most appropriate practitioner 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. In this situation, the Personal Legal Representative Information Sheet and Consent Form would be used (Appendix 9). Where it has been determined that obtaining PeLR informed consent is not appropriate, informed consent will be obtained from a PrLR.

7.2.4 Patient does not regain capacity or dies and no PeLR becomes available

In this event, PrLR informed consent should be obtained.

7.2.5 Documenting consent process

In all cases, the site investigators should record in the participant's medical notes the methods used for obtaining a participant's consent as well as the methods used for providing information with a view to obtaining consent. All attempts made to obtain consent 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, a copy should be given to the person providing informed consent.

7.3 Baseline data

The following baseline data will be recorded from routine care forms:

- Demographic (age and sex) and anthropometric data (height and weight [body mass index and body surface area using the Du Bois formula will be derived]). Ethnic origin is collected because it affects glomerular filtration rate, which could modify the pharmacokinetics of TXA, as it is eliminated 100% by the kidneys. Information on these parameters can be collected at baseline if available or at follow up.
- Information about the injury, time of injury and time of IV TXA administration.
- Vital signs including blood pressure, temperature, heart rate, and respiratory rate.

- Standard clinical tests made on admission will be used to assess shock (base excess, lactate, and renal function).
- Treatments (intravenous fluids and blood products).

These parameters will be used to build a pharmacokinetic model that describes the TXA concentration in the blood over time following the TXA IM injection.

7.4 TXA IM administration and timing of biological samples

Eligible patients would have received 1 gram of TXA as an IV injection.[28] The time of the TXA IV injection is T_{-3}. Blood will be taken about ten minutes later (T_{-2})* and also immediately before the intramuscular TXA injection (T_{-1}). Post injection samples will be taken as per the schedule below. We understand that the care of the patient takes priority over the sampling schema and that sample times will inevitably differ from those indicated. If it is not possible to obtain a sample at the scheduled time, the sample should be collected as soon as feasible with the exact time of collection recorded. The main requirement is that two samples are taken before TXA IM injection and six after - with exact time recorded. Reasons for any delay will be recorded.

Pharmacokinetics: Blood samples (2 mL of venous blood in dry tube without anti-coagulant) will be taken at the following times, except T_{-3} and T_0:

T_{-3} = TXA IV injection

$T_{-2} = T_{-3} + 10$ (± 5 min) if the clinical situation allows*

T_{-1} = immediately before IM injection

T_0 = TXA IM injection (minimum 1h 30 min after IV injection)

$T_1 = T_0 + 15$ min (± 15 min)**

$T_2 = T_0 + 45$ min (± 15 min)**

$T_3 = T_0 + 1$h 30 min (± 30 min)**

$T_4 = T_0 + 3$h (± 1h)**

$T_5 = T_0 + 6$h (± 1h)**

$T_6 = T_0 + 10$h (±1h)**

* *If the clinical situation does not allow the collection of a blood sample within the time interval specified for T_{-2}, that sample should be taken as soon as possible up to 15 minutes before the IM TXA administration and the exact time of collection should be recorded on the patient's CRF.*

** *Because the main requirement is that every patient has six timed samples after the IM administration of TXA, if (in exceptional circumstances) a sample cannot be taken at the optimal stated time, the sample should be taken 15 minutes before the next sample (which can be delayed by 15 minutes if needed) so that every patient has a total of six samples.*

7.5 Collection and storage of biological samples.

Each PK sample requires 2 mL of blood to be taken in collection tubes without anticoagulant and with uncoated interior (BD Vacutainer™ EST™ Blood Collection Tubes). Blood will be taken from a cannula to avoid multiple venepuncture. The total volume of blood taken (16 ml) should have no clinical impact on the patient. The blood samples will then be centrifuged for 10 min at 1500g. The serum

will be transferred to a storage tube that will be labelled with the participant's identification number, date and time of sampling and will be frozen at -80°C.

The serum will be kept frozen at -80°C at the participating hospitals. Once all PK samples for all patients at a site have been collected, they will be sent frozen to Dr Grassin-Delyle's laboratory at UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin (2 avenue de la source de la Bièvre, 78180 Montigny le Bretonneux, France) for PK analysis. No patient identifiable data will be transferred to the laboratory.

Once all analysis for this trial has been completed, all blood samples will be destroyed.

7.6 Follow-up assessments

The following parameters will be recorded during the follow-up time of 7 days or until discharge whichever is earlier:

- **Reaction at site of injection**: Each injection site will be inspected for local reactions at the same time as PK blood sampling and daily thereafter (for 7 days or until prior discharge).

- **Vital signs**: Participants will have their blood pressure, temperature, heart rate and respiratory rate recorded at the time of PK blood sampling.

- **Treatments:** Data on treatments likely to influence PK levels of TXA (blood product transfusion and IV fluids administration) will be collected from time of IM administration up to the time of the last PK sample.

- **Adverse events** as described in Section 9 will be recorded up to 7 days.

7.7 End of trial for participants

The trial ends at death, discharge or at 7 days, whichever occurs first.

7.8 Expected length of participation

Duration of participation for each participant	Treatment period: single dose of TXA (1 gram by 2 IM injections) Follow up: death, discharge or 7 days (whichever is earlier)

7.9 Summary of trial procedures

Procedure	**Pre-hospital**	**Arrival at ED**	**IM TXA**	**Blood sampling period**	**Follow-up (Day 7, death or discharge whichever comes first)**
Clinical administration of IV TXA	X	X (if not received before)			
Eligibility assessment		X			
Consent		X			X
Baseline data collection (from clinical records) Demographics and anthropometric data Vital signs (blood pressure, temperature, heart rate, respiratory rate) Renal function (creatinine) Parameters to assess severity of shock (base excess, blood lactate) Concomitant treatments including blood product transfusion		X			
IM TXA administration (1 gram/10 mL)			X		
Pharmacokinetic blood samples 2 baseline blood samples before the IM injection and 6 post IM blood samples				X	
Reaction at injection sites assessment				X	X
Vital signs: • Blood pressure • Temperature • Respiratory rate • Heart rate				X	X
Concomitant treatments (blood products and IV fluids)				X	
Adverse Events			X	X	X

7.10 Distinction between standard care and research

The only departure from standard care is the second TXA dose is given by IM injection with extra blood sampling. We will obtain data from the medical records (demographic, anthropometric, vital signs, blood test results, receipt of IV fluids and blood products, and adverse events). We will regularly inspect the injection site.

7.11 TXA quantitation

7.11.1 Efficacy

Due to its high specificity, mass spectrometry is recognized as the reference method for drug analysis. Dr Grassin-Delyle's team at Université Versailles Saint Quentin, France is experienced in mass spectrometry and has a record of publication in the development of methods to assess serum levels of TXA.[29-34] TXA will be measured in serum samples with liquid chromatography coupled to mass spectrometry according to an analytical method validated following the EMA guideline on bioanalytical method validation.[29,30]

7.11.2 TXA quantitation from serum samples

Serum samples shipped from the UK hospitals to the Université Versailles Saint Quentin (France) will be prepared for chromatography following the procedure detailed in Fabresse et al.[36] TXA will be measured in samples as previously described.[36] The advantages of this method over the others is the removal of phospholipids from plasma samples, high-sensitivity, wide dynamic range and validation according to the EMA guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009Rev.1 Corr.2). The precision was in the range 1.2-3.0%, and accuracy between 88.4 and 96.6%.

Chromatography will be performed with an UltiMate 3000 Quaternary Rapid Separation Pump (Thermo Scientific Dionex, Les Ulis, France). A 2.6 μm Accucore Urea HILIC column (150 × 3 mm i.d.) (Thermofisher) maintained at 50°C in an UltiMate 3000 Rapid Separation Thermostated Column Compartment (Thermo Scientific Dionex) will be used. Compounds will be ionized with a heated electrospray ionization source and detected with a triple quadrupole Quantiva mass spectrometer (Thermofisher) using multiple reaction monitoring (MRM) in the positive ionization mode. Nitrogen (N2-45 nitrogen generator, VWR International, Fontenay sous bois, France) will be employed as sheath and auxiliary gas and argon (Messer, Puteaux, France) as a collision gas. A typical analytical series consists of 8 calibration standards, 24 samples, 6 quality controls and 10 rinses. For late sampling times where low concentrations can be expected, it may be necessary to adapt the method and add a vacuum evaporation step to concentrate the samples.

7.12 Premature exit of trial participant

Participants may exit the study at any time and for any reason. A previously given consent can be withdrawn. The investigator can withdraw a participant from the trial for any safety reason or if it is in the participant's best interest.

If a participant exits the trial prematurely or withdraws consent or refuses consent for continuation, data collected up to time of premature exit will be used.

7.12.1 Monitoring participants after the premature termination of treatment

In case of an adverse event, the investigator will complete an adverse event report and monitor the participants until the end of her/his participation in the research. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be completed. The serious adverse event will be monitored until the participant recovers or a steady state is reached.

7.12.2 Procedure for replacing participants

If consent procedures are complete but the IM dose is not given, the participant will be replaced. If the IM dose is given but no more than two post IM blood samples are taken, the participant will be replaced.

7.12.3 Full or partial discontinuation of the study

LSHTM (the Sponsor) may prematurely discontinue all or part of the trial, temporarily or permanently, in the following situations:

- If new information about the trial drug, in light of which the objectives of the study are unlikely to be achieved.
- LSHTM reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

If the trial is discontinued prematurely, the LSHTM Clinical Trials Unit (CTU) will inform the relevant REC and the MHRA of its decision within 15 days, together with justification for the decision.

8 TRIAL TREATMENT

8.1 Description and regulatory status of investigational medicinal product(s)

Tranexamic acid formulated for injection used in this trial is UK-licensed and commercially authorised and available on the UK market from several brands/manufacturers at the same concentration.[35]

8.2 Preparation and labelling of Investigational Medicinal Product

TXA is commercially available in the UK and is labelled for IV use. The Sponsor will use an accredited supplier to relabel the ampoules in line with Annex 13 requirements for an open label clinical trial. Sites will chose the most appropriate needle size for IM administration from their clinical stock (between 19 - 25 Gauge and from 1 ½ inches up to 3" for large adults).

Labeling: Each ampoule will be labelled in accordance with Annex 13 requirements for an open label clinical trial.

Accountability: The Investigational Medicinal Product (IMP) will be sent to the named Clinical Trials Pharmacist at each site. The participating 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 conditions: Treatment packs should be stored at ambient temperature at the participating sites. No special temperature monitoring is required. In advance of the trial start, the clinical trials pharmacist/delegate will carry out a risk assessment of suitable storage in the emergency department to ensure the trial drug is available for use without delay.

8.3 Dosage schedules

Each patient will receive one dose of 1 gram of TXA divided in two IM injections (2 vials x 5 mL). Each 5mL will be injected separately in the thigh (rectus femoris or vastus lateralis), gluteal or deltoid muscles. The site of each injection will be recorded in the CRF.

8.4 Known drug reactions and interaction with other therapies

TXA solution for injection should not be added to blood for transfusion, or to injections containing penicillin.

8.5 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 non trial TXA is given during the time of the PK sampling, the dose, route of administration, date and time should be recorded on the CRF.

8.6 Assessment of compliance with treatment

Two IM injections of TXA will be administered by investigators at each site who will record the date, time and body location of each TXA injection. If one or none of the injections is administered, the reason for this will be recorded in the CRF. The following will not be considered non-compliance with

the protocol: where a patient dies before receipt of the IMP or where a clinical reason is given for non-administration of the IMP.

9 PHARMACOVIGILANCE

All patients included in this trial will have a life threatening injury. It is expected that approximately 20% of patients will die from their injury. Events which occur as a consequence of the injury and represents progression of the injury (e.g. anaemia from blood loss, medical or surgical intervention for the injury), or events which commonly occur in this population independent of exposure to TXA IM administration, and those which are study endpoints does not need to be reported as an adverse event. All other events fulfilling the criteria below should be reported. If a patient develops an adverse event, the patient should be treated in line with local procedures.

9.1 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 having been absent at baseline, or if present at baseline, appears to worsen AND is temporally associated with medical treatment or procedure.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" 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. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the Summary of Product Characteristics (SmPC). It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
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 • consists of a congenital anomaly or birth defect

	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. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
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 one of 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 reference safety information: • The Reference Safety Information to be used for this trial is the SmPC for tranexamic acid in Appendix 8

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 The role of the site investigator

The investigator must assess the seriousness criteria of each adverse event and record all serious and non-serious adverse events in the CRF.

The investigator must document serious adverse events as thoroughly as possible and provide a definitive medical diagnosis, if possible. Additionally, the causal relationship between the serious adverse events and the IMP is needed.

When completing the Adverse Event reporting form, the investigator will assign a causality using the definitions in the table below.

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).

If there is any doubt about the causality, the site Principal Investigator (PI) or medical delegate will inform the LSHTM CTU. In the case of discrepant views on causality between the investigator and

others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be recorded and reported onwards as required.

9.2.1 Serious adverse events

The investigator must notify the LSHTM CTU **within 24 hours of the investigator becoming aware** of any adverse event which is assess as being serious (see SAE definition in section 9.1).

9.2.2 Period during which the investigator must the notify the Sponsor of SAEs

The investigator will notify LSHTM CTU without delay of all serious adverse events:

- starting from administration of the trial drug
- throughout the whole follow-up period.

9.2.3 Procedures and deadlines for notifying the Sponsor of SAEs

The investigator should complete a SAE report form. This report must be signed by the investigator.

The investigator should provide as much information as possible on SAE form so that the Sponsor can carry out assessment for onward reporting.

The initial report must be followed up by one or more additional written reports describing the course of the event and any additional information required by the sponsor.

Whenever possible, the investigator will provide LSHTM CTU with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized and the study acronym, the trial participant screening ID number and initials written on each document provided.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has terminated his/her participation in the trial.

The initial SAE report, follow-up reports, and all other documents must be entered directly onto the trial database (eCRF) or sent to the LSHTM CTU by e-mail (traumaim@Lshtm.ac.uk).

When using the eCRF:

- the investigator completes the SAE report form in the eCRF, then validates, prints and signs the form for the ISF.
- In case of failure to connect to the eCRF, the investigator should complete, sign and send a paper CRF by email to traumaim@lshtm.ac.uk or by fax to 020 7299 4663. In this case, LSHTM CTU will enter the SAE report form in the eCRF.

The investigator must comply with all requests for additional information from relevant authorities.

For urgent questions relating to an adverse event report, please contact LSHTM CTU using the emergency phone number in the ISF.

9.3 Role of the Sponsor

The Sponsor, represented by LSHTM CTU, shall continuously assess the safety of the IMP throughout the trial.

9.3.1 Analysis and declaration of serious adverse events

The LSHTM CTU is responsible for assessing:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and IMP and/or study procedures and any other treatments,
    - all serious adverse events for which the investigator and/or the Sponsor suspect a causal relationship with the IMP are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions
    - any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the SmPC, is considered unexpected.
    - the expectedness of the serious adverse reaction based on the SmPC for TXA included as Appendix 8.

Any suspected unexpected serious adverse reaction (SUSAR will be reported using the EudraVigilance European adverse drug reactions database or any UK post-Brexit alternative for reporting to the UK MHRA.

LSHTM CTU will notify all the site PIs about any information reported that could adversely affect the safety of the trial participants.

9.3.2 Analysis and declaration of other safety data

In the event new safety data becomes available, a reassessment of the risk/benefit ratio of the trial or the IMP will be done by the Sponsor.

The Sponsor will inform the MHRA and the REC without delay if it becomes aware of any safety issue and, if applicable, describe which measures have been taken.

9.3.3 Annual safety report

The Sponsor will prepare once yearly throughout the trial duration an annual safety report (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 transmitted on the 6 November each year until final closeout. The Sponsor has several ongoing trials of TXA which reports annually across the European Union. The anniversary date for reporting is 6 November.

9.4 Data Monitoring Committee (DMC)

There is no need to establish a DMC for this trial. TXA is a marketed product with robust safety and efficacy data available for both the oral and IV routes. Although there is less data available on the IM route, we do not anticipate any safety issues. Only participants where TXA is clinically indicated will be included in this trial. Also, the trial includes only 30 participants and will be completed within a short timeframe.

9.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.6 The type and duration of the follow-up of participants after adverse reactions.

Each injection site will be monitored as detailed in section 7.6. Injection sites will be monitored up to Day 7 or until death or discharge whichever is earlier.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved or has reached a stable state.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

Using PFIM 3.2.1 software[36] and based on the population pharmacokinetic parameters determined in a meta-analysis of the different pharmacokinetic studies published in healthy volunteers (Grassin-Delyle's laboratory unpublished data), a sample size of 30 patients will allow estimates (Relative Standard Errors < 30%) of the pharmacokinetic parameters of the intramuscular administration of TXA. Optimal blood sampling times were evaluated and are as follows: 5 to 15 minutes after the IV administration, immediately before the IM administration, and 15, 45 minutes, 1h 30 min, 3h, 6h, and 10h after the IM administration. However, because access to patients who are critically ill and are undergoing multiple interventions cannot be guaranteed at fixed times, flexibility in blood sampling is allowed as detailed in section 7.4. The actual sampling time must be recorded.

10.2 Planned recruitment rate

Thirty trauma patients will be enrolled at the emergency departments at two hospitals over a period of about 9 months. We expect an enrolment rate of between 1-3 patients per month.

10.3 Statistical analysis plan

10.3.1 Safety Population

All participants who receive study medication (IM TXA) will be included in the Safety Population.

10.3.2 Pharmacokinetic Population

All participants who receive one dose of TXA and have at least 2 blood sample to determine serum concentrations of TXA will be included in the PK data analysis.

10.3.3 Safety Parameters

Individual and summary vital signs, skin reaction and adverse events will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate.

Individual and summary blood pressures, heart, and respiratory rate will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate.

Individual and summary parameters of shock (base excess, lactate, renal function) and volume of IV fluids transfused will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate. These measures will be used as covariates in the pharmacokinetics model (see section 10.3.4).

Adverse events will be tabulated and summarised according to the current version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded by System Organ Class and Preferred Term using the MedDRA dictionary. Safety analyses will be carried out using STATA (newest version).

10.3.4 Pharmacokinetic analysis

TXA time-courses will be analysed using the nonlinear mixed effect modelling software program Monolix 2018R1 version (www.lixoft.eu),[37] according to previous works carried out by Dr Grassin Delyle's team.[38-41] Briefly, parameters will be estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the

stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure (to ensure full convergence, the MCMC will be fixed to 20 and the iteration number to 1000). Different error models will be investigated (i.e. multiplicative, proportional and/or additive error models) to describe residual variabilities (expressed as σ, square root of σ^2), and the between-subject variabilities (expressed as ω, square root of the variance ω^2) will be ascribed to an exponential model. The Bayesian information criterion (BIC) will be used to test different hypotheses regarding the model, i.e.:

i. covariate effect(s) on pharmacokinetic parameter(s)
ii. residual variability model (proportional versus proportional plus additive model)
iii. structure of the variance-covariance matrix for the ω parameters.

Main covariates of interest in the population will be age, bodyweight (BW), shock measures and renal function. Parameter estimates will be standardised for a mean standard covariate using an allometric model: $P_i = P_{STD} \times (COV_i/COV_{STD})^{PWR}$ where P_{STD} is the standard value of parameter and P_i and COV_i are the parameter and covariate values of the i^{th} individual. The PWR exponents may be estimated from the data. However, for bodyweight, allometric scaling theory dictates that these are typically 0.75 and 1 for clearance and volumes terms respectively.[46] The goodness-of-fit of each model will be evaluated by visual inspection of the individual concentration-time courses, the observed-predicted (population and individual) concentration scatter plots and the prediction-corrected visual predictive checks.

10.3.5 Interim analysis

There are no planned interim analyses.

10.3.6 Procedure(s) to account for missing data

If one or more blood samples are not collected, the reason for this will be recorded in the CRF,

Individual missing covariate data will be ignored in the pharmacokinetics model.

11 DATA MANAGEMENT

11.1 Data collection

Information required in the research protocol will be collected first onto a paper CRF (for ease of collection in the emergency situation) and transferred to an electronic case report form (eCRF). An explanation should be given by the investigator for each missing data. Correction of discordant data on the eCRF will be resolved through queries. In the eCRF, the changes in the data will be tracked. Anonymization of the patients will be ensured by using the trial participant's screening number as their unique ID. This will recorded on each document needed for the research.

11.2 Source data

Source documents include, but are not limited to, hospital records (from which medical history, previous and concurrent medication, clinical outcomes and adverse events may be reported onto the CRFs), clinical and office log books, laboratory and pharmacy records, diaries and correspondence.

CRF entries will be considered source data if data are entered directly onto the CRF as original recording (e.g. PK samples). Trial data will be kept confidential and stored securely. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant screening ID number and not by name.

11.2.1 Case report forms

Case Report Forms (CRF) to collect data and SAE report forms that will be used in this trial can be found in Appendices 7 and 7a.

11.3 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospitals in the case of hospital medical records, for the statutory period. The Sponsor requires source documents to be kept for 10 years after the end of trial declaration.

11.4 Data Recording and Record Keeping

All trial data will be entered on to paper CRFs and then entered onto the trial database by authorised site staff. The participants will be identified by a unique trial specific number. The name and any other identifying detail will not be included in trial data electronic file used for analysis or publication. An ISF containing the essential documents for the trial will be provided by the CTU. The ISF must be updated by the trial site throughout the course of the trial.

11.5 Access to Source Data

Appropriate agreement will be in place in advance of trial start to allow all parties involved in the study direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the Sponsor's quality control and audit procedures.

Site investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force.

11.6 Data confidentiality

The persons responsible for the quality control of the trial will take all necessary precautions to ensure the confidentiality of information relating to the IMP, the study, the study participants and in particular the identity of the participants and the results obtained.

These persons, as well as the site investigators themselves, are bound by professional secrecy.

During and after the clinical study, all data collected about the study participants and sent to LSHTM CTU by the investigators (or sent to other collaborators) will be anonymised.

Under no circumstances will the names and addresses of patients be shown.

The trial will comply with relevant Data Protection regulations including the EU General Data Protection Regulation.

The Sponsor will ensure that appropriate consent is in place to access any personal information about the patient which is necessary for the quality control of the study.

11.7 Data processing and storage of documents and data

11.7.1 Data entry

Data will be entered electronically directly on to the trial database held by LSHTM CTU.

11.7.2 Data processing outside of the UK

Blood serum samples will be processed within the European Union (France). Anonymised data will be sent within the European Union for analysis.

11.7.3 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the Sponsor for 10 years after the end of the trial. LSHTM CTU are not able to archive source data or the ISF for participating sites, however costs associated with archiving will be considered in the site agreement.

11.7.4 Ownership of the data

LSHTM is the owner of the data of this trial. The data cannot be used or disclosed to a third party without its prior permission.

12 MONITORING, AUDIT & INSPECTION

12.1 General organisation

The Sponsor (LSHTM) will ensure the safety and respect of individuals who have agreed to participate in the trial. The Sponsor have in place quality assurance systems for monitoring the implementation of the study at the study sites.

12.2 Strategy for site opening

There are two participating sites in this trial. The sites have been chosen for their expertise in conducting clinical trials in emergency conditions. An assessment of the trial sites facilities by the Sponsor will be carried out before the trial can be opened. IMP release will only be done by LSHTM CTU when all necessary approvals for the conduct of the trial at site are in place. Documents required to be with LSHTM CTU before IMP release include the following: HRA approval, REC opinion, MHRA approval, signed agreement between the Sponsor and the host organisation, Site PI's CV and GCP training certificate and IMP risk assessment. Recruitment to the trial can only start once IMP have been released and the sites have been trained on the protocol and trial procedures.

12.3 Monitoring

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations guidance provided in the Investigator Site File and the trial's standard operating procedures. A monitoring plan will be made based on the risks identified in the Risk Assessment. The LSHTM CTU will monitor the trial to ensure the rights, safety, and wellbeing of the trial participants and to ensure the accuracy of the data. All site investigators will be trained in the trial procedures and have extensive guidance. LSHTM CTU will require investigators and their institutions to provide access to source data and documents and all trial related documents for monitoring, audits, REC review and regulatory inspection. All trial-related and source documents including medical records, original consent forms and original CRFs must be kept safely. Investigators must plan in advance of the trial start where the trial-related documents will be stored and how they will be accessed. All documents must be made available when required for monitoring/audit/inspection during the course of the trial and for up to 10 years after the end of the overall trial.

12.4 Case report form

All information required by the protocol will be entered onto paper CRFs and then in the eCRFs. The trial sites will have access to the eCRFs via a web-based data collection system. Access will be by individual unique username and password. Automatic consistency checks will ensure the data are verified immediately upon entry. An audit trail will be kept of all changes.

12.5 Management of non-compliances

Any events that occur as a result the investigators or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded on a 'Breach Form' and sent to LSHTM CTU.

LSHTM CTU has its own procedures for managing these non-compliances. All non-compliances must be reported to the Sponsor as soon as possible, and no later than 24 hours of identifying a non-compliance has occurred.

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

a) The safety or physical or mental integrity of the participants of the trial; or
b) The scientific value of the trial

The Sponsor is responsible for reporting all serious breaches to the MHRA and REC in line with its Standard Operating Procedures.

12.6 Audits/inspections

The Sponsor will also be responsible for auditing all aspects of the trial. The site PIs agree to accept the quality assurance audits carried out by the Sponsor as well as the inspections carried out by the MHRA. All data, documents and reports may be subject to regulatory audits and inspections. An audit can be carried out at any time by independent individuals appointed by the Sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

12.7 Principal Investigator's responsibilities

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

- personally supervise the study at site;
- before and if needed during the trial, obtain all institutional appropriate approvals / favourable opinion
- delegate trial related responsibilities only to suitably trained and qualified personnel;
- document delegation of duties to appropriately qualified persons;
- train relevant medical, nursing and other staff to ensure that they remain aware of the state of the current knowledge, the trial and its procedures;
- 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, completed and transmitted to the CTU in a timely manner;
- ensure all adverse events are reported promptly to the CTU;
- ensure blood samples are collected and prepared in line with the protocol and trial guidance;
- ensure the Investigator Site File is up-to-date and complete;
- account for trial drug at their site;
- ensure appropriate storage of trial drug;
- ensure the trial is conducted in accordance with ICH GCP and relevant UK regulations including clinical trial regulations and data protection laws;
- 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 study file, consent forms and data forms for at 10 years after the end of the trial.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Consent

Please, see section 7.2 for details on methods for informing and obtaining consent from the research participants.

13.2 Legal obligations

13.2.1 The Sponsor's role

This trial is sponsored by the LSHTM and its responsibilities coordinated by the LSHTMCTU. The CTU may delegate responsibilities to third parties which will be outlined in relevant agreements. The responsibilities of the CTU will be overseen by the Trial Management Group with day to day responsibilities with the Trial Manager.

13.2.2 Request for approval

The LSHTM CTU is responsible for obtaining approval from the relevant RECs and MHRA before the start of the trial.

13.2.3 Modifications to the trial

Any substantial amendment which may be needed to the protocol must be approved by the Sponsor. After approval is given, prior to implementing the amendment, approval from the relevant REC and MHRA must be obtained.

The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

13.2.4 End of study and final study report

The end of the trial is defined as the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database. A declaration of the end of a clinical trial will be sent to the MHRA within 90 days of the end of the trial.

A final study report will be to be sent to the MHRA and REC within one year of the end of the trial.

13.2 Peer review

The trial was funded after an open competition with blinded peer review by the JP Moulton Charitable Foundation, which has funded over 100 clinical trials since 2004.

13.3 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation is obtained from the MHRA and Favourable REC and Health Research Authority opinion if received.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enrol patients into the study, the CIs/PI or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the CI or designee, in agreement with the Sponsor will submit an application to the appropriate bodies for review and approval. The CI or designee will work with sites

(R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment.

13.4 Protocol compliance

Please, see section 12.5.

13.5 Data protection and patient confidentiality

Please, see section 11.5

13.6 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The personnel involved in this trial has no financial or other competing interests to disclose.

13.7 Indemnity

13.7.1 Sources of funding for the trial

LSHTM has received funding from the JP Moulton Charitable Foundation. Additionally, LSHTM will be funding the data management aspects of this trial. The study is being conducted as an academic collaboration between LSHTM, Royal London Hospital, St George's Hospital and UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin. This trial is eligibile for National Institute for Health Research Clinical Research Network support.

13.7.2 Insurance

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.

13.8 Access to the final trial dataset

Each site will have continuous access to their own data as the trial is ongoing. The final dataset will be reviewed and published by group authorship consisting of members of the Protocol Committee. Of note, each site PI is a member of the Protocol Committee.

Once all pre-planned analyses are completed, the totally anonymised dataset, protocol, published manuscript, data dictionary and any other relevant trial documents will be made freely available on the LSHTM CTU data platform: https://ctu-app.lshtm.ac.uk/freebird/.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

As Sponsor, LSHTM has the right and responsibility to ensure the results of this study are published. The main publication will be done as a group authorship consisting of the Protocol Committee. Once the pre-specified analysis is completed and data made freely available, anyone can use the trial data.

A final study report will be to be sent to the MHRA and REC within one year of the end of the trial.

There are no plans to notify all participants of the outcome of the trial. This is because of the ongoing high risk of death of participants after the end of trial. However, participants can request a copy of the final results and each site will maintain a log of patients/families who would like a copy. LSHTM CTU provide copies to each site to send onwards.

14.1.1 Funders' acknowledgements

LSHTM has a legal responsibility to acknowledge in all relevant publications that they received funding from the JP Moulton Charitable Foundation and LSHTM.

Funders do not have review and publication rights of the data from the trial.

14.2 Authorship eligibility guidelines and any intended use of professional writers

This study is being conducted as an academic collaboration between LSHTM, Royal London Hospital, St George's Hospital and UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin, France. All parties who contribute significantly to this study will be named in the final publication.

Professional medical writers will not be hired to write dissemination material about the results of this trial.

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16 APPENDICES

Appendix 1: Risk Assessment

Appendix 2: Brief Information sheet for patient

Appendix 3: Information Sheet and Informed Consent Form for Patients pre-enrolment

Appendix 4: Brief Information sheet for patient's relative/friend

Appendix 5: Personal Legal Representative Information Sheet and Consent Form pre-enrolment

Appendix 6: Professional Legal Representative Information Sheet and Consent Form pre-enrolment

Appendix 7A: Patient's Invitation Letter

Appendix 7B: Information Sheet and Informed Consent Form for Patients post-enrolment

Appendix 8: Personal Legal Representative Information Sheet and Consent Form post-enrolment

Appendix 9: Professional Legal Representative Information Sheet and Consent Form post-enrolment

Appendix 10: Consent Flow Chart

Appendix 11: Safety Reporting Flow Chart

Appendix 12: Case Report Form

Appendix 12A: SAE Report Form

Appendix 13: Summary of Product Characteristics for Tranexamic acid

Appendix 14: Amendment History

Appendix 14: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	05 July 2019	Roberto Picetti Haleema Shakur-Still	Small modifications to Section 7.2 and the Appendix Section of the Protocol to include the Brief Information Sheet for patients, the Invitation letters for patients regaining capacity and the new versions of the Information and Consent Sheets.