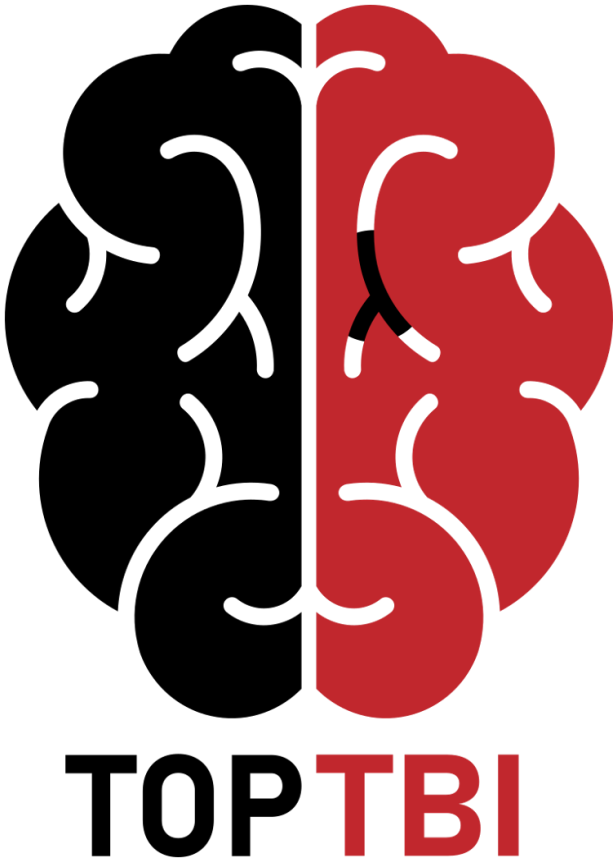

Timing **O**f venous thromboembolism **P**rophylaxis for adult patients with **T**raumatic **B**rain **I**njury (TOP-TBI): a pragmatic, randomised trial

Clinical Trial Protocol

Protocol version: 1.0
Protocol date: 15 October 2024

Table of Contents

TOP-TBI: Summary

Trial Title: **T**iming **O**f venous thromboembolism **P**rophylaxis for adult patients with **T**raumatic **B**rain **I**njury (TOP-TBI): a pragmatic, randomised trial

Protocol Number: CCTU0338

ISRCTN: TBA

IRAS: 1009812

Investigational Product: VTE prophylaxis agents including Low molecular weight heparin (LMWH)

Protocol Version: 1.0, 15 October 2024

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Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust and University of Cambridge

Funder: NIHR Health Technology Assessment Programme

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1. Protocol signatures

I give my approval for the attached protocol entitled Timing Of venous thromboembolism Prophylaxis for adult patients with Traumatic Brain Injury (TOP-TBI): a pragmatic, randomised trial dated 15/10/2024.

Chief Investigator

Name: Mr Angelos Kolias

Signature:

Date:

Site Signatures

I have read the attached protocol entitled “Timing Of venous thromboembolism Prophylaxis for adult patients with Traumatic Brain Injury (TOP-TBI): a pragmatic, randomised trial” dated 15/10/2024 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor’s 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.

Principal Investigator

Name:

Signature:

Date:

2. Protocol Compliance and Breaches of GCP

Prospective, planned non-compliance with or waivers to the protocol are not allowed under the UK regulations on Clinical trials and must not be used.

Protocol non-compliances or breaches are departures from the approved protocol. They can happen at any time but are not planned. They must be adequately documented on the non-compliance log and, where appropriate, the non-compliance report form for ultimate reporting to the Chief Investigator and the Sponsor. See the Trial Procedures Manual for further instructions on how to process non-compliance.

Non-compliance with the protocol, which is found to occur constantly again and again, will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to The Sponsor without any delay.

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4. Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AGEP	Acute Generalised Exanthematous Pustulosis
aPTT	activated partial thromboplastin time
AR	Adverse Reaction
BNF	British National Formulary
CI	Chief Investigator
CNN	Convolutional Neural Network
CRF	Case Report Form
CRN	Clinical Research Network
CT	Computer Tomography
CTA	Clinical Trial Authorisation
CTPA	CT pulmonary angiogram
CTUU	Cambridge Clinical Trials Unit
DALY	Disability-adjusted life years
DSUR	Development Safety Update Report
DVT	Deep Vein thrombosis
ECG	Electrocardiogram
Ecrf	Electronic Case Report Form
EQ-5D-5L	Quality of life questionnaire
FSR	Final Study Report
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GOS-E	Glasgow Outcome Score-Extended
GP	General Practitioner
HEAP	Health Economic Analysis Plan
HES	Hospital Episode Statistics
HIT	Heparin-induced Thrombocytopenia
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ration
ICF	Informed Consent Form
ICS	Intensive Care Society
IHP	Independent Healthcare Professional
IMP	Investigational Medicinal Product
LMWH	Low-molecular-weight heparin
MHRA	Medicines and Healthcare Products Regulatory Agency
MTC	Major Trauma Centre
NACCS	Neuro Anaesthesia & Critical Care Society
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSU	Neuroscience Unit
PE	Pulmonary Embolism
PID	Patient Information Data
PIS	Patient Information Sheet
PTP	Pharmacological VTE Thromboprophylaxis
QALY	Quality-adjusted life year
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event

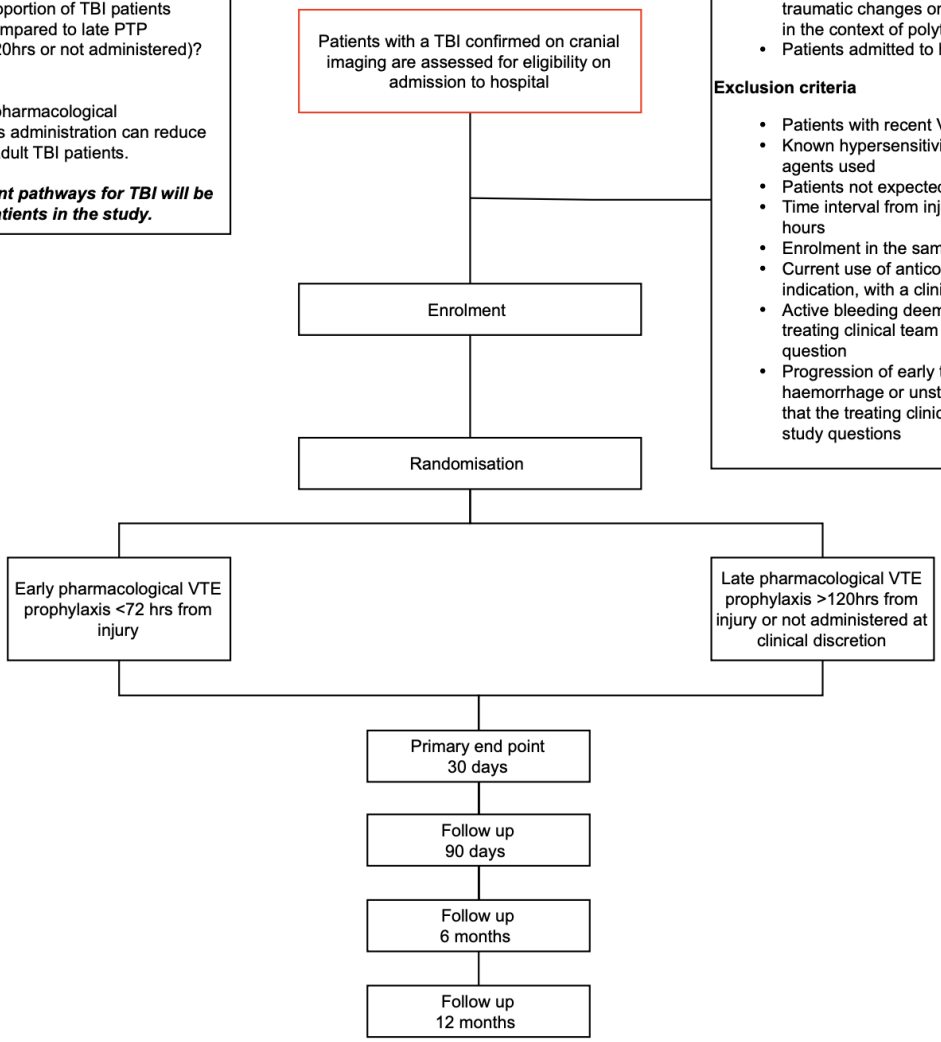
SAR	Serious Adverse Reaction
SBNS	Society of British Neurological Surgeons
SD	Standard Deviation
SRCP	(University of Cambridge, School of Clinical Medicine) Secure Research Computing Platform
SmPC	Summary of Product Characteristic
STEMI	ST-elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic Brain Injury
TMF	Tral Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VTE	Venous Thromboembolism

5. Trial Flow Chart

Research question:
In adult patients admitted to a hospital with a TBI, does early PTP administration (<72 hrs from TBI) reduce the proportion of TBI patients developing VTE compared to late PTP administration (>120hrs or not administered)?

Hypothesis:
Early (<72 hours) pharmacological thromboprophylaxis administration can reduce the risk of VTE in adult TBI patients.

Standard treatment pathways for TBI will be followed for all patients in the study.



Inclusion criteria

- Adult patients (≥ 16) with an acute TBI (acute traumatic changes on CT brain), either in isolation or in the context of polytrauma
- Patients admitted to hospital within 72 hours of injury

Exclusion criteria

- Patients with recent VTE (within 3 months before TBI)
- Known hypersensitivity to any VTE prophylaxis agents used
- Patients not expected to live beyond 72 hours
- Time interval from injury to randomisation exceeds 72 hours
- Enrolment in the same study within last 12 months
- Current use of anticoagulation for an alternative indication, with a clinical decision to continue
- Active bleeding deemed serious enough that the treating clinical team lack equipoise for the study question
- Progression of early traumatic intracranial haemorrhage or unstable neurological condition, such that the treating clinical team lack equipoise for the study questions

Primary outcome measure:

- Clinically relevant VTE within 30 days from randomisation, to include any confirmed diagnosis of symptomatic DVT, pulmonary embolism or death related to VTE

Secondary outcome measures:

- Proximal DVT at asymptomatic screening ultrasound (only relevant for sites where they undertake screening ultrasound as part of routine clinical practice)
- Progression of intracranial haemorrhage within 14 days after randomisation requiring neurosurgical intervention
- Progression of intracranial haemorrhage on routinely performed imaging
- Adverse events including major and clinically relevant non major bleeding events (assessed and reported in accordance with criteria published by the International Society of Thrombosis and Haemostasis)
- VTE at 90 days
- 7-day, 30-day, and 12-month mortality
- Glasgow Outcome Scale-Extended (GOS-E) at 6 and 12 months
- Quality of life (EQ5D-5L) at Day 30 or discharge, 6 and 12 months
- Length of stay of index admission
- Economic analysis

6. Introduction

6.1 Background

Every year in the UK, an estimated 1.4 million people suffer a Traumatic Brain Injury (TBI) and 200,000 people with TBI are admitted to hospital (1). Following a TBI, patients are at considerable risk of morbidity and mortality for several reasons, including the development of venous thromboembolism (VTE) (2). The most common types of VTE are deep vein thrombosis (DVT) and pulmonary embolism (PE). These problems can complicate recovery from TBI, lead to a longer-term reduction in quality of life and can occasionally be fatal.

Recent systematic reviews have reported a VTE incidence rate following TBI of approximately 10% (3–5). The aetiology of provoked VTE in TBI patients is multifactorial, including prolonged immobility, motor deficits, presence of extracranial injuries, inflammatory cascades, and hyper-coagulability (5–7). The prothrombotic state following traumatic injury has been attributed to many factors, including decreased levels of functional protein C and abnormal antithrombin levels (8).

VTE events are of great clinical concern. TBI patients already face complex recovery from their initial injury, and additional complications, including VTE, have been shown to worsen their outcomes by lengthening hospital stays and reducing their likelihood of being discharged home (9). Therefore, developing effective strategies to prevent VTE in patients with TBI is essential and a priority in this patient group.

In hospitalised patients, national guidelines recommend using mechanical VTE prophylaxis and early initiation of pharmacological VTE prophylaxis (PTP) for appropriate patient populations (10). In a broad population, this has reduced VTE-related deaths up to 90 days after discharge by 15.4% in the last 12 years (11). However, there are no clear national guidelines on VTE prophylaxis following TBI, including PTP; risk assessment models have not been validated in these patients (12,13). This lack of evidence is also reflected in the Brain Trauma Foundation guidelines (4th edition), stating there is insufficient Level I or II evidence to make recommendations on the timing of PTP in TBI (13). Recent work in patients without TBI suggests a lower bar for prescribing thromboprophylaxis could improve outcomes and make the best use of NHS resources (9,14).

Low-molecular-weight heparin (LMWH) agents are the first choice for PTP due to their favourable safety profile and ease of administration (15). Several studies have evaluated the rate of VTE and TBI progression following early implementation of LMWH PTP. They have been summarised in 7 systematic reviews (3,4,16–20). Three reviews performed a pooled meta-analysis of rates of VTE between patients treated with early or late pharmacological VTE prophylaxis. The 2013 and 2016 meta-analyses included the same 5 studies with a 72-hour cut-off between early and late thromboprophylaxis. Of 1624 patients in total, the pooled risk ratio for VTE was 0.52 (95% CI 0.37-0.73) in favour of early PTP (3,19). The 2018 meta-analysis included 11 studies grouped into 3 early subgroups (<24, <48, or <72h) of PTP, with a pooled odds ratio across all time groups of 0.58 (95% CI 0.38-0.87), again favouring early PTP (16). The meta-analyses did not include a randomised double-blinded placebo-controlled pilot trial conducted in 2012, recruiting 62 patients to receive LMWH (n=34) or placebo (n=28) at <96h from TBI (21). One DVT was reported in the placebo arm, but no VTE in the LMWH arm. Additional systematic reviews without meta-analyses report reduced VTE with early PTP (4,17,18,20). TBI progression rate was assessed by pooling individual study results, with no statistically significant difference in rate found between early and late arms overall (3,19).

The literature demonstrates a reasonable safety profile with early PTP administration and supports the

clinical effectiveness of early PTP. This evidence has limitations specific to observational methodology.

Current national guidance does not make any recommendations regarding PTP timing. The current risk assessment model recommended by NICE highlights any neurosurgical admission as a risk factor for bleeding and suggests that *'clinical staff should consider if bleeding risk is sufficient to preclude pharmacological intervention*'. NICE guidance states that PTP should be offered to people with serious or major trauma as soon as possible after the risk assessment when the risk of VTE outweighs the risk of bleeding but also that PTP should not be offered to patients with traumatic intracranial haemorrhage until the patient's condition has stabilised. These recommendations are entirely open to clinician interpretation and discretion, resulting in significant variation in practice even for patients with similar characteristics (10). Our service evaluation suggests these recommendations may dissuade clinicians from prescribing PTP.

6.2 Why is this research required?

VTE during hospitalisation is the leading cause of disability-adjusted life-years (DALYs) lost in low-income and middle-income countries and the second most common cause in high-income countries (22, 23). VTE incidence rises with increasing age, placing the rising number of elderly TBI patients at significant risk (23). TBI patients are at considerable risk of developing complications if VTE occurs, as standard treatment options (therapeutic anticoagulation) may complicate recovery and adversely affect long-term functional outcomes, prolonging hospitalisation and increasing inpatient costs (24). PEs are a leading cause of delayed mortality in TBI patients, lengthening hospital stays and reducing the likelihood of being discharged home (25–27). A considerable body of evidence suggests that administration of PTP can reduce the incidence of VTE in patients with TBI (22, 24). This, in turn, can reduce mortality and morbidity and improve long-term functional outcomes and quality of life of patients with TBI. However, there is often a reluctance to initiate PTP early due to the lack of high-quality evidence demonstrating superior clinical effectiveness. This results in heterogeneous management of VTE risk in TBI patients with PTP use being dependent on the individual clinician, hospital, or service practice. There is a need to generate high-quality new knowledge, which this trial has the capacity to do. The results of a high-quality study will be used to inform practice guidelines in the NHS and beyond. The simplicity of the intervention being studied, the wide availability of LMWH, and our comprehensive dissemination plan mean that the TOP-TBI outputs can be rapidly incorporated into patient care and pathways.

The study is supported by the Society of British Neurological Surgeons (SBNS), Neuro Anaesthesia & Critical Care Society (NACCS), and Intensive Care Society (ICS).

6.3 Preliminary work

We have undertaken a retrospective cohort study and a UK-wide survey gathering data on the timing of PTP in patients following TBI. Our retrospective study included 731 patients over a six-month period and had participation from five neurosurgical centres. This study showed that 1) there was much heterogeneity in the timing of initiating PTP among different centres, 2) patients with major extracranial injuries were more likely to receive PTP and 3) PTP did not appear to exacerbate haemorrhagic intracranial lesions. Our UK-wide survey included responses from 61 individuals from 26 neuroscience units. The results showed 1) 85% of respondents agreed there is no high-quality evidence on the timing of starting PTP after an acute TBI and 2) the most common factors contributing to decision-making before starting VTE prophylaxis included progression of intracranial haemorrhage, new intracranial haemorrhage and prevention of VTE events. Thus, our preliminary work provides further evidence for the pressuring need for standardised guidelines on this subject.

6.4 PTP Agents and Mechanism of Action

Our preliminary work has shown that LMWH are the most used drugs for pharmacological thromboprophylaxis in the UK in patients with TBI. However, there may be instances where another drug (that is not a LMWH) may be used for PTP.

For example, Muslim religious leaders have previously issued guidance that use of porcine derived LMWHs are suitable for use in life-threatening conditions, but their use should be discussed with individual patients, if this is possible. Alternatively, Fondaparinux, as a synthetic anticoagulant, may be a suitable alternative for patients who wish not to receive porcine material.

We plan to allow use of local trust protocols for anticoagulants for PTP with respect to the agent used, weight adjustment and renal dosing regimens, and will extend this to use of alternative agents for those patients/families who wish to participate in the trial but pursue non porcine options.

This will ensure the trial remains pragmatic and inclusive to patients from all populations.

We provide an overview and the mechanism of action of the most used PTP (LMWH) below.

Overview

Low molecular weight heparins (LMWHs) are a family of drugs named “Parenteral anticoagulants”. LMWHs include the following drugs: dalteparin sodium, enoxaparin sodium and tinzaparin sodium. The National Institute for Health and Care Excellence (NICE) and the British National Formulary (BNF) have stated that LMWHs have approval for the following:

- DVT prophylaxis in medium and high-risk patient groups (surgical, orthopaedic and medical patients)
- Treatment of VTE in pregnancy
- Treatment of VTE in non-pregnant women
- Treatment of STEMI
- Unstable angina
- Prevention of clotting in extracorporeal circuits

Mechanism of action

Low molecular weight heparins are anticoagulant drugs acting by inhibition of the final common pathway of the coagulation cascade. The overall aim of the coagulation cascade is to fluid blood into a clot and thus prevent bleeding. The final aspect of the common pathway is to convert fibrinogen into fibrin by the activity of thrombin. LMWH inhibits coagulation by activating antithrombin III. Antithrombin III binds to and inhibits factor Xa. By inhibiting factor Xa, antithrombin III prevents the activation of the final common pathway. Factor Xa inactivation means prothrombin is not activated to thrombin, and thus fibrinogen is not converted to fibrin for the formation of a clot. LMWH is a small fragment of a larger mucopolysaccharide, heparin. Heparin works similarly by binding antithrombin III and activating it. Heparin also has a binding site for thrombin so that thrombin can interact with antithrombin III and heparin, thus inhibiting coagulation. Heparin has a faster onset of anticoagulant action as it will inhibit Xa and thrombin, while LMWH acts only on Xa inhibition (28).

LMWH is obtained by fractionation of polymeric heparin. It differs from unfractionated heparin in several ways, including the average molecular weight; the need for only once or twice daily dosing; the absence of monitoring the activated partial thromboplastin time (aPTT); and the lower risk of bleeding, osteoporosis, and heparin-induced thrombocytopenia (HIT). In addition, the anticoagulant effect of

heparin is reversible with protamine sulphate, whereas its effect on LMWH is limited (29).

There are many agents that are licensed to provide VTE prophylaxis. The agent used differs depending on the Trust policy. However, they all prevent thrombus formation or extension of an existing thrombus in the venous side of the circulation. A thrombus consists of a fibrin web enmeshed with platelets and red cells.

Table 1: The table below gives an overview of the different agents available for VTE prophylaxis. NICE guidelines provide further details on their use and administration.

Heparin	● Short duration of action ● Often referred to as "standard" or heparin (unfractionated) to distinguish it from low molecular heparins ● Used in patients at high risk of bleeding since its effects can be terminated quickly by stopping the infusion
Low molecular weight heparins (LMWH)	● Drugs under this class include: dalteparin sodium, enoxaparin sodium and tinzaparin sodium ● Preferred over heparin (unfractionated) in the prevention of VTE since they are as effective and have a lower risk of heparin induced thrombocytopenia ● The prophylactic regime does not require anticoagulant monitoring ● Duration of action is longer than heparin (unfractionated) thus once daily subcutaneous administration possible
Heparinoids	● Drugs under this class include: danaparoid sodium ● Used primarily for prophylaxis of DVT in patients undergoing general or orthopaedic surgery and patients who develop heparin induced thrombocytopenia
Fondaparinux sodium	● Used for VTE prophylaxis in patients undergoing major orthopaedic surgery of the hip or leg or abdominal surgery or medical patients who are immobilised because of acute illness
Oral anticoagulants	● Drugs under this class include: Apixaban, Rivaroxaban, Dabigatran, Edoxaban and Warfarin ● Apixaban, Rivaroxaban, Dabigatran, Edoxabam are licenced for the prevention of recurrent DVT and PE in adults ● Warfarin is licenced for prophylaxis for DVT and PE

Traumatic brain injury patients are likely to have many other pathologies; thus, a clinical decision may be made to use a specific drug for PTP that may not be licenced. To ensure the trial remains pragmatic, the drug used for PTP can be based on hospital guidelines/clinician discretion, even if its use is deemed unlicensed. However, from our survey of 26 neuroscience centres in the UK, the most used LMWH for VTE prophylaxis in patients with TBI.

Patients enrolled on this trial can only be prescribed agents listed in this table.

7. Rationale of the trial

The overall aim of the TOP-TBI trial is to define best practices in the timing of venous thromboembolism prophylaxis in adult patients following a traumatic brain injury. We describe the trial below in the PICO format and in more detail thereafter.

Population	Adult (≥16 of age) patients who have sustained an acute traumatic brain injury and require admission to a hospital
Intervention	Early pharmacological thromboprophylaxis (PTP) administration (<72 hours from injury)
Control	Late PTP administration (prescription of PTP deferred by a minimum of 120 hours from injury or PTP not prescribed at clinical discretion)
Outcome	Clinically relevant Venous thromboembolism (VTE) within 30 days from randomisation

8. Trial design

8.1 Statement of design

TOP-TBI is a multi-centre, parallel-group, pragmatic, randomised superiority trial to determine the clinical- and cost-effectiveness of early PTP administration versus late administration for adult patients with TBI.

The study will be preceded by an internal pilot to confirm recruitment, randomisation, treatment, and follow-up assessments. We have defined robust progression criteria (section 8.3) based on recently published recommendations (30). On reaching the pre-defined success criteria, the internal pilot studies will run seamlessly into the main trial.

8.2 Number of centres

Patients will be recruited primarily from adult neuroscience units (NSU) in the NHS. We anticipate that we will include the majority of Major Trauma Centres (MTC), approximately 20 UK sites, as these are the hospitals where most of the target patient population are directly transferred after a serious TBI.

The pilot stage will last 6 months, and we will recruit 150 patients. After successfully completing the pilot stage, the substantive trial stage will follow and will encompass, where possible, all remaining neuroscience centres and selected major acute NHS hospitals in the UK. If feasible, we will also aim to expand the trial to our overseas partners who have participated in our previous trials over the last 10 years.

Initiation of sites will be undertaken according to CCTU internal processes. Conditions and documentation required for site activation will be detailed on the trial-specific Participating Initiation Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

8.2.1 Principal Investigator Responsibilities

The PI's responsibilities will be listed in the Participating Site Agreement; they will be expected to retain oversight of the trial conduct and documentation at the site, attend the site initiation visit (SIV), maintain the ISF, ensure staff receive the appropriate training and that they are fully aware of their delegated responsibilities, record and report safety events within expected timelines, and update the lead site coordination team if there have been changes at the site that would impact on the sites ability to contribute to the clinical trial.

8.3 Number of participants

We will recruit 1512 patients in total (150 in the internal pilot and 1362 in the substantive study). The pilot phase will last approximately 6 months. Progression criteria based on recruitment for the pilot phase to run into the substantive phase are described in the table below.

	Red	Amber	Green
% of rate proposed	<50% (≤74)	50-99% (74-149)	100% (150)
Number of sites opened	<7	7-12	13
Average number of patients/site/month	<1.0	1.0-1.98	2
	Discuss with oversight groups (TMG, TSC) consider feasibility of continuing to main trial; draw up a recovery or closedown plan to discuss with NIHR	Discuss with oversight groups (TMG and TSC) and propose a recovery plan to NIHR	Proceed to main trial

Further progression criteria to progress from the pilot phase to the substantive phase are as follows:

- If the loss to follow-up exceeds 10% without an identifiable and correctable reason, it would not be feasible to progress to the main phase without substantial changes in the study design
- No ethical or safety concerns raised by the Trial Steering Committee (TSC)

8.4 Participants Trial Duration

Participants will be enrolled on the trial during their stay in the hospital and, following their discharge, will be followed up for up to 12 months. Their trial participation will end when their 12-month follow-up assessment has been completed.

8.5 Trial aims and objectives

Aim

To evaluate the clinical- and cost-effectiveness of early PTP administration versus late PTP administration for adult patients with traumatic brain injury.

8.5.1 Primary objective

Recruit 1512 patients in a randomised trial (150 in the internal pilot, 1362 in the substantive study) to estimate the absolute difference in the proportion of patients developing VTE between the two arms

(early vs late PTP administration).

8.5.2 Secondary objectives

- Compare the consequences of early versus late PTP administration on functional neurological outcome (assessed using the Glasgow Outcome Score Extended) and quality of life using the EQ-5D-5L [44]
- Compare all-cause mortality between the two arms
- Compare intracranial haemorrhage progression and all serious adverse events between the two arms
- Undertake a detailed economic evaluation.

Early and late PTP administration are defined later in the protocol.

The drug / agent administered for pharmacological thromboprophylaxis (PTP) will be based on local hospital policy – any agent listed in Table 1 above is allowed.

8.6 Trial outcome measures

8.6.1 Primary outcome measure

Clinically relevant VTE within 30 days from randomisation, including any confirmed diagnosis of symptomatic DVT, pulmonary embolism, or death related to VTE.

The definition of ***clinically relevant*** VTE is as follows:

- Any ***symptomatic*** DVT or PE event where the treating team has made a working diagnosis for a DVT or PE based on symptoms and or clinical signs and subsequently investigations requested to verify the diagnosis (e.g., ultrasound / CT pulmonary angiogram (CTPA).

DVT or PE occurrence

Symptomatic DVT or PE will be investigated as per standard clinical practice either by compression Doppler ultrasound of the femoral and popliteal veins or CTPA, as appropriate.

8.6.2 Secondary outcome measures

- Proximal DVT at asymptomatic screening ultrasound (*only relevant for sites where they undertake screening ultrasound as part of routine clinical practice*)
- Progression of intracranial haemorrhage within 14 days after randomisation requiring neurosurgical intervention
- Progression of intracranial haemorrhage on routinely performed imaging
- Adverse events, of special interest (AESI) including major and clinically relevant bleeding events (bleeding events are assessed and reported in accordance with criteria published by the International Society of Thrombosis and Haemostasis) (see Appendix 1)
- VTE at 90 days
- 7-day, 30-day, and 12-month mortality
- Glasgow Outcome Scale-Extended (GOS-E) at 6 and 12 months

- Quality of life (EQ5D-5L) at Day 30 or discharge, 6 and 12 months
- Length of stay of index admission
- Economic analysis (see section 16.5)

Given patients with TBI are prone to VTE events, some hospital practices undertake a screening ultrasound to investigate for asymptomatic DVTs. Sites will be allowed to perform screening ultrasound at their discretion; however, this trial will only include ***asymptomatic proximal DVT*** diagnosed by ultrasound. A proximal DVT is defined as a DVT that is in the popliteal, femoral or iliac veins. A DVT that is located below the knee and is confined to the calf veins (peroneal, posterior, anterior tibial, and muscular veins) without a proximal component will not be recorded. This is because up to 25% of patients admitted to an intensive care environment can have asymptomatic distal DVTs that are of no clinical relevance.

The trial will allow any ***asymptomatic proximal DVT*** as part of asymptomatic screening ultrasound diagnosed from the day of randomisation up until day 29 post randomisation. This will be recorded as a secondary outcome.

9. Selection and withdrawal of participants

9.1 Inclusion criteria

- Adult patients (≥ 16 years of age)
- Acute TBI (defined as acute traumatic changes on the CT brain, either in isolation or in the context of polytrauma)
- Patients admitted to hospital within 72 hours of injury

9.2 Exclusion criteria

- Patients with recent VTE (within 3 months before TBI)
- Known hypersensitivity to any VTE prophylaxis agents used
- Patients are not expected to live beyond 72 hours
- The time interval from injury to randomisation exceeds 72 hours
- Participation in the same study within the last 12 months
- Current use of anticoagulation for an alternative indication, with a clinical decision to continue
- Active bleeding was deemed serious enough that the treating clinical team lacked equipoise for the study question
- Progression of early traumatic intracranial haemorrhage or unstable neurological condition, such that the treating clinical team lack equipoise for the study questions

Patients who fit the inclusion criteria and are on pre-existing anticoagulation (e.g. Warfarin for atrial fibrillation) should be managed as per standard hospital protocol. This would routinely involve stopping and reversing the agent. If there is a clinical indication to continue the anticoagulation for a reason other than for VTE prophylaxis, the patient will be excluded.

9.3 Treatment assignment

Patients who fulfil the eligibility criteria will be randomly assigned to the early pharmacological thromboprophylaxis (PTP) administration arm (<72 hours) or the late PTP administration arm (prescription of PTP deferred by a minimum of 120 hours or PTP not prescribed if deemed unnecessary by the clinical team).

Masking

It will not be possible to mask the intervention as we consider it unsafe, impractical, and costly. For example, if there is progression of an intracranial haemorrhage it is important for the clinical team managing the patient to understand the timing and number of doses administered of PTP for patient safety and to guide decision making on use of reversal agents. Our design includes blinded assessment of several secondary outcomes (e.g. GOS-E) to minimise bias from knowledge of treatment assignment.

9.3.1 Early PTP administration trial arm

Upon randomisation, patients will be administered a PTP agent within 72 hours of injury. The agent will continue to be administered until a clinical decision to stop. The VTE prophylaxis agent used route of administration and dose will be as per local hospital practice. The treating team will be encouraged to follow NICE guidance regarding the type and initiation of mechanical VTE prophylaxis.

Following multi-stakeholder discussions, including patient representatives, we decided the definition of early PTP administration as being at any time point up to 72 hours from TBI. This cut-off is also supported by the existing literature and by the findings of our survey. There is also mechanistic evidence to support this threshold for initiation - previous work highlights a 24-48h time point as the transition period for trauma-induced coagulopathy from a hypo-coagulable state to a hyper-coagulable one (32,33). Our group of clinical stakeholders agreed that this time period allows the necessary time to consider other injuries and interventions, facilitate interval brain imaging as necessary and provide the necessary assurance on clinical trajectory.

9.3.2 Late PTP administration trial arm

Upon randomisation, patients will have PTP omitted. However, if deemed necessary by the clinical team, PTP prophylaxis can be administered 120 hours after injury. This will be continued until a clinical decision to stop. The VTE prophylaxis agent used route of administration and dose will be as per local hospital practice. The treating team will be encouraged to follow NICE guidance regarding the type and initiation of mechanical VTE prophylaxis.

We discussed the definition of late PTP at length with our multi-stakeholder group and patient representatives considering the feedback received at the stage 1 application. Our clinical stakeholders had significant reservations about being asked to defer PTP for >7 days in keeping with the currently running Canadian randomised trial (34). Our service evaluation data supports the proposal of deferring PTP in the late arm by a minimum of 5 days (120h), as the median time to PTP from TBI was 5 days in this population and in a recent prospective study in critically ill trauma patients the median time to VTE was 6 days (35). However, our advisory group highlighted the potential bias that may occur with mandated prophylaxis at 5 days, when our service evaluation suggests that 50% of this population currently receive no prophylaxis at all within routine care. As such, in the late arm, PTP will not be offered for the first 120 hours after injury; after 120 hours, PTP can be prescribed if deemed necessary by the clinical team. We believe these decisions are also supported by the existing literature as referenced above and offer the maximum opportunity for pragmatic recruitment, separation of

interventions and evaluation of the specific research question as to whether early initiation is better than managed consideration of risk in current practice.

9.3.3. Difference between current & planned care pathways

There is no standardised NHS pathway for PTP following TBI. The decision to start PTP and the timing of such is left to the clinical team's discretion (5, 12). The NICE guidance (Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism NICE guideline [NG89]) states that PTP should be offered to people with serious or major trauma as soon as possible after the risk assessment when the risk of VTE outweighs the risk of bleeding but also that PTP should not be offered to patients with traumatic intracranial haemorrhage until the patient's condition has stabilised. These recommendations are entirely open to clinician interpretation and discretion, resulting in significant variation in practice even for patients with similar characteristics.

The allocated initiation and timing of VTE prophylaxis is the only difference in the planned care pathway for this study with all other aspects of clinical care following standard pathways.

Patients will be screened for eligibility promptly after admission, and written consent (or delegated consent by next of kin (personal legal representative) or professional consultee (Independent healthcare professional) will be sought prior to enrolment and randomisation. This tiered consent approach has been successfully used in recent TBI trials (36, 37). Patients deteriorating neurologically will usually have a repeat CT brain imaging with further management as required. Patients developing symptoms of a VTE will be managed as per normal clinical pathways. These usually include Doppler ultrasound if a deep vein thrombosis is suspected or a CTPA if a pulmonary embolism is suspected, with treatment dose anticoagulation for three months initiated as required, or siting of an inferior vena cava filter if the treating team consider therapeutic anticoagulation to be absolutely contraindicated. Clinical follow-up for the TBI is usually 3-6 months after discharge. If a VTE has been diagnosed, this can either be managed by the patient's GP, or it may be necessary to follow up in a thrombosis clinic, respiratory clinic and/or referral to a cardiac-pulmonary rehabilitation programme for those who have suffered a significant, symptomatic VTE.

9.3.4. Randomisation

A secure web-based randomisation service (Sealed Envelope) will be used for the randomisation of eligible patients. Suitably trained staff will access the secure website and enter the necessary information. The system will provide an immediate allocation along with the patient identifier number for the trial. A confirmatory email will be sent to the email addresses of the study team members at the site randomising the patient. Trial investigators (or delegates) from the central team will be available 24-hours in case of problems or queries with the randomisation system. The presence of extracranial injury and initial admission to the ward vs critical care will stratify allocation. Stratified block randomisation will be used.

Early PTP arm - defined as administration of PTP within 72 hours of TBI

Late PTP arm - defined as administration of PTP after a minimum of 120 hours from TBI or PTP not administered at clinical discretion. PTP **should not** be administered within 120 hours and administration will be recorded as protocol deviation

9.4 Participant withdrawal criteria

Primary reasons for withdrawal may include:

- Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Withdrawal from treatment - participants may voluntarily withdraw from treatment for any reason at any time but continue to provide follow-up data (via patient completed questionnaires and/or NHS England data or the Scottish, Welsh or Northern Irish equivalents, where applicable)
- Withdrawal from trial - participants may voluntarily withdraw from treatment for any reason at any time and withdraw from data collection
- Participants will be withdrawn at any time if the investigator concludes that it would be in the participant's best interest for any reason

Each participant has the right to discontinue their participation in the trial at any time. If an unconscious participant regains capacity and makes a request to be withdrawn from the trial, then this will be accepted. Incapacitated participants may withdraw from the trial if the consultee requests withdrawal.

As the trial is on an intention-to-treat basis, any data collected will remain in the trial, and the participant will continue to be followed up unless consent to continue data collection has been withdrawn. Initially, participants who have been withdrawn from the trial will not be replaced as the power calculation for the trial allows for a 5% loss to follow-up; however, the withdrawal rate will be monitored, and participant replacement will be at the discretion of the Trial Steering Committee should it exceed 5%.

All discontinuations and withdrawals will be documented in the CRF. If a participant wishes to discontinue, anonymised data collected up until that point will be included in the analysis.

10. Trial treatments

10.1 Treatment summary

The IMPs in this trial are VTE prophylaxis agents used in standard clinical practice (listed in ***Table 1***). This trial has been accepted as Type A against the competent authority risk-adaptation criteria, i.e. 'no higher than the risk of standard medical care'

All prescribing, storage, administration and dosing decisions will be taken in line with local Trust guidelines and the published summary of product characteristics (SmPC) for each PTP agent.

10.2 Concomitant therapy

Any concomitant therapy clinically required will be permitted. Contraindications are listed in section 4.3 of the relevant SmPCs. A list of drug interactions is detailed in section 4.5 of the relevant SmPCs for both drugs. Any concomitant therapies which interact with the trial drugs will be recorded. Potential drug interactions with concomitant medications should be managed as per standard clinical practice, including therapeutic drug monitoring as appropriate.

10.3 Accountability and dispensing

10.3.1 Pharmacy responsibilities

The IMP will be provided directly using standard hospital stock during inpatient stay (including use of ward stock where appropriate) with no requirement for trial-specific dispensing.

10.3.2 Drug accountability

Drug accountability is not required as the drug will be administered in line with routine standard care practices. Compliance will be measured using inpatient records.

11. Procedures and assessments

11.1 Participant identification

All patients who have been admitted to a hospital with a traumatic brain injury will be screened for eligibility. A member of the clinical team will assess the potential eligibility of these patients based on the inclusion/exclusion criteria outlined earlier in the protocol.

11.2 Consent

The REC must approve the Informed Consent Form (ICF) and must follow GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. Once consent has been obtained, a copy of the signed ICF will be sent via secure transfer (e.g. nhs.net) to the trial coordination centre for verification that it has been completed correctly. The informed consent form used for this trial and any change made during the course of this trial must be prospectively approved by the REC. The investigator will retain the original of each participant's signed informed consent form.

Should a participant or participant's legal representative require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators A locally translated PIS may be provided if required.

Consent must be taken prior to trial randomisation

Where potential participants fulfil the eligibility criteria, they will be approached by a member of the research team who will provide the PIS and clarify any information from the potential participant which may preclude recruitment. Wherever possible, informed consent will be obtained from the potential participant; however, due to the nature of the condition, this may not be possible.

Patient legal representative available in the hospital

In potential participants lacking capacity, a legal representative will be sought. If the legal representative is available in the hospital, is contactable, or is due to visit the potential participant within a reasonable timescale, then they will be provided with information about the trial and asked if they will provide consent for the potential participant before enrolment. This will take place during their visit to the patient.

For the purposes of sites in England, Wales and Northern Ireland, a legal representative is defined as:

A person not connected with the conduct of the trial who is:

a) Suitable to act as the legal representative by virtue of their relationship with the adult, and
b) Available and willing to do so

For the purposes of sites in Scotland, a legal representative is defined as:

a) Any guardian or welfare attorney who has the power to consent to the adult's participation in research
b) If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000

The patient's legal representative is not available in the hospital

Due to the condition of these patients, there will be those who will have no known legal representative or where the legal representative is not contactable or not able to visit the hospital at short enough notice to be able to enrol the potential participant within the required 72 hour time frame. In such cases, we advocate enrolment would be possible with written agreement from an independent clinician. If no legal representative is available for discussion, then an independent clinician (Independent Healthcare Professional) will be approached. If a legal representative visits the hospital later, then the trial will be discussed with them, and their consent sought at that time point to continue in the trial.

Participants who regain capacity whilst in the hospital will be informed about the clinical trial, and consent to continue will be sought. If, at any stage, either the legal representative or the participant chooses to withhold consent, then the participant will be withdrawn from the trial.

Participants who regain capacity following discharge will be contacted by phone and posted a PIS and ICF as soon as possible to complete and return to trial team.

Independent healthcare professional (IHP) definition

For the purposes of the TOP-TBI trial, the Independent Healthcare Professional (IHP) is defined as:

A person who is not connected with the conduct of the trial, specifically:

a) The sponsor of the trial.
b) A person who undertakes activities connected with the management of the trial.
c) An investigator of the trial or,
d) A health care professional who is a member of the investigator's delegated team for the purposes of the trial.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial, will be communicated to the participant or participants personal legal representative as soon as possible, verbally if the participant is in hospital, by post if they have been discharged.

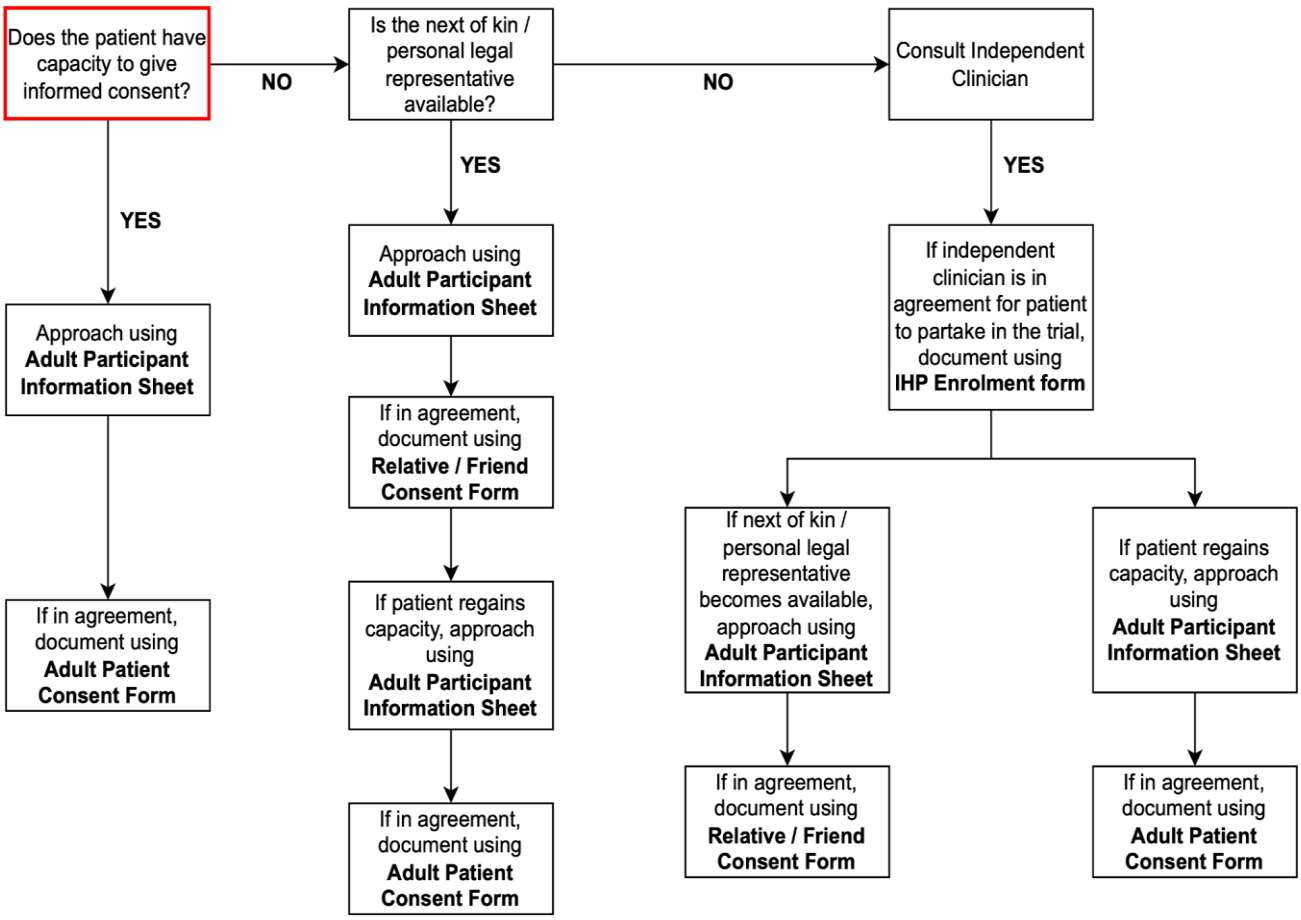


***Figure 1*: Consent flowchart.**

11.3 Screening evaluation

11.3.1 Screening assessments

Trial-specific assessments will only be conducted after written informed consent (from the participant, the participant's legal representative or independent healthcare professional). Medical history precluding eligibility will be obtained from either the patient's case notes or after discussion with the potential participant (or the potential participant's representative, if available).

11.3.2 Participant registration / randomisation

Upon completion of consent and screening, participants will be enrolled on the TOP-TBI trial. A unique participant ID will be allocated to each participant using a computer randomisation system (Sealed Envelope).

A de-identified record of the patients approached, along with the numbers of, and reasons for, screen failures and refusal of consent, will be kept at each site on a Screening Log and reported to the Trial Coordinating Centre when requested. This information will be used to identify any barriers to recruitment and allow improvement measures to be identified and implemented in a timely manner.

Following randomisation, a letter will be sent to the participant's GP, informing them about the participant's participation.

11.4 Screening and Baseline Assessments

All participants will have a medical history taken and a clinical examination as part of the routine standard care. The following are to be recorded in the CRF:

- Inclusion/exclusion criteria review
- Informed consent process followed and consent or authorisation for enrolment obtained (signed consent form sent to the trial coordination centre for verification within 24 working hours)
- Routine review of clinical laboratory results
- ECG (if indicated by local policy)
- Standard of Care:
    - Patient medical history (including co-morbidities and relevant medications, including use of anticoagulation)
    - If pre-existing anticoagulation is present, the timing of any reversal agents used
    - Patient demography
    - Injury-related events - date of TBI, date of possible intubation, other injuries
    - Neurological status
    - Imaging review

11.5 Trial assessments

11.5.1 Timing of assessments

Participants will be monitored as per routine clinical practice until discharge and thereafter at 30 days (+/- 5 days), 90 days (+/- 15 days), 6 months and 12 months (+/- 1 month) to score clinical outcomes.

11.5.2 Assessments at time point

- Adverse events of special interest (AESI) during treatment and follow up timepoints up to 12 months. including major and clinically relevant bleeding events
- Asymptomatic DVT assessment with an ultrasound scan during hospital stay (*only relevant for all sites that perform screening ultrasound* as part of routine clinical practice
- Assessment for VTE during hospital admission, 30 days and 90 days
- Progression of intracranial haemorrhage on routinely performed imaging within 14 days after randomisation requiring neurosurgical intervention
- Quality of life (EQ5D-5L) at Day 30 or discharge, 6 and 12 months
- Mortality at 7-days, 30 days and 12 months
- Glasgow Outcome Scale-Extended (GOS-E) at 6 and 12 months
- Length of stay of index admission
- Economic analysis at 12 months

Method of follow-up

Prospective follow-up data (at 30 days - primary endpoint), 90 days, 6- and 12-months post-enrolment) will be collected electronically via email or online formats such as Qualtrics or MS Forms or via postal questionnaires or telephone interviews by blinded study personnel if participants cannot complete forms electronically/return postal questionnaires. The questionnaires will include questions on any longer-term effects of VTE, the extended Glasgow Outcome Scale (GOSE, only 6 and 12 month FU) and EQ-5D-5L questionnaire (30 days, 6- and 12-month FU). Re-admission and out-patient data will be captured from Hospital Episode Statistics (HES) data.

11.5.3 Assessments at the end of trial

At the end of the trial, a health economic evaluation will be performed (details in section 16.5).

11.6 Table for schedule of assessments (*Table 2*)

	Screening/ Baseline (within 72 hours of TBI)	Treatment Phase (within 72 hours of TBI OR >120 hours of TBI)	Day 7	Day 14	Day 30 (+/- 5 days) OR Discharge	Follow up phase		
						Day 90 (+/- 15 days)	6 months (+/- 1 month)	12 months (+/- 1 month
Eligibility assessment	X							
Informed consent	X							
Randomisation	X							
IMP administration		X						
Safety assessments (AESI/SARs)	X	X	X	X	X	X	X	X
Intracranial haemorrhage				X				
Mortality			X		X			X
VTE occurrence	X				X	X		
GOSE							X	X
EQ-5D-5L					X		X	X
Economic evaluation								X

11.7 Long term follow-up assessments

Participants will be followed up for 12 months post-randomisation by questionnaire. Assessments will not necessarily require a face-to-face interview. Participants will be given the option of conducting assessments by email, postal mail (via return in a self-addressed, stamped envelope sent to their provided contact address e.g. home, rehabilitation centre), or by telephone. Follow up assessments may also be completed during routine clinic visits. If participants who are sent the follow-up questionnaires by email or postal mail do not return them after approximately 2 weeks, they will be contacted by telephone. If the time point after an assessment exceeds 8 weeks, and there is no response, every effort will be made to obtain required information via other means e.g. by contacting the next of kin, the patient's GP, local hospital or rehabilitation centre.

11.8 End of trial participation

Participants will continue the normal standard of care after participating in the trial. A participant is deemed to have completed the trial once they have completed their 12-month follow up assessment.

11.9 Trial restrictions

There are no trial-related restrictions in addition to standard care. Regardless of the trial arm the participant is assigned to and the trial medications being/not being taken, the treating clinician will assess the participant regularly and will decide on the clinical course for the patient as part of routine standard care. This may involve withholding PTP if deemed clinically necessary.

12. Assessment of safety

This trial is a Type A study (low risk), as all the IMPs being used are licensed medications and the dose and frequency of administration of these IMPS will be as per routine clinical care (with only the time-point of administration being varied). Therefore, safety assessments are not of primary concern (unless they are SARs or SUSARs).

Principal investigators are not required to report to the central coordinating team any AEs or ARs unless these fulfil the criteria for a SAR or SUSAR.

12.1 Definitions

12.1.1 Adverse event (AE)

Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with using an investigational medicinal product, whether considered related to the investigational medicinal product.

Recording of adverse events must start from the point of Informed Consent regardless of whether a participant has yet received a medicinal product.

The safety profiles of all drugs used for VTE prophylaxis are well established, and due to the pathology of TBI, trial participants will be regularly monitored and assessed in the intensive care environment at regular intervals throughout the trial, over and above routine clinical care. Given the pragmatic nature of the trial and that the potential risk associated with the trial drug is 'no higher than standard care',

only AEs of special interest (AESI) will be recorded on CRF and sent to the coordination centre as listed below.

Adverse events of special interest (AESI) – assessed and reported in accordance with criteria published by the International Society of Thrombosis and Haemostasis. – see Appendix 1.

The following should all be recorded on the AESI form in the eCRF.

- Thrombocytopenia
- Thrombocytosis
- Prosthetic cardiac valve thrombosis
- Cutaneous vasculitis
- Eosinophilia
- Skin reactions
- Angioedema
- Priapism
- Stevens-Johnson syndrome
- Acute generalised exanthematous pustulosis (AGEP)

12.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

12.1.3 Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information (RSI). When the outcome of the adverse reaction is not consistent with the applicable RSI, this adverse reaction should be considered unexpected. The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on participant /event outcome or action criteria.

12.1.4 Serious Adverse Event or Serious Adverse Reaction (SAE / SAR)

Any untoward medical occurrence at any dose:

- results in death
- is life-threatening
- requires re-hospitalization or prolongation of existing inpatients´ hospitalisation, where it is not considered to be due to the initial trauma
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered ‘serious’

Life-threatening in the definition of a serious adverse event or serious adverse reaction 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.

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information.

12.1.6 Reference Safety Information (RSI)

A list of medical events that define which reactions are expected for the IMP within a given trial and thus determines which Serious Adverse Reactions (SARs) require expedited reporting.

For this trial, the Reference Safety Information contains a clearly identified section 4.8 of the Summary of Product Characteristics (SmPC) for different drug classes.

12.1.7 Table for IMP class with SmPCs and text revision date for RSIIMP class	RSI	Text revision Date
LMWH	Inhixa 4,000 IU (40 mg)/0.4 mL solution for injection	23/05/2023
Low molecular weight sulphated glycosaminoglycuronans	Danaparoid Sodium 750 anti-Xa units/0.6 ml, solution for injection	01/2021
Direct oral Anticoagulants (DOAC)	Pradaxa 150 mg hard capsules	12/04/2024
Synthetic pentasaccharide	Arixtra Fondaparinux sodium solution for injection 2.5 mg/ 0.5 ml	05/12/2023
Heparin	Heparin (Mucous) Injection BP 5,000 IU	28/09/2018

12.1.8 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest MHRA-approved version of the RSI. As explained in section 12.1.6. This must be used when deciding as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as in section 12.5

12.1.9 Expected Adverse Events/Serious Adverse Events (AE/SAE)

Due to the nature of TBI, affected individuals can often develop surgical and medical complications. Expected systemic or surgical complications associated with TBI will not be recorded as SAEs.

12.4 Evaluation of AESI; SAR / SUSAR

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product. The investigator should evaluate individual adverse events. This includes the evaluation of its seriousness and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality).

12.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4. This defines whether the event is an adverse event, a serious adverse event or a serious adverse reaction.

12.4.2 Assessment of causality

Definitely	A causal relationship is clinically/biologically certain. This is therefore an Adverse Reaction
Probably	A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. This is therefore an Adverse Reaction
Possible	A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. This is therefore an Adverse Reaction
Unlikely	A causal relation is improbable and another documented cause of the AE is most plausible. This is therefore an Adverse Event
Unrelated	A causal relationship can be definitely excluded, and another documented cause of the AE is most plausible. This is therefore an Adverse Event

- Unlikely and Unrelated casualties are considered NOT to be trial drug-related
- Definitely, Probably and Possible casualties are considered to be trial drug-related

A pre-existing condition must not be recorded as an AE or an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

12.4.3 Clinical assessment of severity

Mild	The participant is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate	The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe	Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event

12.4.4 Recording of adverse events and Adverse Events of Special Interest

No AEs or ARs will be recorded or reported as part of the trial. Adverse events and adverse reactions should be recorded in the patient's medical notes as part of their routine care, as determined by their treating clinician.

Only Adverse Events of Special Interest (AESIs) will be recorded in the trial as part of secondary outcome data collection in the AESI eCRF. AESI that will be collected in the trial include those below:

- Thrombocytopenia
- Thrombocytosis
- Prosthetic cardiac valve thrombosis
- Cutaneous vasculitis
- Eosinophilia
- Skin reactions
- Angioedema
- Priapism
- Stevens-Johnson syndrome
- Acute generalised exanthematous pustulosis (AGEP)

12.5 Recording and reporting serious adverse events (SAEs) and serious adverse reactions (SARs)

SAEs will not be recorded or reported as part of the trial. Only SAEs for secondary outcome data (ie AESI) will be recorded in the SAE CRF for the duration of the trial.

SAEs should be recorded in the patients normal medical record as part of their routine care as determined by their treating clinician. All SAEs must be assessed by the PI or delegate for causality/relatedness to determine if the event meets the criteria for reporting to the CI and Sponsor as a Serious Adverse Reaction (SAR). See below for SAR reporting requirements.

Only SARS and SUSARs must be reported to the Chief Investigator using the trial-specific SAR reporting form within 24 hours of their event awareness. The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SARs and SUSARs to the Sponsor immediately but not more than 24 hours after the first notification. The sponsor must keep detailed records of all SARs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all reportable serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk-to-benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

For this trial, only Adverse Reactions that are serious (SARs) or unexpected (SUSARS) will require expedited reporting to the Sponsor.

Principal investigators must record and report SARs and SUSARs to the Sponsor within 24 hours of becoming aware of the event using the SAR form provided.

SARs/SUSARs will only be collected and reported during trial treatment

Any/all SAR reports which do not contain the expectedness assessment will be automatically considered as a SUSAR, and be subject to expedited reporting until such time as an expectedness assessment is documented and reported to the CI & Sponsor. Please see section 12.1.6 for the Reference Safety Information to be used in this trial

The completed SAR Reporting form will be emailed to the coordination centre. Details of where to report the SARs can be found on the TOP-TBI SAR Reporting form and the front cover of the protocol.

12.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 4.8 for the Reference Safety Information for this trial.

12.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described to the:

- Sponsor
- Competent authorities in the concerned member states (e.g., MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

12.6.2 When to report?

12.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 12.6.1 must be notified as soon as possible but no later than 7 calendar days after the trial team and Sponsor have first knowledge of the minimum criteria for expedited reporting. In each case, relevant follow-up information should be sought, and a report completed as soon as possible. It should be communicated to all parties within an additional 8 calendar days.

12.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 12.6.1.as soon as possible but no later than 15 calendar days after first knowing the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

12.6.3 How to report?

12.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product
b) an identifiable participant (e.g. trial participant code number)

c) an adverse event assessed as serious and unexpected and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source

and, when available and applicable:

- a unique clinical trial identification (ISRCTN number or in the case of non-European Community trials, the sponsor's trial protocol code number)
- a unique case identification (i.e. sponsor's case identification number)

12.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate causality analysis should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct a follow-up of the long-term outcome of a particular reaction.

12.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content, as defined by the competent authority, should be adhered to.

13. Pregnancy Reporting

Pregnancies in participants will not be recorded or reported in this trial unless they meet the criteria of SAR, in which case the SAR reporting form will need to be completed.

14. Evaluation of Results (Definitions and Response/Evaluation of Outcome Measures)

All data will be presented to the TSC, who will meet regularly throughout the trial and who will provide overall supervision of the trial.

14.1 Response criteria

14.1.1 Mortality

This will be measured from the date of randomisation up to the 12-month follow-up and will be reported for all deaths due to all causes. The cause of death is to be recorded if known.

14.1.2 Quality of life and disability

Quality of life will be assessed by employing the EQ-5D-5L questionnaire to generate quality-adjusted life years.
The GOS-E outcome instrument will be used to assess disability and recovery.

14.1.3 Assessment of DVT or PE occurrence

Symptomatic DVT or PE will be investigated as per standard clinical practice either by compression Doppler ultrasound of the femoral and popliteal veins or CTPA, as appropriate.

14.1.4. Progression of intracranial haemorrhage

This will be detected via routinely performed imaging

15. Statistics

15.1 Statistical methods

The principal statistical analysis will be performed on an intention-to-treat basis and will include all randomised patients, regardless of subsequent treatment compliance.

Primary analysis

Our primary outcome will be VTE within 30 days of TBI. A survival analysis approach will be used to model the time to VTE and account for censorings before 30 days due to dropout. A Cox proportional hazards model will adjust for baseline covariates, including the randomisation strata (presence of extra-cranial injury and initial admission to ward vs critical care), with further details finalised in the statistical analysis plan. The difference in absolute VTE rates at 30 days will be the primary estimate, as opposed to a hazard ratio. The g-formula approach will be used to estimate the absolute difference standardised across the study population of baseline covariates, with bootstrapping used to provide a confidence interval and p-value. Using VTE rates at 30 days as the primary outcome standardises this study with existing literature on VTE rates quoted by NICE.

Secondary analysis

Further secondary endpoints will be summarised using appropriate techniques according to whether the variable is binary, categorical, continuous or time-to-event. Categorical and binary variables will be summarised using bar charts, frequency tables and logistic regression comparisons. The GOSE will be analysed with an ordinal method adjusting for baseline covariates. Continuous variables will be summarised, broken down by treatment arm, using Box plots, mean, median, SD, max, min and compared using linear regression. Time-to-event variables will be summarised using Kaplan-Meier plots and compared using the log-rank test or Cox proportional hazards model.

The selected secondary endpoints reflect all the outcomes highlighted by the original NIHR commissioning brief. The GOSE can reveal the impact of TBI on the level of consciousness, activities of daily living, functional independence, work and quality of life (31) and will be used to assess longer-term functional outcomes for study participants. Further secondary endpoints will be summarised using appropriate techniques according to whether the variable is binary, categorical, continuous or time-to-event. Categorical and binary variables will be summarised using bar charts, frequency tables and logistic regression comparisons. Continuous variables will be summarised, broken down by treatment arm, using Box plots, mean, median, SD, max, min and compared using linear regression. Time-to-event variables will be summarised using Kaplan-Meier plots and compared using the log-rank test.

Subgroup analysis

We will explore subgroups focussing on those factors most relevant to the research question, which are TBI severity and type, extracranial injuries and body mass index. The study statistician will prepare a detailed statistical analysis plan.

Convolutional neural network (CNN) CT scan analysis

All CTs obtained for subjects during routine care will be uploaded onto a secure image repository. Images will be pseudo-anonymised and defaced. Lesion progression on CT will be assessed using a convolutional neural network capable of multiclass segmentation, which has already been developed and validated on a broad range of clinical sites and scanners as part of CENTER-TBI, a prospective European TBI cohort study (38).

15.2 Interim analysis

An interim analysis may be performed after an appropriate number of participants (to be decided by TSC) have observed 30 days follow-up, shortly before recruitment is scheduled to be halted, to confirm the sample size. The TSC and statistical team will agree jointly on the most appropriate timing of this interim analysis, considering the case mix and parameters the TSC wishes to estimate. If the sample size needs to be revised, we can incorporate the uncertainty in absolute VTE rates to achieve an acceptable conditional power as determined by the TSC. The interim analysis will be outlined in the TSC Charter.

15.3 Number of participants to be enrolled

The number of participants to be enrolled is 1512 patients. The rationale for this sample size is as follows. The literature shows that a 5% decrease in clinically important VTE rate is deemed a plausible and clinically important treatment effect (39–41). 1164 patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 10% in the "late" group (16, 17, 42) to 5% in the "early" group. However, should the assumed rate in the “late” group be an underestimate, then power will be lost. A comparison of 12% vs 7%, would need 1441 patients. Should the treatment effect be slightly smaller, e.g. a 4.6% reduction equivalent to a comparison of 10% vs 5.4%, then the power of 90% would be maintained with 1441 patients. Hence, adjusting for a loss to follow-up of up to 5%, a robust total sample size of 1512 will be recruited.

The rationale for a 5% loss to follow-up rate is that patients who suffer brain injury often have persistent cognitive difficulties, thus creating challenges with follow-up assessments. However, this 5% is a conservative estimate, and our previous trials drop-rate ranged from 1-3% (43). In recent neurotrauma trials delivered by Cambridge CTU, loss to follow-up was < 4% at 6 months (2.3% for the RESCUEicp RCT, 3.3% for the Dex-CSDH RCT and 3.7% for RESCUE-ASDH RTC). Given that this trial’s primary endpoint is 30 days, which is much shorter than 6 months, we are confident that loss to follow-up will be minimal. However, we will monitor this closely during the pilot and substantive phases to ensure it does not exceed.

15.4 Criteria for the premature termination of the trial

There are no defined criteria for the premature discontinuation of the trial. Following the pilot phase, the trial will progress into the substantive study provided certain criteria based on recruitment are met (see section 8.3) However, the TSC will make recommendations on discontinuing the trial following a review of the ongoing data presented at regularly scheduled meetings.

15.5 Procedure to account for missing or spurious data

For the primary analysis, missing data will be assumed to be missing at random. A sensitivity analysis will be carried out by performing a complete case analysis. As the relevant covariates must be recorded before the participant can be randomised, we aim to have minimal missing baseline data. There is also an excellent track record for UK-led neurosurgical studies in achieving extremely high rates for follow-up (STICH, STICH II and RESCUE studies).

15.6 Economic evaluation

An economic analysis will be undertaken to compare the cost-effectiveness of early PTP versus late PTP, and a 12-month trial economic evaluation will be conducted. Costs will be estimated from the viewpoint of the NHS and include LMWH, hospital admissions, potentially related medication use, investigations, readmissions and outpatient appointments using data from HES.The main outcome

measure will be the EQ-5D-5L (44) at day 30/discharge, 6 and 12-month follow-up, enabling Quality Adjusted Life Year (QALY) scores to be estimated. Based on a pre-specified Health Economic Analysis Plan (HEAP), the analysis will be undertaken to estimate the incremental cost and incremental effect (QALY gain) associated with early PTP compared to late PTP. Assuming dominance does not occur (where one option is estimated to be more effective and less costly than the other option), the incremental cost-effectiveness ratio (ICER) of early PTP will be estimated and assessed concerning a range of cost-effectiveness thresholds e.g., £20,000-£30,000 per QALY has been recommended by NICE. The associated level of uncertainty will also be characterised by estimating the cost-effectiveness acceptability curve / conducting sensitivity analysis. This methodological approach has been adopted in a previous trial of TBI patients (37) and will enable recommendations as to the cost-effectiveness of early PTP to be made.

15.7 Definition of the end of the trial

The end of the main trial will be the date of the last participant's final assessment/loss to follow-up.

16. Data handling and record keeping

16.1 eCRF

Electronic case report forms (eCRFs) will be used to collect the data. All data will be entered into a secure electronic database. The database, which will be MHRA and GDPR-compliant, will be secured by appropriate access control and password protection.

All trial data will be transferred into the CRF which will be de-identified. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The investigator or designee must complete, date and sign the CRFs in a timely manner. It remains the responsibility of the investigator for the timing, completeness and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Participating sites will be provided with eCRF completion guidelines and given training on data entry.

The central coordinating team will check the data entered into the trial database for errors, inconsistencies and omissions. If missing or questionable data are identified, the central coordinating team will request that the data be clarified.

16.2 Use of Personal Identifiable Data

Trial participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the trial. The TOP-TBI trial management team will hold Personal identifiable data (PID) on all participants, including name, date of birth, gender, NHS number or equivalent, home address and postcode, telephone number and email address where applicable. Personal identifiable data (PID) will be accessible to limited members of the TOP-TBI trial team within the Cambridge Clinical Trials Unit; the sponsor monitors auditors and inspectors as required. It is necessary to 1) perform linkage to national datasets: NHS England, Secure Anonymised Information Linkage (SAIL) databank, Public Health Wales, electronic Data Research and Innovation Service (eDRIS), Public Health Scotland and Belfast Health and Social Care Trust, and 2) to contact participants for follow-up assessments and is therefore imperative to the conduct of the trial.

All PIDs downloaded from NHS England and the equivalent national health record organisations will be stored securely on the University of Cambridge, School of Clinical Medicine Secure Research Computing Platform (SRCP). The SRCP is registered and approved under the NHS Digital Data Security and Protection Toolkit and is ISO 27001 certified.

16.2 Source data

To enable peer review, monitoring, audit and/or inspection, the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., hospital records) and all original signed informed consent forms. The electronic CRFs should also be readily available.

In this trial, the following documentation will be considered as source data:

- Patient medical notes, electronic and/or paper as applicable
- Radiology Reports
- Screening Logs
- Informed Consent Forms
- Questionnaires
- Source data worksheets will be provided to sites as required to assist them in documenting medical history, concomitant medications, and AESI.

16.3 Data protection & participant confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of GDPR, the Data Protection Act 2018 and the Trust Policy regarding the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

17. Trial steering committee

As this trial is a low-risk Type A and involves licensed IMPs with well-documented safety characteristics, the trial will only have a Trial Steering Committee (TSC) that can also review SARs/SUSARs. The TSC will provide overall supervision with respect to the conduct of the trial as well as oversee the ethical and safety aspects of the trial and will advise the TMG. Full details of the TSC membership and remit can be found in the TSC charter.

18. Ethical and regulatory considerations

18.1 Ethical committee review

Before the start of the trial or implementation of any amendment, we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents, if applicable, from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports (DSURs) will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

18.2 Regulatory compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

18.3 Health Research Authority (HRA)

HRA approval is required for all UK trials before commencement.

18.4 Protocol amendments

Protocol amendments must be reviewed, and agreement received from the Sponsor for all proposed amendments before submission to the HRA, REC and/or MHRA. Substantial and significant protocol amendments will also be reviewed by the NIHR before submission. The only circumstance in which an amendment may be initiated before HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, the accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

18.5 Peer review

The trial proposal has been through the NIHR peer review process as a requirement of the HTA award. It has also been discussed and widely accepted by the Academic Committee of the Society of British Neurological Surgeons, the Age and Ageing National Specialty Group of the NIHR CCRN and the British Neurosurgical Trainee Research Collaborative. The support of the UK Neurosurgical Research Network will allow us to roll out the substantive trial across the NHS.

18.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the Declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.7 Good Clinical Practice (GCP) Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training before undertaking any responsibilities on this trial. This training should be updated every 3 years or in accordance with your Trust's policy.

19. Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused due to protocol design and for non-negligent harm arising through participation in the clinical trial.

This trial is funded by the National Institute for Health Research (NIHR) HTA Programme Grant (NIHR152722). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

20. Monitoring, Audit and Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially. The Sponsor's monitoring frequency will be determined by an initial risk assessment performed before the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed, and the monitoring frequency adjusted as necessary.
Monitoring of participating sites should occur in line with the trial specific monitoring. Remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

21. Publication policy

Ownership of the data arising from this trial resides with the coordinating trial team. On completion of the trial, the data will be analysed and tabulated, and a Final Trial Report (FTR) will be prepared. We intend to disseminate the findings of the TOP-TBI trial *via* high-impact factor journals, the HTA journal and presentations at national and international meetings. We will target conferences organised for the different health professionals who care for patients with TBI, including those in neurosurgery, intensive care medicine, neurology, rehabilitation medicine, and emergency medicine. Research findings will be disseminated to relevant service user groups and charities (Thrombosis UK and Headway) through newsletters, website posts and public presentations. The TOP-TBI study website will also include dedicated pages for members of the public. We propose to hold open days in some of the hospital departments participating in the study where members of the public will be invited to find out about the study.

22. Archiving

As per current regulation, once the trial has come to an end and the analysis has been reported to the regulatory authorities, essential trial documentation as part of the TMF will be archived in keeping with the Sponsor's policy and applicable regulations for a period of 5 years

All trial-related documentation and data as part of the investigator site file (including the site-level pharmacy file) will be archived following the participating site's standard operating procedures and the Sponsor's timelines. These procedures state suitable locations to be specified at the time of archiving with limited access to named members of the research team only.

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Appendix 1

Criteria for assessing and reporting major and clinically relevant non major bleeding events in accordance with criteria published by the International Society of Thrombosis and Haemostasis

1. Fatal bleeding, and/or

2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or

3. Extrasurgical site bleeding causing a fall in hemoglobin level of20gL)1 (1.24 mmol L)1) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding, and/or

4. Surgical site bleeding that requires a second intervention open, arthroscopic, endovascular or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or

5. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in haemoglobin level of at least 20 g L)1 (1.24 mmol L)1), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.

6. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).

7. The population is those who have received at least one dose of the study drug.

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