Acronym: TREATT

TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia

A double blind, randomised controlled trial evaluating the safety and efficacy of tranexamic acid in patients with haematological malignancies with severe thrombocytopenia

Version: 3.1

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Protocol Development Group:

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General Information

This document was constructed using the National Health Service Blood and Transplant Clinical Trials Unit (NHSBT CTU) Protocol Template, and incorporates the SPIRIT guidelines 2013 (1, 2). It describes the TREATT trial, coordinated by the NHSBT CTU, and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the Trial Manager to confirm they have the most up to date version.

Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2013, the Principles of Good Clinical Practice (GCP), European Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, the UK Policy Framework for Health and Social Care Research the Australian National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Research Involving Humans (March 2007) and any other applicable national regulations.

Sponsor

The NHSBT is the primary trial sponsor and has delegated responsibility for the overall management of the TREATT trial to the NHSBT CTU. Queries relating to the NHSBT sponsorship of the trial should be addressed to the National Research Manager, c/o R&D Office, NHSBT, 500 North Bristol Park, Northway, Filton, Bristol, BS34 7QH, email research.office@nhsbt.nhs.uk or via the trial team.

Funding

The TREATT trial is funded by a five year grant from the NHSBT Research and Development Committee, number 12-01-CSU, and a five-year grant from the NHMRC (#1085062).

Authorisations and Approvals

This trial was approved by NIHR Clinical Research Network and is, therefore, part of the Haematology CSG and Haematology Oncology research network portfolio.

Trial Registration

This trial is registered with the ISCRTN clinical trials database: ISRCTN73545489, and the ClinicalTrials.gov database: NCT03136445.

Trial Administration

Please direct all enquiries to the Trial Manager in the first instance. Clinical queries will be passed to the Chief Investigator via the Trial Manager.

CTU Details

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For full details of Trial Committees, please refer to Section 16

Trial Synopsis

Scientific title of clinical trial	A double-blind, randomised controlled trial evaluating the safety and efficacy of antifibrinolytics (tranexamic acid) in patients with haematological malignancies with severe thrombocytopenia
Public title of clinical trial	TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia
Protocol Short Title/Acronym	TREATT
Protocol Version and Date	3.1 30/07/2018
Primary Sponsor	NHS Blood and Transplant
Funders	NHS Blood and Transplant and NHMRC (Australia)
Primary Clinical Trials Registry number	ISRCTN73545489
Date Trial Registered	25 / 03 / 2015
Secondary Identifying Numbers	None
Trial design	• Phase III • Randomised, double-blind, placebo-controlled, parallel, superiority trial • Participants will be randomised to receive tranexamic acid or a matching placebo in a 1:1 ratio, stratified by site. Randomisation will further be balanced within blocks of varying undisclosed sizes.
Health Condition(s) or Problem(s) Studied	Patients with haematological malignancies receiving intensive chemotherapy and/or stem cell transplantation.
Key inclusion and exclusion criteria	**Participant inclusion criteria:** Patients are eligible for this trial if: 1. Aged ≥ 18 years of age 2. Confirmed diagnosis of a haematological malignancy 3. Undergoing, or planning to undergo, chemotherapy or haematopoietic stem cell transplantation 4. Anticipated to have a hypoproliferative thrombocytopenia resulting in a platelet count of ≤ $10x10^9$/L for ≥ 5 days 5. Able to comply with treatment and monitoring **Participant exclusion criteria:** A patient will not be eligible for this study if he/she fulfils one or more of the following criteria: 6. Patients with a past history or current diagnosis of arterial or venous thromboembolic disease including myocardial infarction, peripheral vascular disease and retinal arterial or venous thrombosis. 7. Diagnosis of acute promyelocytic leukaemia (APML) and undergoing induction chemotherapy

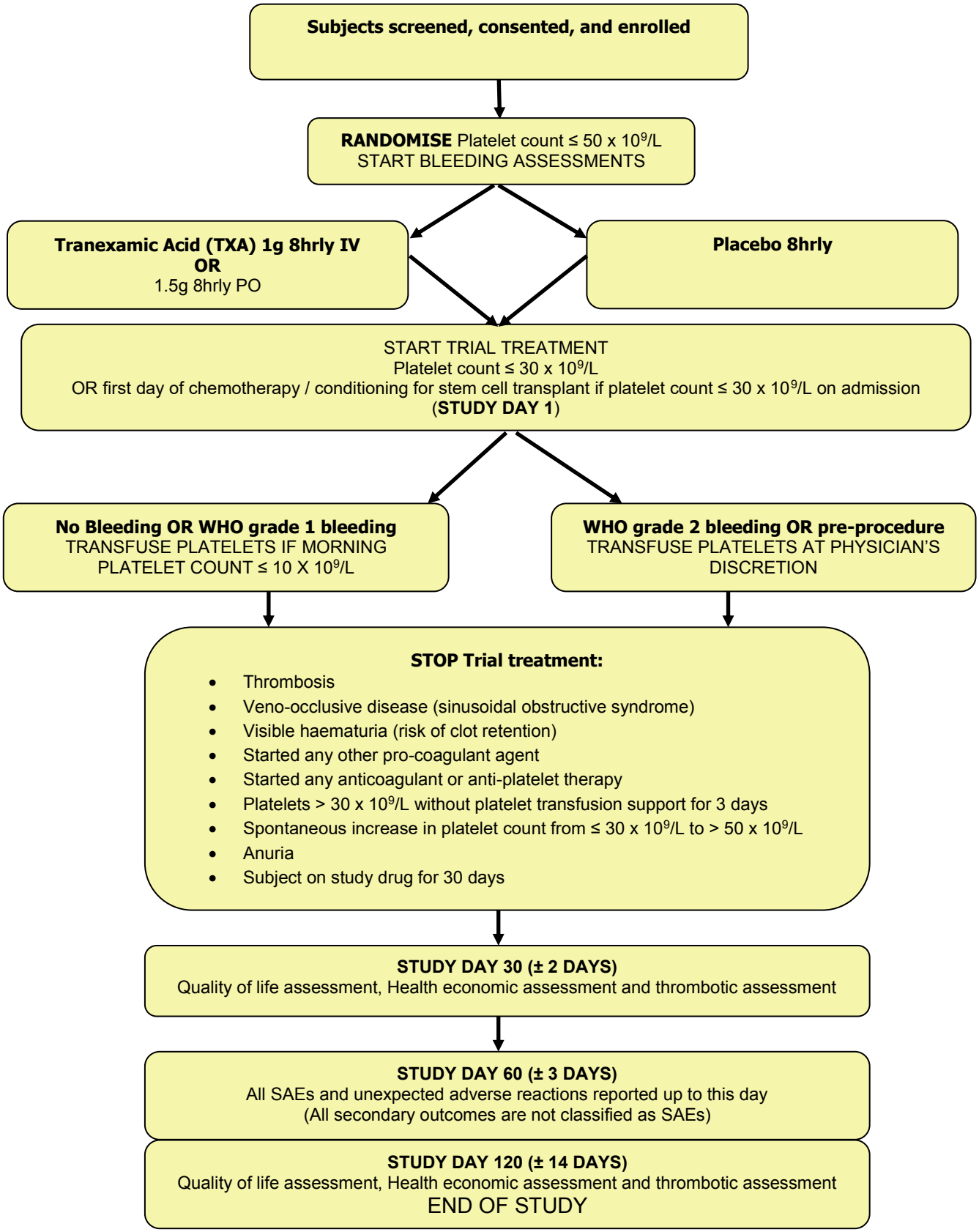
	8. Patients with a diagnosis/previous history of veno-occlusive disease (also called sinusoidal obstruction syndrome) 9. Patients with known inherited or acquired prothrombotic disorders e.g. a. Lupus anticoagulant b. Positive antiphospholipids 10. Patients receiving any pro-coagulant agents (e.g. DDAVP, recombinant Factor VIIa or Prothrombin Complex Concentrates (PCC) within 48 hours of enrolment, or with known hypercoagulable state 11. Patients receiving L-asparaginase as part of their current cycle of treatment 12. History of immune thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) 13. Patients with overt DIC (See Appendix 3 in the protocol for definition) 14. Patients requiring a platelet transfusion threshold >$10x10^9$/L at time of randomisation. (This refers to patients who require their platelet count to be maintained at a certain specified level on an ongoing basis, and excludes a transient rise in the threshold due to sepsis.) 15. Patients with a known inherited or acquired bleeding disorder e.g. a. Acquired storage pool deficiency b. Paraproteinaemia with platelet inhibition 16. Patients receiving anticoagulant therapy or anti-platelet therapy 17. Patients with visible haematuria at time of randomisation 18. Patients with anuria (defined as urine output < 10 mls/hr over 24 hours). 19. Patients with severe renal impairment (eGFR ≤30 ml/min/1.73m^2) 20. Patients with a previous history of epilepsy, convulsions, fits or seizures 21. Patients who are pregnant or breast-feeding 22. Allergic to tranexamic acid. 23. Patients enrolled in other trials involving platelet transfusions, anti-fibrinolytics, platelet growth factors or other pro-coagulant agents. 24. Patients previously randomised into this trial at any stage of their treatment.
Setting	Haematology wards and clinics
Interventions to be compared	**Administration of Trial treatment**

	Trial treatment will be started as per randomisation assignment. Either as soon as possible within 24 hours, and no later than 72 hours, of the first recorded platelet count ≤ 30 x 10^9/L, OR if the participant was admitted with a platelet count already below 30 x 10^9/L as soon as possible within 24 hours, and no later than 72 hours after the start of chemotherapy or conditioning for a stem cell transplant. ***All participants will start with Intravenous administration*** The trial treatment (Tranexamic acid 1g/placebo) will be administered intravenously as a slow IV bolus over 10 minutes every 8 hours. If the participant is well enough they can switch to: ***Oral administration*** The trial treatment (Tranexamic acid 1.5g/placebo) will be administered orally as 3 X 500mg tablets every 8 hours.
Trial hypothesis	The hypothesis is that in patients with haematological malignancies, during a period of severe thrombocytopenia, prophylactic use of antifibrinolytics will decrease bleeding or death and the demand for platelet transfusions.
Primary outcome measure(s)	**Primary Outcome** Estimated proportion of participants who died or had bleeding of WHO grade 2 or above during the first 30 days of the trial. **Starting from the first administration of trial treatment**
Secondary outcome measure (s)	**Secondary Efficacy Outcomes** **(all measured during first 30 days of the trial** from the first administration of trial treatment • Proportion of days with bleeding (WHO grade 2 or above) • Time to first episode of bleeding of WHO grade 2 or greater for those participants who bled • Highest grade of bleeding a participant experiences • Number of platelet transfusions/participant • Number of red cell transfusions/participant • Proportion of participants surviving at least 30 days without a platelet transfusion • Proportion of participants surviving at least 30 days without a red cell transfusion • Quality of life **Secondary Safety Outcomes** • Number of thrombotic events from first administration of trial treatment up to and including 120 days after the first dose of trial treatment is administered, per day at risk • Number of participants developing Veno-occlusive Disease (VOD; Sinusoidal obstructive syndrome, SOS) within 60 days of first administration of trial treatment • All-cause mortality during the first 30 days and the first 120 days after the first dose of trial treatment is administered • Death due to thrombosis during the first 120 days after the first dose of trial treatment is administered

	• Death due to bleeding during the first 30 days after the first dose of trial treatment is administered • Number of serious adverse events from first administration of trial treatment until 60 days after the first dose of trial treatment is administered **Other outcomes** (all measured during the first 30 days of the trial **from the first** administration of trial treatment Proportion of days with thrombocytopenia (≤10x10^9/L, ≤30x10^9/L, ≤50 x 10^9/L) Proportion of days with fever (highest daily temperature ≥ 38.1°C) of days spent in hospital, up to study day 30Reasons for platelet and red cell transfusions **Sub-group analyses** Sub-group analyses will be performed for the primary outcome for the following variables in the main analysis: • Country of participant (UK vs. Australia), if evidence of heterogeneity between UK and Australian participants is identified in the interim analysis • Platelet count at consent (≤30x10^9/L vs. > 30x10^9/L) • Treatment compliance during first 30 days of the trial (withdrawal of consent for trial treatment vs. no withdrawal of consent)
Duration of Trial	Duration of recruitment – The trial will be recruiting over 4½ years. **Duration of intervention** The trial treatment will be started within 24 hours (and no more than 72 hours) after the platelet count falls to ≤30x10^9/L, or if the participant was admitted with a platelet count already below 30 x 10^9/L, starting from the first day of chemotherapy or conditioning for a stem cell transplant, and continued until the platelet count is >30x10^9/L for 3 consecutive days without platelet transfusion support, or until the participant has received 30 days of treatment. The main data collection for efficacy endpoints will continue for 30 days from commencement of trial treatment. **Duration of follow-up for each participant** Adverse event data will be collected for 60 days after the first dose of trial treatment is administered, and long-term safety data regarding thromboembolic events will be collected by telephone call 120 days after the first dose of trial treatment is administered. The telephone call or participant visit 4 months (120 days) after the start of the trial will define the end of the trial. **Duration of trial** The planned trial duration is 5 years from initiation of first site to completion of analysis.

Countries of recruitment	UK Australia
Target Sample Size	616 participants at UK and Australian trial sites 308 subjects will be enrolled to receive TXA and 308 to receive the placebo
Date of first enrolment	June 2015
Recruitment Status	Recruiting: participants are being recruited
Ancillary Studies/sub-studies	At selected centres, additional blood samples will be collected from recruited participants and stored, for later central analysis, to explore the pathways of fibrinolysis and the mechanisms of action of tranexamic acid.
Contact Details for Public Queries	TREATT@nhsbt.nhs.uk
Contact Details for Scientific Queries	Dr Lise Estcourt; lise.estcourt@nhsbt.nhs.uk
CTU Project Manager	Claire Dyer
Lay Summary of Trial	Patients with cancers of the blood often develop low blood cell counts either as a consequence of the disease or the treatment by chemotherapy or stem cell transplantation. Platelet transfusions are commonly given to raise any low platelet count and reduce the risk of clinical bleeding (prophylaxis) or stop active bleeding (therapy). But recent studies have indicated that many patients continue to experience bleeding, despite the use of platelet transfusions. Tranexamic acid is a type of drug that is called an antifibrinolytic. These drugs act to reduce the breakdown of clots formed in response to bleeding. These drugs have been used widely in both elective and emergency surgery and have been shown to decrease blood loss and the use of red cell transfusions. The purpose of this study is to test whether giving tranexamic acid to patients receiving treatment for blood cancers reduces the risk of bleeding or death, and the need for platelet transfusions. Participants will be randomised to receive tranexamic acid (given intravenously through a drip, or orally) or a placebo. We will measure the rates of bleeding daily using a short structured assessment of bleeding, and we will record the number of transfusions given to participants.

Trial Schema



Trial Schedule (Assessments)

Trial Assessment	Enrolment (Consent)	Days between enrolment and randomisation	Day R Day of randomisation platelet count ≤ 50x109/l	Days between Day R and study day 1	Day 1	Day 2	Days 3 - 11	Day 12 (± 2)	Days 13 -29	Day 30 (± 2)	Day 60 (± 3)	Day 120 (± 14)
Demographics and medical history	X											
Eligibility Assessment	X		X		X (Prior to starting drug)							
Informed consent	X											
Transfusion requirements			X	X	X	X	X	X	X	X		
Bleeding Assessment			X	X	X	X	X	X	X	X		
Trial treatment accountability					X	X	X	X	X	X		
Quality of life assessment			X					X		X		X
Health economic evaluation										X		X
Thrombotic Assessment	Medical notes		Medical notes	Medical notes	Medical notes	Medical notes	Medical notes	Medical notes	Medical notes	Face to face OR Telephone follow-up		Face to face OR Telephone follow-up
Highest recorded temperature each day			X		X	X	X	X	X			
SAE Assessment			X	X	X	X	X	X	X	X	X	

Trial Schedule (Investigations)

Trial Assessment	Enrolment	Days between enrolment and randomisation	Day R Day of randomisation platelet count ≤ $50x10^9/l$	Days between Day R and study day 1	Day 1	Day 2	Days 3 -11	Day 12 (± 2)	Days 13 -29	Day 30 (± 2)
Pregnancy Test (if applicable)	X									
Urine dipstick	X									
Haemoglobin	X		X		X	X	X	X	X	X
Platelet count	X	X	X	X	X	X	X	X	X	X
Prothrombin Time (or INR if PT not available)	X		X							
Serum creatinine (U&E)	X		X		X	X	Three times a week or as SOC	X	Three times a week or as SOC	X
Liver function tests: bilirubin and albumin	X		X				Required if VOD is reported/ suspected 3 times a week		Required if VOD is reported/suspected 3 times a week	
HLA Antibody screen†	X									
INVESTIGATIONS ONLY TO BE PERFORMED AT SELECTED PARTICIPATING CENTRES										
Assays for fibrinolysis	X		X			X			Required three times a week	

X: measurement required

† HLA Antibodies to be rechecked if participant becomes refractory to platelet transfusions please see section 6.4.1

Contents

Abbreviations and Glossary

AE	Adverse event
AR	Adverse reaction
BSA	Body Surface Area
CF	Consent form
CI	Chief Investigator
CI	Count Increment
CLRN	Comprehensive Local Research Network
COM	Clinical Operations Manager
CRF	Case Report Form
CTU	NHSBT Clinical Trials Unit
DCF	Data Clarification Form
DH	Department of Health
DMC	Data Monitoring Committee
DM	Data Manager
ERC	Endpoint Review Committee
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
ISRCTN	International standard randomised controlled trial number
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare Regulatory Authority
MRC	Medical Research Council
NHMRC	National Health and Medical Research Council, Australia
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIHR	National Institute for Health Research
NIHR-CSP	National Institute for Health Research Coordinated System for gaining NHS Permission
NRES	National Research Ethics Service
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
R&D	Research and Development
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SABRE	Serious Adverse Blood Reactions and Events
SAE	Serious adverse event
SAR	Serious adverse reaction
SHOT	Serious Hazards of Transfusion
SOC	Standard of Care
SOP	Standard operating procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration (Australia)
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1. Background

1.1. Introduction

Patients with haematological malignancies often develop severe thrombocytopenia either as a consequence of the disease or its treatment, including chemotherapy and stem cell transplantation. Platelet transfusions are commonly administered, in this situation, to raise the low platelet count and reduce the risk of clinical bleeding (prophylaxis) or stop active bleeding (therapy). Many audits have indicated that the most common indication for administration of platelet transfusions to thrombocytopenic patients with haematological malignancies is prophylaxis (up to 69%) (3-7). (8, 9).

However, recent studies (described below) have raised questions about the effectiveness of platelet transfusions to reduce clinical bleeding, and many patients experience bleeding despite use of prophylactic platelets. In addition to this, platelet transfusions are not without risks. Adverse events may range from mild reactions, such as fever (one in five transfusions) (10) to more serious and even life threatening events such as bacterial sepsis from transfusion transmitted infection (one in 10,000 transfusions)(10) or transfusion-related acute lung injury (TRALI)(11). Patients may also become refractory to platelet transfusions, the incidence of which increases with the number of platelet transfusions a patient receives (12). Once refractory, the ability to treat bleeding with platelet transfusions becomes more difficult requiring expensive, specially matched platelet transfusions that are difficult to source. Platelet transfusions are a limited and expensive resource, and demand for these components is rising in many countries, raising concerns about future shortages in the supply of platelets.

Any treatment that could reduce reliance on platelet transfusion support would have major cost-saving implications. Around 302,000 adult doses of platelets are issued in the UK each year (13) at an annual cost of approximately £68.5 million (14) and up to two thirds (67%) of these are given to patients with haematological malignancies (3, 6, 15). Tranexamic acid is an antifibrinolytic drug that has been widely used in surgery to reduce clinical bleeding and need for transfusion, but few studies have evaluated use of this drug in patients with haematological malignancies.

1.2. Summary of existing knowledge

Recent clinical research has focused on the optimal dose for platelet transfusion (PLADO (16) and SToP (17)), or the threshold level of platelet counts for prophylactic platelet transfusions (Rebulla (18)). PLADO was a multicentre trial in the US, in which haematology patients receiving intensive chemotherapy or a stem cell transplant were randomised to receive low, medium or high dose prophylactic platelet transfusions (1.1 x 1011 platelets/m^2 body surface area; 2.2 x 1011/m^2; and 4.4 x 1011 /m^2, respectively). A total of 1,351 patients were enrolled at 26 sites in the United States. In PLADO, rates of bleeding were 69 to 71% for patients in each dose arm of the study, when defined as WHO Grade 2 to 4. A spectrum of bleeding was observed, from skin changes to, less commonly, intracranial haemorrhage.

More recently, two RCTs have been completed which have evaluated the role of prophylactic platelet transfusions (8, 19, 20). TOPPS was an RCT that assessed whether a policy of no-prophylactic platelet transfusions was non-inferior to a policy of prophylactic platelet transfusions (20). The primary outcome was WHO grade 2 to 4 bleeding. Prophylactic platelet transfusions were given at a platelet count threshold of <10x10^9/L, which represents the current standard of practice in patients with haematological malignancies. Six hundred patients (301 no-prophylaxis, 299 prophylaxis) were randomised across 14 sites in the UK and Australia between 2006 and 2011. A WHO grade 2-4 bleed grade occurred in 50% (151/300) of patients in the no-prophylaxis group compared to 43% (128/298) of patients in the prophylaxis group (adjusted difference in proportions 8.4%, 90% CI 1.7-15.2%).

Several themes have emerged from the findings of these platelet RCTs:
A significant proportion of patients develop bleeding at some stage during the period of thrombocytopenia despite prophylactic platelet transfusions.
A general result across all platelet transfusion trials of dose and threshold, including the two largest studies (16, 18), has been no difference in haemostatic outcomes between trial arms (i.e. no increased bleeding in the restrictive policy arms for transfusion by lower threshold or dose).
There is a lack of a relationship between platelet count and bleeding risk, except at very low platelet counts. PLADO reported that patients had similar rates of bleeding (17%) with morning platelet counts within the wide range of 6 to 80 x 109/L (16).
The burden of bleeding varies in sub-groups of patients, e.g. higher bleeding rates in patients with acute leukaemia or receiving an allogeneic stem cell transplant (SCT), lower rates in patients receiving an autologous SCT(21).

Taken together, these findings suggest that current policies for prophylactic platelet transfusions have a limited role in reducing much of the bleeding seen in haematology patients undergoing intensive chemotherapy and/or stem cell transplantation. There is a need for new treatment strategies to minimise the burden of bleeding, particularly in high risk groups of patients.

1.3. Need for a trial of Tranexamic Acid

One approach is to administer anti-fibrinolytics. The fibrinolytic system acts to prevent blood clots from growing excessively away from the site of damage, and conversely, delayed processes of breakdown of fibrin clots would be expected to enhance localised clot formation and, crucially, stability.

Tranexamic acid (TXA) is a lysine analogue that is a competitive inhibitor of plasminogen activation and, at higher concentrations, non-competitive inhibitor of plasmin (22). TXA is the only lysine analogue currently licensed in the UK and Australia.

1.4. Dose selection of intervention

Antifibrinolytics have been used widely in both elective and emergency surgery and have been shown to decrease blood loss and the use of red cell transfusions. In a recent Cochrane review (23) of over 25,000 patients the use of TXA, epsilon aminocaproic acid (EACA) and another antifibrinolytic, aprotonin[1], were assessed on their ability to minimise peri-operative blood transfusions. In this review, 65 trials compared TXA with control; 16 trials compared EACA with control and 10 trials compared TXA with EACA. Both drugs decreased the need for allogeneic blood transfusions (relative reduction of 39% (TXA) 19% (EACA)). The profile for the use of these drugs has also been raised by their therapeutic use in CRASH-2 (25-27), a recent large RCT that showed TXA decreased the mortality rate in trauma patients.

A small number of RCTs and other studies have been identified in a recently completed systematic review into their use of antifibrinolytics in patients with haematological malignancies (28). Overall, the results suggest a reduction in platelet transfusion usage when platelet transfusions were only given if patients bled (29, 30), with a possible reduction in the number of bleeds (29). However, there are significant methodological limitations to

[1]Aprotonin was commonly used in the past, but is now rarely used due to concerns over increased cardiovascular complications and death [21, 22], (24. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008 May 29;358(22):2319-31. 23. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011(3):CD001886.).

these studies, limiting the strength of these conclusions. Moreover, the sample sizes were small. In addition, since all the RCTs are 15 to 20 years old the management and supportive care of haematology patients has changed dramatically.

In the peri-operative Cochrane review (23), the use of TXA was not associated with an increased risk of mortality, myocardial infarction, DVT, stroke, incidence of renal dysfunction, or length of hospital stay. In the CRASH-2 study there were fewer deaths due to arterial or venous thrombosis [RR 0.69; 95% CI 0.44 to 1.07)) in the TXA arm of the study, although this was not statistically significant (P = 0.096)(27).

1.5. Explanation for choice of comparator

This study is designed as a placebo controlled trial, to provide the most robust evidence. There is no 'gold standard' standard for comparison and TXA is not commonly used as prophylaxis in this clinical setting.

1.6. Potential benefits and risks of Intervention

Although it can be hypothesised that antifibrinolytics may decrease the risk of severe and life-threatening bleeding and decrease patients' exposure to blood components, these drugs also have the potential to increase the rate of thromboembolism. Patients with an underlying malignancy have a higher rate of thromboembolic disease. In a retrospective cohort study of thromboembolism in hospitalised neutropenic cancer patients, 4% (593/14,600) of acute leukaemia patients developed venous thromboembolism (VTE) and 1.9% (279/14,600) of patients with acute leukaemia developed arterial thromboembolism (31). A meta-analysis of 29 different cohorts of patients with lymphoma gave an estimate of 6.4% (95% confidence interval 6.1 to 6.9%) (32). The one year incidence of symptomatic VTE in patients undergoing stem cell transplantation has been estimated at 3.7% (33). The most common type of venous thromboembolism in this group of patients is line associated thrombosis with an estimated incidence of 2.6 to 5% (33, 34).

1.7. Specific objectives or hypotheses

The hypothesis is that in patients with haematological malignancies, during a period of severe thrombocytopenia, prophylactic use of antifibrinolytics would decrease bleeding and the demand for platelet transfusions. There may also be additional benefits for patients such as improved quality of life during their in-patient stay and earlier discharge home. Given the importance of understanding the cost-effectiveness of new treatments, this trial proposal will also incorporate a health economic analysis.

1.8. Description of trial design

This is a double-blind, placebo controlled parallel group trial to assess the safety and efficacy of tranexamic acid at reducing bleeding in patients with haematological malignancies and severe thrombocytopenia. Participants will be randomised to receive TXA or placebo.

2. Trial Setting

This trial will be conducted in the haematology wards of participating hospitals in the UK and Australia.

3. Selection of Sites/Clinicians

Centre selection in UK will be based on the presence of appropriate clinical and research infrastructure including adequate local resources and facilities to support recruitment, and adequate qualified staff to conduct the trial properly and safely. Therefore recruiting centres

will be drawn from those involved in TOPPS (20) who have experience of conducting platelet studies..

The trial management group (TMG) will invite eligible centres and will discuss the resources required for conducting the trial, including the importance of delivering training and education to the clinical staff on the use of the bleeding assessment tool.

All UK local laboratories should be Clinical Pathology Accreditation accredited, and National External Quality Assurance Scheme participants. Australian centres will be NATA/RCPA accredited.

3.1. Site/Investigator Inclusion Criteria

To participate in the TREATT trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been prepared by the TREATT Trial Management Group (TMG) and are defined below.
PI Qualifications and Agreements
The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up to date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, and/or the regulatory authorities.

3.2. Site/Investigator Exclusion Criteria

The General Medical Council's List of Registered Medical Practitioners, or the Australian Health Practitioner Regulation Agency, will be consulted to ensure all potential PIs are licensed to practice. Any PI without a current licence or with a history of non-fitness to practice should not be approached.

3.3. Recruitment

The site selection process will include a rigorous evaluation of the site's potential rate of accrual to the trial, which will include a review of types of patient treated, an assessment of how many would be eligible, and how many may be recruited given the site level resource and any barriers to recruitment such as other trials competing to recruit the same patient population.

4. Selection of Participants

There will be no exceptions to eligibility requirements at the time of randomisation. Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below.

4.1. Participant Inclusion Criteria

Patients are eligible for this trial if:

1. Aged ≥18 years of age
2. Confirmed diagnosis of a haematological malignancy
3. Undergoing chemotherapy, or chemotherapy is planned, or haematopoietic stem cell transplantation
4. Anticipated to have a hypoproliferative thrombocytopenia resulting in a platelet count of $\leq 10 \times 10^9$/L for ≥ 5 days
5. Able to comply with treatment and monitoring

4.2. Participant Exclusion Criteria

A patient will not be eligible for this trial if he/she fulfils one or more of the following criteria:

1. Patients with a past history or current diagnosis of arterial or venous thromboembolic disease including myocardial infarction, peripheral vascular disease and retinal arterial or venous thrombosis.
2. Diagnosis of acute promyelocytic leukaemia (APML) and undergoing induction chemotherapy
3. Patients with a diagnosis/previous history of veno-occlusive disease (also called sinusoidal obstruction syndrome)
4. Patients with known inherited or acquired prothrombotic disorders e.g.
    a. Lupus anticoagulant
    b. Positive antiphospholipids
5. Patients receiving any pro-coagulant agents (e.g. DDAVP, recombinant Factor VIIa or Prothrombin Complex Concentrates (PCC) within 48 hours of enrolment, or with known hypercoagulable state
6. Patients receiving L-asparaginase as part of their current cycle of treatment
7. History of immune thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS)
8. Patients with overt DIC (See Appendix 3 in the protocol for definition)
9. Patients requiring a platelet transfusion threshold >$10x10^9$/L at time of randomisation. (This refers to patients who require their platelet count to be maintained at a certain specified level on an ongoing basis, and excludes a transient rise in the threshold due to sepsis.)
10. Patients with a known inherited or acquired bleeding disorder e.g.
    a. Acquired storage pool deficiency
    b. Paraproteinaemia with platelet inhibition
11. Patients receiving anticoagulant therapy or anti-platelet therapy
12. Patients with visible haematuria at time of randomisation
13. Patients with anuria (defined as urine output < 10 mls/hr over 24 hours).
14. Patients with severe renal impairment (eGFR ≤30 ml/min/$1.73m^2$)
15. Patients with a previous history of epilepsy, convulsions, fits or seizures
16. Patients who are pregnant or breast-feeding
17. Allergic to tranexamic acid.
18. Patients enrolled in other trials involving platelet transfusions, anti-fibrinolytics, platelet growth factors or other pro-coagulant agents.
19. Patients previously randomised into this trial at any stage of their treatment.

4.3. Co-Enrolment Guidelines

Please refer to Section 5.7

4.4. Screening/Recruitment

A screening log will be completed on all patients admitted to the participating units with a haematological malignancy and undergoing chemotherapy or a stem cell transplant who are expected to develop a hypoproliferative thrombocytopenia resulting in a platelet count of ≤$10x10^9$/L for ≥5 days. The log will include main diagnosis and treatment plan. It will include

patients approached but in whom consent was not obtained for the trial (with reasons) and therefore will define how representative randomised patients are as a group relative to the group of eligible patients who were not randomised.

The local PI or delegate will be responsible for identifying suitable patients and inviting them to participate in the trial.

Each participant will be assigned a unique trial number consisting of 6 digits, the first 3 digits denoting the centre number and the remaining 3 the participant number from 001 to 999. The trial number will be recorded on the screening log.

The eligibility checklist will be completed.

Consent from eligible patients will be sought using the participant information sheet and consent form.

When the consented participant's platelet count falls to ≤50x10^9/L, the PI or delegate will access the on-line randomisation system to randomise the participant (see section 5.5 for further details.)

5. Randomisation

5.1. Allocation – sequence generation

See Section 11.1

5.2. Allocation – concealment mechanism

Participants will be randomised using an online randomisation service (*SealedEnvelope*). Following confirmation of site number and eligibility criteria, a randomisation number will be issued by the system.

5.3. Allocation – implementation

An unblinded NHSBT statistician, independent of the trial team, will generate the randomisation list in accordance with the protocol. A site specific list of coded treatment allocations will also be provided to the trial pharmacist at each site by the same independent NHSBT statistician to enable the pharmacist to dispense the correct trial treatment. Supplies of active and placebo trial treatment will be provided to the hospital pharmacies, labelled with a code so the pharmacist does not know which is active and which placebo.

5.4. Stratification and Randomisation

Participants will be randomised to receive tranexamic acid or a matching placebo in a 1:1 ratio, stratified by site. Randomisation will be balanced within blocks of varying undisclosed sizes.

5.5. Randomisation Practicalities

There will be no exception to eligibility requirements at the time of randomisation.

Eligibility for randomisation will be assessed with reference to the specific inclusion and exclusion criteria.

When a consented participant's platelet count falls to ≤50x10^9/L, the PI or delegate will complete the trial registration/randomisation form and access the web based randomisation

service to randomise the participant. If a patient's platelet count is ≤50x10^9/L on admission to hospital because they have a newly diagnosed haematological malignancy or refractory disease the patient should be approached for randomisation as soon as possible.

Following randomisation, the randomisation service will e-mail confirmation of the randomisation number to the PI and Trial Manager.

The local PI/delegate is responsible for informing the participant's consultant/physician of the patient's participation in the trial, and for placing a label indicating trial participation on the cover of the patient's medical notes.

The PI/delegate will be responsible for immediately telephoning the pharmacy and speaking with the trials pharmacist, informing them of a patient's participation in the trial and their trial number. A written prescription for trial medication will then be sent to the pharmacy, along with written confirmation of the randomisation number (for example the print-out from the randomisation system). These documents must be received by the clinical trials pharmacist before trial medication may be dispensed.

The trial treatment will be dispensed to the ward to be stored appropriately. Note: the trial treatment shall be commenced as soon as possible within 24, and not later than 72 hours of the first recorded platelet count of ≤30x10^9/L. If a patient's platelet count is ≤30x10^9/L on admission to hospital because they have a newly diagnosed haematological malignancy or refractory disease the patient should be approached for randomisation and commenced on trial treatment within 24, and not later than 72 hours of starting intensive chemotherapy treatment or conditioning for stem cell transplant.

The PI/delegate must update the centre's screening log by remembering to add trial numbers for all patients randomised.

RANDOMISATIONS

To randomise, please visit

www.sealedenvelope.com

choose the TREATT trial from the drop down list and log-on as instructed

If difficulties are experienced using the randomisation website, then please contact the Trial Manager, who will be able to randomise the patient on your behalf.

5.6. Randomisation Codes

The randomisation service will send confirmation to the PI of the randomisation number and inform the Trial Manager.

5.7. Co-enrolment Guidelines

Participants should not be enrolled in other trials involving platelet transfusions, anti-fibrinolytics, platelet growth factors or other pro-coagulant agents. Co-enrolment in any other trial will be dependent upon the rules stipulated in that trial protocol, and should be discussed with the CI for the other trial.

5.8. Blinding

In this trial, the participants, the PI, the ward nurses, ward pharmacist, all other site staff, and all members of the TMG will be blinded to treatment allocation. The clinical trial pharmacists at each centre will be semi-blinded, in that they will know which participants are in each group, but not what the group is.

5.9. Unblinding

In general, there should be no need to unblind the allocated treatment. Unblinding should be done only in those rare cases when the clinician believes that clinical management depends importantly upon knowledge of whether the participant is receiving TXA or placebo. In those few cases when urgent unblinding is considered necessary, the PI will be given access to the web-based service (www.sealedenvelope.com). Details of this shall be in the Site File. The person performing the unblinding will be sent an e-mail detailing a participant's treatment allocation. The NHSBT 24-hour telephone number is also available: 0300 123 2323; this will enable the investigator to contact the CI out of hours.

6. Treatment of Participants

6.1. Introduction

This trial has an intervention arm and a control arm. These are described in the sections below.

Trial treatment will be started as per randomisation assignment as soon as possible within 24 hours, and no later than 72 hours, of the first recorded platelet count ≤ 30 x 10^9/L, or if the participant was admitted with a platelet count already below 30 x 10^9/L as soon as possible within 24 hours, and no later than 72 hours, after the start of chemotherapy or conditioning for a stem cell transplant

The participant's eligibility criteria MUST be rechecked to ensure they are still eligible prior to first administration of the trial treatment.

The period of time between randomisation and initiation of the trial treatment will allow time for pharmacy to prepare and dispense the trial treatment.

During their inpatient stay haematology patients may experience severe nausea and vomiting, diarrhoea, or significant mucositis. This may impair their ability to tolerate or absorb an orally administered medication. Therefore the trial treatment will initially be given by intravenous administration until the participant is well and able to tolerate the oral medication. The treating physician can then switch the medication to its oral formulation. The date on which the participant is switched from IV to oral formulation will be documented. The participant must receive at least one dose of the IV formulation before transferring to oral. Participants can return to IV after commencing oral IMP, this must be documented, but care must be taken to ensure the correct dose is prescribed.

If the participant has not met the stopping criteria when they are ready for discharge oral IMP should be prescribed.
In other patient groups the dose of tranexamic acid is the same whether it is given therapeutically or prophylactically. Due to differences in bioavailability 1g IV is equivalent to 1.5g PO. This dose is similar to the doses given in the three previous RCTs that have been performed (See Investigator Brochure for further information).

6.2. Interventions

6.2.1. CTIMP to be studied

Tranexamic acid (TXA).
Dose schedule TXA 1g every eight hours IV or 1.5g every eight hours PO.

Comparator or placebo
Placebo (saline) if administration is IV.
Placebo capsule or tablet matched for appearance to TXA if oral.

6.2.2. Description of Trial Drug

Tranexamic acid (Cyklokapron) is trans-4-(aminomethyl)cyclohexanecarboxylic acid, which acts as an inhibitor of fibrinolysis. At the dose used in this study it is a competitive inhibitor of plasminogen activation. Each 10mL vial contains 1g of tranexamic acid (100mg/mL) as an aqueous solution. Vials should be stored between 15° to 25°C. Do not Freeze. Tranexamic acid Injection is administered by infusion, utilising the usual compatible intravenous vehicles (e.g., Sterile Water for Injection, Sodium Chloride for Injection, 5% Dextrose or Ringer's Injection), or slow IV bolus. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The oral preparation will consist of identical tablets from July 2018 (further details available in the Investigator Brochure).

These will be supplied to the clinical trials pharmacist in containers, from which . the pharmacist will dispense the required number (according to the randomisation schedule) for the participant.

6.2.3. Blinding of Trial treatment

For intravenous treatment the local investigational drug pharmacy will receive boxes of nine glass vials containing either active drug or placebo. Each box will have a tear off label indicating A or B. Thus, the clinical trials pharmacist will be aware that the participant is receiving treatment A or treatment B; the clinical staff, ward pharmacist and participant will be unaware of the randomisation, as the tear off portion of the label will be removed before dispensing. When a subject is randomised to the trial, the randomiser will receive a randomisation number for the participant and will send confirmation of this, along with a prescription for trial treatment to the clinical trials pharmacist. The clinical trials pharmacist will consult the randomisation list supplied and dispense the trial treatment allocated to the randomisation number.

Labelling of the trial treatment has been changed from Tranexamic acid/placebo to TREATT Trial IMP to prevent inadvertent use of local pharmacy stock TXA.

6.2.4. Administration of Trial treatment

The trial treatment will be started as per randomisation assignment as soon as possible, ideally within 24 hours, and no later than 72 hours, of the first recorded platelet count $\leq 30 \times 10^9$/L. Or, if a patient's platelet count is $\leq 30 \times 10^9$/L on admission to hospital because they have a newly diagnosed haematological malignancy or refractory disease the patient should be approached for randomisation and commenced on trial treatment within 24 hours,

and no later than 72 hours, of starting intensive chemotherapy treatment or conditioning for a stem cell transplant.

The IV preparation of trial treatment will be administered as a slow IV bolus over 10 minutes every eight hours.
The IV preparation may also be given as an infusion and centres are advised to follow local pharmacy practice for TXA.
IV Tranexamic acid / placebo may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions.

The IV trial treatment must not be mixed with blood.

The IV trial treatment must not be mixed with solutions containing penicillin.

Three tablets of the oral preparation must be taken with water every eight hours.

6.2.5. Dose Adjustment of Trial treatment in Renal Insufficiency

Renal impairment
In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contraindicated in patients with severe renal impairment. For patients with mild to moderate renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Serum creatinine		Dose IV	Dose PO	Administration
µmol/l	mg/10 ml			
120 to 249	1.35 to 2.82	10 mg/kg BW	15 mg/kg BW	Every 12 hours
250 to 500	2.82 to 5.65	10 mg/kg BW	15 mg/kg BW	Every 24 hours
> 500	> 5.65	5 mg/kg BW	Omit dose	Every 24 hours

Oral suggested doses	**If creatinine 120 to 249**	**If creatinine 250 to 500**
Participants < 50 kg	500mg BD	500mg OD
Participants 50 to 83 kg	1g BD	1g OD
Participants 84 to 116 kg	1.5g BD	1.5g OD
Participants **> 117** kg	2g BD	2g OD

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment.

6.2.6. Discontinuation of Trial treatment

The trial treatment will be permanently discontinued as soon as any one of the following situations occurs:

1. It has been 30 days since the participant first started the randomised trial treatment.
2. The participant has a spontaneous increase in platelet count from $<30x10^9$/L to $>50x10^9$/L.
3. The participant has had 3 consecutive days with morning platelet counts $>30x10^9$/L, and no requirement for platelet or granulocyte transfusion, or stem cell transplant.
4. The participant receives open label tranexamic acid, other antifibrinolytic agent or procoagulant drug, (e.g., DDAVP, recombinant Factor VIIa, or Prothrombin Complex Concentrates). Use of these agents will be recorded in trial data.
5. The participant begins anticoagulant or antiplatelet therapy.
6. The participant has visible haematuria.
7. The participant has a diagnosis of thrombosis.
8. The participant becomes anuric (defined as urine output <10mls/hr over 24 hours).
9. The participant develops sinusoidal obstructive syndrome (SOS, Veno-occlusive Disease, VOD)

Note: If the trial treatment is discontinued it must not be restarted while the participant remains in the trial.

In addition to the reasons stated above participants may stop treatment early or be stopped early for any of the following reasons:

- Disease progression.
- Unacceptable adverse reaction
- Any change in the participant's condition that justifies the discontinuation of treatment in the opinion of the clinician.
- Withdrawal of consent.

In consenting to the trial, participants are consenting to the trial treatment, trial follow up and data collection. As the participant's participation in the trial is entirely voluntary they may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason whilst fully respecting the participant's rights.
Participants will remain in the trial for the purpose of follow up and data analysis, unless they withdraw their consent from all stages of the trial, in which case, they should be withdrawn. Data collected up until the time of withdrawal will be retained and included in the analysis.

6.3. Adherence to intervention

Daily trial treatment accountability will be performed. Any unused medication will be collected by the research nurse from the ward (if participant is an inpatient) or participant (if participant is an outpatient) and returned to the local trial pharmacist. The pharmacist will document the amount dispensed and returned for each study participant.

6.4. Concomitant Care

6.4.1. Platelet transfusions

Prophylactic platelet transfusions will be given at threshold counts of less than or equal to 10 x 10^9/L. A single adult dose should be given on the same day that a platelet count is recorded as less than or equal to $10x10^9$/L, and continued on a daily basis until the platelet count is greater than $10x10^9$/L.

Therapeutic platelet transfusions may also be given following objective and documented signs or symptoms of bleeding at WHO Grade 2, 3, or 4 or in accordance with the local physicians' usual practice.

Prior to planned invasive procedures; physicians will be allowed to increase the transfusion dose and/or threshold in keeping with their current practice.
Clinicians can exercise discretion to transfuse platelets for any reason should they feel there is a clinical reason to do so; the rationale must be clearly recorded on the daily transfusion data form. There is no justification to prescribe platelet transfusions pre-emptively above the defined threshold, if for example the participant's platelet count appears to be falling just prior to a weekend.

In the UK, recommendations for platelet transfusion practice are provided in the BCSH guidelines (35). All platelet components are leucoreduced, around 80% are collected by apheresis, and common hospital practice is to transfuse ABO and RhD identical platelets. In Australia, relevant guidance is provided in the national Patient Blood Management Guidelines available at https://www.blood.gov.au/pbm-guidelines
. The type (apheresis or pooled platelets prepared from whole blood) and the dose of platelet transfusion will not be specified.

If a participant develops platelet refractoriness (defined as two sequential transfusions with a 24 hour platelet increment < $5x10^9$/L), a serum sample will be drawn for lymphocytotoxic antibodies. If the panel reactive antibody (PRA) is ≥20%, the participant will be presumed to be alloimmune platelet refractory and may be given either HLA-matched or cross-match compatible platelet transfusions. If the PRA is <20%, local practice will be followed to treat the refractoriness. The participant will remain in the trial and data will continue to be collected on the participant.

6.4.2. Red Cell Transfusions

As a low haematocrit has been associated with an increased bleeding risk (36-38) a common policy to guide red cell transfusion support according to the BCSH Guidelines (UK) and in Australia the national Patient Blood Management Guidelines will be followed, available at https://www.blood.gov.au/pbm-guidelines
.This threshold for red cell transfusion (in the absence of blood loss due to bleeding) will be a Hb value of less than 80g/L.

All transfusion components in the U.K. and Australia, including red cells, are standardised and will conform to national specifications. All allogeneic blood components produced in the U.K. and Australia have been subjected to a pre-storage leucocyte filtration process.

No other medication changes are directed in this protocol, and standard care will otherwise be followed.

6.4.3. Contraception

Women of childbearing potential must use effective contraception while receiving the trial treatment. Examples would include the use of the male or female condom, or diaphragm with spermicide. Women of child bearing potential will be excluded if they are sexually active and not using a reliable form of contraception.

6.4.4. Medications Not Permitted

Whilst in receipt of trial medication, participants must not be given any other antifibrinolytic agent or procoagulant drug, (e.g., DDAVP, recombinant Factor VIIa, or Prothrombin Complex Concentrates), nor open label tranexamic acid.

6.5. Co-enrolment guidelines

Please refer to Section 5.7 for details.

6.6. Ancillary and post-trial care

There is no reason why participants could not be prescribed therapeutic tranexamic acid after completion of study period (this will be recorded).

7. Trial Outcomes

7.1. Primary Outcome Measure

Estimated proportion of participants who died or had bleeding of WHO grade 2 or above during the first 30 days of the trial **from the first day of trial treatment**

A time-to-event analysis will be used to determine this proportion to ensure that all participants are included in the primary outcome analysis, not just those who are followed up for the full 30 days. Any participants lost to follow-up will be included in the analysis and censored at the time that they were lost.

7.2. Secondary Outcome Measures

7.2.1. Secondary Efficacy Outcomes

All measured during first 30 days of the trial, i.e. **from the first day of trial treatment.**

- Proportion of days with bleeding (WHO grade 2 or above)
- Time to first episode of bleeding of WHO grade 2 or greater
- Highest grade of bleeding a participant experiences
- Number of platelet transfusions/participant
- Number of red cell transfusions/participant
- Proportion of participants surviving up to 30 days without a platelet transfusion
- Proportion of participants surviving up to 30 days without a red cell transfusion
- Quality of life

7.2.2. Secondary Safety Outcomes

- Number of thrombotic events from first administration of trial treatment up to and including 120 days after the first dose of trial treatment is administered, per day at risk
- Number of participants developing Veno-occlusive Disease (VOD; Sinusoidal obstructive syndrome, SOS) within 60 days of first administration of trial treatment
- All-cause mortality during the first 30 days and the first 120 days after the first dose of trial treatment is administered
- Death due to thrombosis during the first 120 days after the first dose of trial treatment is administered
- Death due to bleeding during the first 30 days after the first dose of trial treatment is administered
- Number of serious adverse events from first administration of trial treatment until 60 days after the first dose of trial treatment is administered

7.2.3. Other outcomes

All measured during first 30 days of the trial, i.e. **from the first dose of trial treatment**

- Proportion of days with thrombocytopenia (≤$10x10^9$/L, ≤$30x10^9$/L, ≤$50x10^9$/L)
- Proportion of days with fever (highest daily temperature ≥ 38.1°C) of days spent in hospital, up to study day 30
- Reasons for platelet and red cell transfusions

7.3. Sub-group analyses

Subgroup analyses will be performed for the primary outcome for the following variables in the main analysis:

- Country of participant (UK vs. Australia), if evidence of heterogeneity between UK and Australian participants is identified in the interim analysis
- Platelet count at consent (≤30x10^9/L vs. > 30x10^9/L)
- Treatment compliance during first 30 days of the trial (withdrawal of consent for trial treatment vs. no withdrawal of consent)

8. Assessments and Follow-up

8.1. Trial Assessment Schedule

Please see study schedules Pages 13 & 14

8.2. Procedures for Assessing Efficacy

8.2.1. Bleeding Assessment

Bleeding assessment will commence when the participant is randomised and stopped when one of the following occurs:

- It has been 30 days since the trial treatment was commenced
- Or in those cases where trial treatment was *not* started, 30 days from platelet count ≤30 x 10^9/L or the commencement of chemotherapy/stem cell conditioning therapy
- The participant dies.
- Participant withdraws his/her consent to having bleeding assessments performed.
- Site investigator withdraws the participant from all further study assessments.

Bleeding assessments will be conducted using a tool based upon that used in the recent TOPPS trial (20) and further developed by an international working group – the BEST collaborative (46). If a participant is an out-patient between day of randomisation and trial treatment starting they will be asked to inform the research team if they have had any bleeding at home. Simple guidance notes will be provided to assist with this.

Rates of recorded bleeding are known to vary considerably between trials. Reasons for this variability have been explored and published through a review organised by the BEST collaboration, and include different patient groups and bleeding definitions, and variable follow up periods (39).

In the TREATT trial, a number of measures will be taken to standardise documentation and recording of bleeding, including trained assessors, monitoring and education. In the recent TOPPS (20) trial, where completeness of bleeding outcome documentation was excellent, a bleeding assessment was completed on 93% (8405/9030) of days for patients in the no-prophylaxis group, and 97% (8733/8970) of days in the prophylaxis group. The majority of patients in both arms had bleeding information collected on each trial day (median no-prophylaxis 30 days (IQR 29 to 30); median prophylaxis 30 days (IQR 30 to 30)).

For inpatients, bleeding assessments will be performed using the bleeding assessment tool which includes a physical assessment of the participant, patient interview (if possible) and review of patient chart and laboratory data. Research staff will perform the physical assessment and interview before reviewing the participant's charts, medical notes and

laboratory data to allow an objective assessment. Research staff will perform the bleeding assessment at approximately the same time each day.

All participants who are discharged home before completion of the trial study period (30 days from commencement of the trial treatment) will be asked to complete a daily diary. Participants will be provided with clear guidance notes to assist them in self-assessment of bleeding. They will be asked to respond with a yes/no answer as to whether they have experienced any bleeding on that day.
If a participant reports no bleeding on their bleeding diary this will be recorded as a WHO grade 0 bleed. If the participant does report bleeding they are asked to consult with their haematology care team. If the clinical team consider the bleeding to be significant then the participant should be reviewed and a bleeding assessment will be conducted by a member of the research team. If the haematology team considers the bleeding to be clinically insignificant, this will be recorded as WHO grade 1

Additionally, all participants at home will be contacted by the local research staff on day 30 from first dose of the trial treatment to review the diary and confirm arrangements to collect all completed forms, which will be forwarded on to the data manager for entry into the trial database.

Local research staff completing the daily assessments will receive training and have guide notes to help them collect these data.

8.2.2. Assigning a grade to a bleed

Grade of bleed (WHO Grading System - see 20.2) will be assigned centrally by means of a computer algorithm at the time of analysis.

8.3. Procedures for Assessing Safety

8.3.1. Thrombotic Assessment

For in-patients, medical chart notes and imaging studies will be reviewed daily for documentation of any thrombotic events. For out-patients, the local research nurses will attempt to contact the participant directly, and if contact is not made, the participants' local physician / GP will be contacted.
Safety outcomes will include recording symptomatic thrombotic events that occur during the study period and up to 120 days (+/-7) after the first dose of the trial treatment is administered.

8.3.2. Interval Medical Events/Serious Adverse Events

A member of the research team will contact the participant in person or by telephone to ask them about any interval medical events or serious adverse events after discharge from hospital. If the research team are unable to contact the participant directly, their local physician/GP will be contacted.

8.4. Other Measurements

The following data will be collected:

Demographics and Medical History
This will include:

- Weight

- Height
- Date of birth
- Gender
- Ethnic origin
- Diagnosis (disease and type or treatment: i.e. chemotherapy or type of stem cell transplant)
- If receiving allogeneic transplant, whether HLA matched or mismatched
- Type and date of transplant or first day of other treatment
- Previous co-morbidities
- Renal impairment
- Previous fungal infection

Laboratory Studies (All study centres)

- Urine dipstick (at enrolment)
- Haemoglobin and platelet count, required daily when participant is an in-patient and 3 times a week, or as Standard of Care, when participant is an out-patient
- Coagulation profile (PT or INR), at randomisation.
- Serum creatinine (required at enrolment, randomisation, study days 1&2, and then 3 times a week on Monday, Wednesday and Friday, or as SOC, when participant is on trial treatment)
- Liver function tests including bilirubin and albumin required if VOD suspected / reported three times a week
- HLA antibody screen - required at enrolment, and repeated if a participant develops platelet refractoriness (defined as two sequential transfusions with a 24 hour platelet increment $<5x10^9/L$)

Laboratory Studies (Selected study centres)

- Fibrinolysis assay (central/local lab) – sub-study
- C-reactive protein (CRP) (this is required daily when participant is an in-patient if it is measured routinely at the participating hospital)
- Immature platelet fraction (this is required daily when participant is an in-patient and at least 3 times per week, when participant is an out-patient

Transfusions given during study (from enrolment to study day 30)

- Data on platelet, granulocyte or stem cell transfusion
  - Reason for transfusion (prophylaxis, invasive procedure, active bleeding, risk of significant bleeding, other)
- Data on red cell transfusions
  - Number of units transfused
  - Reason for transfusion (anaemia, active bleeding, other)

Fever

- Highest temperature within each 24 hour period (defined as 8am to 8am) when participant is an inpatient

Quality of Life Assessment

- Quality of life assessment (EQ5D & FACT-Th) at randomisation, day 12 (±2) and day 30 (±2). EQ-5D at day 120 (±7).

Health economic analysis (from study day 1 to study day 120)

- Number of hospital admissions, and duration of stay
- Number of ITU admissions and duration of stay
- Number of day unit admissions

- Number of hospital outpatient visits
- Yes/No question as to whether the participant has had any further treatment for their haematological malignancy
- Whether the participant has active haematological disease at day 120

8.5. Loss to Follow-Up

If the local research team are unable to contact a participant to obtain follow-up data, consent will be obtained on enrolment to the trial to contact their family physician / General Practitioner.

- **Death**

Data will be recorded on all-cause mortality, mortality due to bleeding and mortality due to thrombosis.

- **Discontinuation of Trial treatment**

Participants are free to stop the trial treatment at any time. The date will be recorded, along with the reason, on a designated trial treatment discontinuation form. In the event of the participant stopping the trial treatment, the participant will still be followed for all trial outcomes according to the protocol, unless they have specifically withdrawn consent for further data collection.

- **Withdrawals**

Participants may withdraw or be withdrawn from the trial at any time for any of the following reasons:

1. Participant withdraws consent
2. Investigator withdraws participant from the trial
3. Death

- **End of trial for each participant**

The trial end date for each participant will be the date of the last telephone call or outpatient visit at study day 120.

8.6. Trial Closure

The trial will be closed to recruitment when the required number of participants has been recruited and the last participant has completed the trial intervention period (to Day 30).

9. Safety Reporting

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section.
In general, investigators should report adverse events as diseases or syndromes whenever possible, instead of reporting individual component symptoms, signs, laboratory abnormalities or sequelae.

9.1. Definitions of Adverse Events

The definitions to be applied to adverse events occurring during this trial are given in Table 9a below. When an adverse event occurs, the PI or delegate should first classify the event according to table 9a below. Events of interest and that require to be reported are any:

- Unexpected Adverse Reactions
- Serious Adverse Events

that occur during the trial period that are **not already listed as primary or secondary outcomes**. Any other adverse event does not need to be recorded.

Table 9a: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence affecting a trial participant during the course of a clinical trial and which does not necessarily have to have a causal relationship with participation in the research.
Adverse reaction to an investigational medicinal product (AR)	An adverse event when there is at least a possibility that it is causally linked to a trial drug or intervention.
Unexpected Adverse Reaction (UAR)	An unexpected adverse reaction is an AR in which the nature or severity of the reaction is not consistent with the known side effects of the trial drug or intervention. There need only be an index of suspicion that the event is a previously unreported reaction to a trial drug or intervention.
Serious Adverse Event (SAE) or serious adverse reaction (SAR)	Any adverse event (AE) or adverse reaction (AR) that meets any of the following criteria: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity, results in a congenital anomaly/birth defect • any other adverse event that, based upon appropriate medical judgment, may jeopardise the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A suspected unexpected serious adverse reaction is an unexpected occurrence of a SAR; in which the nature or severity of the reaction is not consistent with the known side effects of the trial drug or intervention. There need only be an index of suspicion that the event is a previously unreported reaction to a trial drug or intervention.
Unanticipated problem involving risks to subjects or others (UP)	Any incident, experience, or outcome that meets all of the following criteria: a. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the REC-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; b. related or possibly related to a subject's participation in the research; and c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognised

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

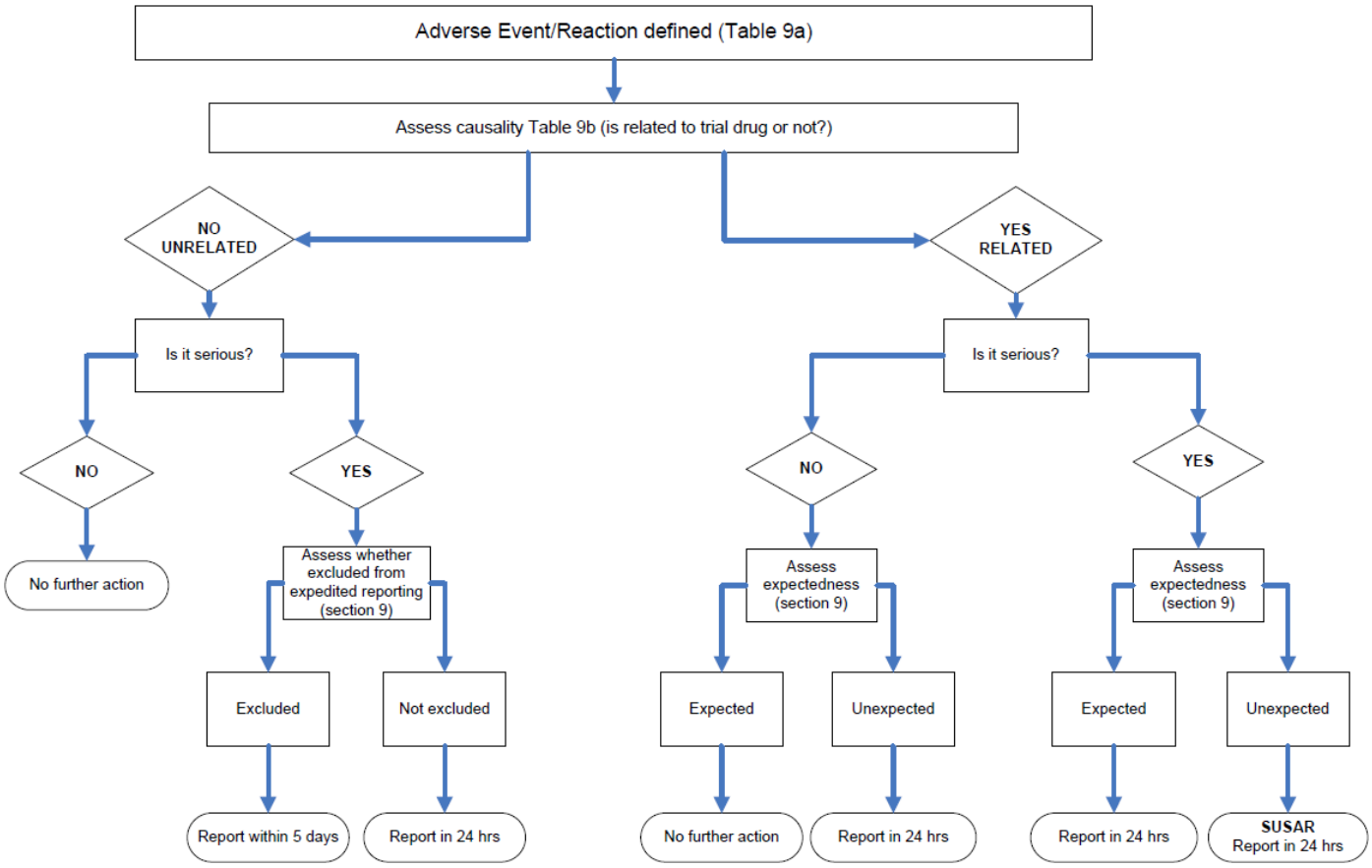
9.2. Investigator Responsibilities

The Chief Investigator (CI) has overall responsibility for the conduct of the trial. As this is a multi-site trial, the Principal Investigator (PI) has responsibility for the research at their local

site and is responsible for informing the CTU of all reportable serious or unexpected adverse events or reactions that occur at their site following the flow chart and guidelines below.

9.2.1. Investigator Assessment of Adverse Events

Causality
The causality of all AEs should be assessed by the PI (or delegate) using table 9b below. There are 5 categories: unrelated, unlikely, possible, probable and definitely related.
Table 9b: Definitions of Causality



Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little 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 or intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment or intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	The evidence is clearly in favor of attributing the adverse reaction to the trial treatment or intervention

Definitely	There is conclusive evidence beyond reasonable doubt attributing the adverse reaction to the trial treatment or intervention.

Seriousness
When an AE or AR occurs, the investigator responsible for the care of the patient must assess whether or not the event is serious using the definitions in Table 9a: definitions. If the event is serious and is on the list of expected events in section 9.1, then the details must be recorded on the SAE form within five working days. If the event is a SUSAR it must be recorded on the SAE form and sent to the CTU within 24 hours of becoming aware of it.

Expectedness
For all events and reactions, the Investigator must assess the expectedness. Please refer to the Investigator Brochure Section 8 for a list of expected serious adverse reactions to the trial treatment. This is the reference safety information for the trial.

Additional information on expected adverse reactions is available in Section 4.8 of the Summary of Product Characteristics (found in Section 16 of the Investigator Brochure) for a list of expected adverse reactions to the oral trial treatment and in Section 7 of the investigator brochure for the intravenous trial treatment.

9.3. Adverse Event Reporting

9.3.1. Adverse Events that Require Expedited Reporting (within 24 hours)

Any SAEs (related or unrelated) or unexpected (but not serious) adverse reactions must be reported within 24 hours of the PI becoming aware of the event, unless they have been specifically excluded from expedited reporting (see section 9.3.2).

9.3.2. Trial Specific Exceptions to Expedited SAE Notification (within 5 working days)

These are SAEs that are associated with the disease that the participants will be suffering from, and will not impact on the scientific interpretation of the results of the trial.

Due to the seriousness of the disease(s) the patients in this trial are suffering from, the following situations that fulfil the definition of an SAE are excluded from expedited notification, but should be recorded on the SAE form and reported within five working days:

- Elective hospitalisation to evaluate the treatment management plan for the patient's disorder, or for procedures
- Elective hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial treatment
- Admission to the intensive care unit
- Severe sepsis
- Major organ dysfunction
- Any other serious event related to the underlying disease or medication used to treat the disease
- Death as a result of disease progression

Any event that does not meet the above definitions does not need to be recorded at all.

9.3.3. Investigator Notification

- The CTU should be notified as soon as possible and within 24 hours of the investigator becoming aware of any SAE that has occurred, unless it has been excluded from expedited reporting.
- The SAE form must be completed by the Investigator (the consultant named on the delegation of responsibilities log who is responsible for the patient's care). In the absence of the Investigator, the form should be completed by a member of the site trial team and sent to CTU. The responsible Investigator should subsequently check, annotate and sign the form and send to the CTU as soon as possible. The initial report must be followed by detailed written reports as appropriate.
- The Investigator must record all SAEs that occur during the trial period on the SAE form. They are required to notify the CTU within five working days of becoming aware of an SAE that has been excluded from expedited reporting.
- The investigator must follow-up all reported SAEs until resolution or the event is considered stable.
- The CTU should be notified within 24 hours of the investigator becoming aware of an UAR that has occurred. The severity of an UAR will be graded by the CTU using MedDra terminology (Medical Dictionary for Regulatory Activities, Version 17.1, September 2014, and as updated from time to time. The Investigator must supply the CTU, REC and relevant NHS Trust R&D with any supplementary information they request.

9.4. Sponsor's Responsibilities

- The CTU (Sponsor) will forward all adverse reactions, SAEs and major safety outcome reports received to the Chief Investigator (or a medically qualified delegate) for review.
- As thromboembolism and mortality are the main safety outcomes of interest, these will be reported to the DMC as they occur, within a time frame to be determined by the DMC. The DMC may wish to view unblinded or partially unblinded data.
- The CTU will review all SAE reports and forward to the DMC for review, as often as instructed by them, and also provide them as listings for review at DMC meetings. These will be copied to the Chief Investigator for review.
- Agree the planned content of both blinded and unblinded DMC reports with DMC members prior to the inclusion of the first trial participant.
- The CTU is undertaking the duties of trial sponsor and is responsible for the reporting of any SUSARs to the MHRA or its equivalent and to the research ethics committee (REC) in all countries participating in the trial, and for preparing annual safety reports to the MHRA and the REC. The reporting time-frames for SUSARs will be according to the current national regulations for the participating countries. In the UK this will be in accordance with European Directive 2001/20/EC.

9.5. Statutory Reporting

Hospital staffs remain responsible for reporting all transfusion-related adverse events to SHOT/SABRE according to standard procedures, as required under the regulations of the EU Blood Directive. Unexpected adverse reactions should also be reported via the Yellow card system. Staffs at the institution are also responsible for notifying their local R&D department of SAEs (as per the institutions standard local procedure).

NOTIFICATION OF SAEs

Within twenty-four hours of becoming aware of an event, please send a completed SAE form to the NHSBT Clinical Trials Unit, unless SAE has been excluded from expedited reporting

Email **to**: serious_adverse_events@nhsbt.nhs.uk

10. Quality Assurance and Control

10.1. Risk Assessment

A Risk assessment has been conducted which acknowledges the potential risks to the trial. This section provides an overview of the Quality Assurance (QA) and Quality Control (QC) measures that will be put in place to ensure the trial is performed and data generated and recorded in accordance with the principles of ICH GCP.

10.2. Central Monitoring at CTU

The CTU data managers will review all data received for errors and missing data points. Central monitoring procedures for data verification and issue and resolution of queries raised will be detailed in a separate data management plan.

10.3. On-Site Monitoring

The frequency, type and intensity for routine monitoring and the requirements for "for cause" monitoring will be detailed in a separate monitoring plan.

10.3.1. Direct access to patient records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patient consent must be obtained for this.

10.3.2. Confidentiality

The data will be handled in accordance with the principles of the UK Data Protection Act.

10.4. Auditing

In addition to potential audits by the MHRA or the local R&D department, NHSBT reserves the right to conduct site audits, either as part of its on-going audit programme, or in response to adverse observations during monitoring visits.

11. Statistical Considerations

11.1. Method of Generating Allocation Sequence

Participants will be randomised to antifibrinolytic therapy or placebo in a 1:1 fashion, stratified by site. Randomisation will further be balanced within blocks of varying, undisclosed sizes.

11.2. Outcome Measures

See section 7.

11.3. Sample size

11.3.1. Minimal Clinically Important Difference (MCID)

Based on the experience of similar patients in the TOPPS trial, in the absence of antifibrinolytic therapy, it is anticipated that 43% of eligible patients would experience death or WHO Grade 2 bleeding or higher within the first 30 days. In such a background setting of bleeding, the trial investigators anticipate less than a 10% relative reduction in bleeding rates would not be sufficient to substantially change clinical practice, because the absolute risk reduction of 4.3% would mean that it would be necessary to treat approximately 23.3 patients in order for the treatment to have an impact on 1 patient ("Number Needed to Treat" (NNT) = 23.3).

As much as a 26% relative reduction in bleeding rates would likely be judged sufficient to change clinical practice, because the associated NNT = 8.9 patients might be acceptable, provided no new safety issues related to anti-fibrinolysis in the thrombocytopenic population are uncovered.

We thus evaluate the planned sample size of the trial relative to these hypothesised effects as a reference.

11.3.2. Primary efficacy outcomes

616 participants will be accrued to the UK/Australian clinical trial.
The participants will be randomised in a double blind fashion to receive TXA or a matching placebo.

The clinical trial will be conducted with the primary endpoint of decreased proportion of death or WHO Grade 2 or higher bleeding among all patients receiving TXA versus placebo over 30 days. The type 1 error will be controlled at a two-sided level of 0.05. The primary endpoint will be analysed using the Kaplan-Meier (KM) method to estimate the probability of bleeding or death within 30 days in the analysis populations. Power and sample size calculations are based on a log-rank test for comparing two survival curves, as described in Collett (40).

It is anticipated that the UK and Australia will be able to recruit 616 participants for this trial. Under the assumption that anti-fibrinolysis results in a decrease of death or WHO Grade 2 bleeding from 43% to 32%, the 616 participants will provide 80% power to detect an observed absolute decrease in bleeding rates of 11% (a relative reduction of 26% with a NNT of 8.9) and will be judged statistically significant at the two-sided 0.05 level. The planned trial size of 616 subjects includes an additional 5% of participants above the required sample size of 586. This 5% figure is more than the proportion of participants within TOPPS (4%) that dropped their platelet count below 50 x 10^9/L but did not drop their platelet below 30 x10^9/L. This therefore accounts for the number of participants within the trial who are randomised but never receive the trial treatment.

We do not expect there to be a problem with the assessment of the primary outcome of bleeding over the 30 day trial period, starting from the first day of administration of trial treatment.,
In the recent TOPPS trial, completeness of bleeding outcome documentation was excellent. A bleeding assessment was completed on 93% (8405/9030) of days for patients in the no-prophylaxis group, and 97% (8733/8970) of days in the prophylaxis group. The majority of patients in both arms had bleeding information completed on each trial day (median no-

prophylaxis 30 days (IQR 29 to 30); median prophylaxis 30 days (IQR 30 to 30)). There were also only 6 deaths (1% of patients) while on the trial.

11.3.3. Safety outcomes

This trial is not powered to definitively establish the safety of the treatment with respect to the frequency of VTE. However, with the planned enrolment of 616 patients, an observed difference in frequency of VTE of 3.6% on the placebo arm and 5% or less on the TXA arm would result in a 95% confidence interval that excluded a relative risk of 3.5.

11.3.4. Health economic evaluation

The cost-effectiveness analysis will be performed based upon the data from the patients recruited to the UK component of TREATT. Although the trial is necessarily powered for the primary clinical endpoint of proportion of patients who die or have WHO Grade 2 or above bleeding over 30 days, we are confident that a reliable estimate of the cost-effectiveness of TXA for this patient group can be generated.

11.4. Interim Monitoring and Analyses

TREATT proposes to investigate the efficacy and safety of anti-fibrinolytic therapy in thrombocytopenic patients. In order to better address the often urgent nature of treatment administration, patients will be randomised earlier (when the platelet count is less than $50x10^9$/L) than when the trial treatment is administered (when the platelet count is less than $30x10^9$/L). The TREATT investigators have thus identified separate analysis populations to test the trial hypotheses.

Analysis Populations

- **Efficacy population**

The population used for efficacy analyses will be a modified intent to treat population (mITT) including all eligible randomised patients whose platelet count falls to $30x10^9$/L or below. Data gathered for 30 days from the time the first dose of trial treatment is administered, or is planned to be administered for those participants who did not receive treatment. . Randomised participants whose platelet counts do not fall to $30x10^9$/L or below will be excluded from the analysis, as will participants who develop exclusion criteria prior to their count falling to $30x10^9$/L or below. These exclusions are deemed appropriate as the early randomisation is for pragmatic reasons only. Characteristics of all randomised patients will be compared to the mITT population to ensure that excluded participants are similar across the arms.

Unless otherwise specified, all analyses will be by this mITT. All subjects who fulfil the mITT requirements will be included in the analyses, in the treatment group to which they were randomly assigned. Subjects who were prescribed trial treatment will be included in the analyses, even if they stop trial treatment “early”, or receive prophylactic transfusions not in accordance with the protocol.

Rationale: Owing to the emergent nature of treatment of thrombocytopenic patients, participants are randomised in a double blind fashion to the treatment arms when platelet levels drop below $50x10^9$/L. This will allow time for the pharmacy to prepare the trial treatment, and for the trial treatment to be available when the platelet count falls to $30x10^9$/L or below. This has been instituted for pragmatic reasons and will guard against delays in the availability of the trial treatment.

The main primary outcome analysis will be based on the mITT population. However, a per-protocol analysis of the primary outcome will also be performed. This per-protocol analysis will exclude all participants who were randomised in error and all participants who did not adhere to a set of minimum compliance criteria during the first 30 days of the trial. The criteria are:

- The participant commenced trial treatment within 72 hours of the first recorded platelet count ≤ 30 x 10^9/L, OR if the participant was admitted with a platelet count already below 30 x 10^9/L within 72 hours after the start of chemotherapy or conditioning for a stem cell transplant.
- The participant received trial treatment and only received the trial treatment prescribed to them and did not receive open label tranexamic acid, other antifibrinolytic agent or procoagulant drug
- The participant only received the correct dose of the trial treatment prescribed to them

- The participant did not receive trial treatment after the point at which discontinuation of trial treatment should have occurred

Participants who did not meet all the eligibility criteria and/or met at least one of the exclusion criteria will be considered as randomised in error.

- **Safety population (apart from thrombotic events)**

The population used for safety analyses will be all participants who receive any amount of trial treatment, using data gathered from first administration of trial treatment until up to 120 days after first administration of trial treatment.

- **Thrombotic Event Safety population**

The population used for safety analyses of thrombotic events will be all participants who receive any amount of trial treatment, using data gathered from time of randomisation until 120 days after first administration of trial treatment.

- **Stopping rules**

Owing to the need to establish both the efficacy and safety of anti-fibrinolytic therapy, the intention is that TREATT will not stop randomising participants if anti-fibrinolytic therapy appears to show effectiveness in an interim analysis. This is because the trial will need to collect additional information on safety endpoints. This is judged important due to the low power the trial has to detect increased rates of thromboembolic events. Because TXA is currently being used off-label in thrombocytopenic patients, it is similarly judged important that any deleterious effect of anti-fibrinolytic therapy with respect to bleeding in thrombocytopenic patients be documented at a level that would be clinically and statistically credible. An interim analysis will be performed after 300 participants have been in the trial for 30 days. The independent DMC will have overall oversight and can recommend terminating the trial early for these or any other safety concerns. A summary of SAEs, UARs, thrombotic events and veno-occlusive disease will be provided to the DMC. In addition, a multivariate test for heterogeneity of UK and Australian baseline patient characteristics will be performed. Sex, diagnosis, (acute leukaemia or not), treatment plan (autograft or not) and haemoglobin at randomisation will be compared using Hotelling's T-squared test. Sample proportions for categorical variables will be considered to be approximately normally distributed for the purposes of the multivariate test. Only strong evidence of a difference between UK and Australian participants will be considered as evidence of heterogeneity. If evidence of heterogeneity between UK and Australian participants is identified in the interim analysis, subgroup analysis by country of participant will be performed for the primary outcome in the main analysis,

11.5. Analysis Plan (Brief)

11.5.1. Analysis of primary and secondary outcomes

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues. A full statistical analysis plan will be drawn up prior to closure of the trial database. All analyses will be adjusted for the stratification variable (recruitment site).

Primary efficacy analysis

The proportion of participants who die or have bleeding of grade 2 or above by WHO criteria during the first 30 days from the first dose of trial treatment, or planned first dose for those participants who did not receive treatment,, will be estimated by the Kaplan-Meier method and compared using Cox regression analysis. All participants whose platelet count dropped to $30x10^9$/L or below, regardless of length of follow-up will be included.

Secondary efficacy outcomes

- Proportion of days with bleeding up to study day 30; this will be compared using logistic regression. Nesting at participant level will be accounted for by including a random participant effect.
- Time to first episode of bleeding of WHO grade 2 or greater up to study day 30 will be estimated using the cumulative incidence function, with the competing risk of death prior to bleeding of WHO grade 2 or greater. Cox regression analysis will be used to compare the two treatment groups. Participants who have not experienced bleeding of WHO grade 2 or greater will be censored at day 30 or at the point of last contact, whichever is first. Participants who died prior to study day 30 and did not experience bleeding of WHO grade 2 or greater will be censored at the time of death.
- Highest grade of bleeding a participant experiences up to study day 30; this will be modelled using an ordinal logistic regression model, modelling grade as an ordinal categorical outcome.
- Number of platelet transfusions/participant up to study day 30 will be compared using a negative binomial model. The model will include an offset to account for the number of days the participant spent in hospital, up to 30 days..
- Number of red cell transfusions/participant up to study day 30 will be compared using a negative binomial model. The model will include an offset to account for the number of days the participant spent in hospital, up to 30 days.
- Proportion of participants surviving at least 30 days without a platelet transfusion will be estimated by the Kaplan-Meier method and compared using Cox regression analysis. The event of interest is time to first platelet transfusion or death.
- Proportion of participants surviving at least 30 days without a red cell transfusion will be estimated by the Kaplan-Meier method and compared using Cox regression analysis. The event of interest is time to first red cell transfusion or death.

Safety outcomes

- Number of thrombotic events from first administration of trial treatment up to and including 120 days after the first dose of trial treatment is received, per day at risk will be described by arm.
- Number of participants developing Veno-occlusive Disease (VOD; Sinusoidal obstructive syndrome, SOS) within 60 days of first administration of trial treatment will be described by arm.

- All-cause mortality during the first 30 days and 120 days after the first dose of trial treatment is administered will be will be estimated by the Kaplan-Meier method and compared using Cox regression analysis..
- Death due to thrombosis during the first 120 days after the first dose of trial treatment is administered will be estimated using the cumulative incidence function, with the competing risk of death due to other causes. Cox regression analysis will be used to compare death due to thrombosis between treatment arms. Participants who have not died will be censored at day 120 or at the point of last contact, whichever is first. Participants who died prior to day 120 from causes other than thrombosis will be censored at the time of death. If numbers of deaths due to thrombosis are very small, the number of deaths will simply be described by arm.
- Death due to bleeding during the first 30 days after the first administration of trial treatment is received will be estimated using the cumulative incidence function, with the competing risk of death due to other causes. Cox regression analysis will be used to compare death due to bleeding between treatment arms.
- Number of serious adverse events from first administration of trial treatment until 60 days after the first dose of trial treatment is administered, per day at risk, will be summarised by arm, including number of symptomatic thrombotic events (venous thromboembolisms and arterial ischaemic events), veno-occlusive disease, sepsis, organ failure and death.

Other outcomes

- Proportion of days with thrombocytopenia (<$10x10^9$/L, <$30x10^9$/L, <$50x10^9$/L) will be analysed using logistic regression.
- Proportion of days with fever (highest daily temperature ≥ 38.1°C) of days spent in hospital, up to study day 30, will be analysed using logistic regression.
- Reasons for platelet and red cell transfusions; the reasons will be described by arm.

11.5.2. Other Analyses

Analyses for the sub-studies will be specified in separate analysis plans.

11.5.3. Sub-group Analyses

Subgroup analyses will be performed for the primary outcome in the main analysis by including an interaction term. Analysis will be performed using the same methods as for the primary outcome, except a treatment-covariate interaction will be included in the model for each of the following variables in turn:

- Country of participant (UK vs. Australia), if evidence of heterogeneity between UK and Australian participants is identified in the interim analysis
- Platelet count at consent (≤$30x10^9$/L vs. > $30x10^9$/L)
- Treatment compliance during first 30 days of the trial (withdrawal of consent for trial treatment vs. no withdrawal of consent)

11.5.4. Analysis Population and Missing Data

For pragmatic reasons participants discharged from the hospital prior to 30 days post first dose of trial treatment will not have as intense surveillance for trial events as will those who remained in the hospital. They will complete a daily bleeding diary and be contacted to determine any clinically important bleeding events. If a participant reports no bleeding on their bleeding diary this will be recorded as a WHO grade 0 bleed. If the participant does report bleeding they are asked to consult with their haematology care team. If this team considers the bleeding to be clinically significant then the participant should be reviewed and

a bleeding assessment conducted by a member of the research team. If the haematology team consider the bleeding to be clinically insignificant, then this will be recorded as WHO grade 1.

TREATT is to be conducted in patients who are undergoing intensive chemotherapy or stem cell transplantation, and thus we do anticipate that some participants may die due to their underlying disease, overwhelming infection, or other complications of their therapy.

Some participants may also withdraw consent or be withdrawn during the conduct of the trial. In either of these cases, it is impossible to know whether such participants are either less or more likely to experience bleeding had they not experienced early censoring. Sensitivity analyses will be performed to account for this.

12. Ancillary Studies

12.1. Fibrinolysis Study

A laboratory study to understand the mechanisms of action of TXA will be built into the proposal at selected centres. The specific tests for laboratory assessment of fibrinolysis will depend upon the results of analysis of samples from 50 patients collected within a pilot prospective observational cohort study (ATHENA)(41). This is an optional sub-study and the results of the tests for fibrinolysis will be for research purposes only. Samples will be frozen and analysed in batches. The results of these tests will have no impact on the day to day management of trial participants.

12.2. Health Economic Evaluation

A health economic evaluation for UK participants will form an integral part of this trial, and will ascertain whether from the perspective of the health care provider, prophylactic use of TXA is likely to constitute a cost-effective use of scarce resources.

Detailed data will be collected on the resources consumed by each participant during their hospital inpatient stay, including information on TXA given, transfusions of platelets, red blood cells and FFP, treatment for major bleeds, thromboembolic events, time in ITU, and on wards. Following hospital discharge, participants will be followed up by research nurse at 30 days and 120 days after starting the study drug, and asked about health care contacts including hospital re-admissions, day hospital attendances, outpatient clinic attendances and A&E visits,. These data will be costed using national average unit costs from established sources.

Participants will be asked to complete the EuroQol EQ-5D-5L questionnaire (a generic measure of health related quality of life routinely used in cost-effectiveness studies) at baseline, and at 10-14 days, 30 days, and 120 days post-start of study drug. Responses will be converted into a single index score using the UK social tariff and used to weight patient survival and facilitate the calculation of quality adjusted life years (QALYs) for each patient.

Costs and effects in each arm of the trial will be compared. Cost-effectiveness will be expressed using a number of metrics, including cost per bleed averted, and cost per QALY. Uncertainty around the study results will be explored using one-way, and probabilistic sensitivity analysis. Cost-effectiveness acceptability curves will be used to determine the probability that TXA is cost-effective at various thresholds of willingness to pay for health gain.

Quality of Life Study
A quality of life study will also be performed. Quality of life will be assessed at baseline, and at 10 to 14 days, 30 days, and 120 days after start of the trial treatment using the EuroQol EQ-5D-5L questionnaire (a generic measure of health related quality of life routinely used in cost-effectiveness studies – see section immediately above).The FACT-Th questionnaire (a measure of health related quality of life that has been specifically designed for thrombocytopenic cancer patients (42)) will be administered at baseline, and at 10-14 days and 30 days after start of the trial treatment.
For those participants who have been randomised, but then did not start treatment QoL will be measured up to 30 days only.

13. Ethical and Regulatory Issues

13.1. Compliance

This trial complies with the Declaration of Helsinki [2013 Declaration of Helsinki] (45).
It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the UK Policy Framework for Health and Social Care Research

13.1.1. Site Compliance

The site will comply with the above. An agreement will be in place between the site and CTU, setting out respective roles and responsibilities.

The site will inform the CTU as soon as they are aware of a possible serious breach of compliance, so the CTU can report the breach if necessary, within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a serious breach is one that is likely to affect to a significant degree:
The safety or physical or mental integrity of the subjects in the trial, or
The scientific value of the trial.

13.1.2. Data Collection and retention

The Principal Investigator has overall responsibility for data collection at Sites. Participant data will be entered onto the trial database designed and administered by the NHSBT CTU data management team using MACRO-v4.2.3.3850, a commercially available FDA 21 CRF Part 11 compliant clinical trial database system produced by InferMed. Following completion of analysis, the trial database will be archived in accordance with NHSBT's policies.

The sites must keep the signed Informed Consent forms, all trial documentation and source documents collected during the trial in a secure location (e.g. locked filing cabinets in a room with restricted access). All data must be accessible to the competent authorities and the Sponsor with suitable notice for inspection. All trial documentation must be retained for at least 5 years after trial completion or termination. In addition, the Investigator must not discard or destroy any trial specific materials unless otherwise instructed by NHSBT.

13.1.3. Access to Data

The CTU will oversee any data sharing process, with input from the TSC.

13.2. Ethical Conduct of the Trial

This trial has been designed as a placebo controlled trial, to provide the most robust evidence for the effectiveness and safety of prophylactic tranexamic acid in patients with haematological malignancies. Tranexamic acid is not used in routine practice for this indication.

13.3. Ethical Considerations

Issues relevant to ethical considerations are described fully in the Participant Information Sheet. The right of the patient to refuse to participate in the trial without giving reasons will be respected.

After the patient has entered the trial, the clinician is free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the participant's best interest, and the reason for doing so should be recorded. Similarly, the participant must remain free to withdraw at any time from protocol treatment without giving reasons and without prejudicing any further treatment. All participants who come off protocol therapy for whatever reason will still need to remain within the trial for the purposes of follow-up and data analysis.

In the UK, research ethics approval will be required. A copy of a centre's R&D approval must be lodged with the Trial Office before entry of patients can commence at that centre. Centres are required to go through a registration process with the Trial Office before recruitment is started. The institution's Research and Development Office must complete the site agreement with the sponsor.

In Australia, this protocol will be submitted to a Human Research and Ethics Committee (HREC) according to the NHMRC National Statement on Ethical Conduct in Research Involving Humans for each institution. Approval of the protocol and related documents will be obtained prior to the start of the study at each site. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC as required by that committee. No subject will be enrolled into the trial until The Therapeutic Goods Administration (TGA) has been notified. Copies of all submissions to and correspondence (approvals and disapprovals) from the HREC must be maintained on file at the trial site.

Before initiation of the trial at each clinical site, the protocol, all informed consent forms and any information to be provided to the prospective participant will be submitted to a Research Ethics Committee for ethical approval. Any subsequent amendments will be submitted and approved by the same Research Ethics Committee.

13.4. Consent

Main Trial

Informed consent will be sought by the Principal Investigators or appropriately trained delegate. At this point the patient will receive a written information sheet (Participant Information Sheet) about the study, to keep, as well as a further verbal explanation to address any questions they may have.

Each patient will be asked to sign the consent form before study participation. Patients will not be allowed to take part in the study unless fully-informed consent has been obtained.

The patients will also be informed that they have the right to withdraw from the study at any time and this will not affect their future treatment in any way. Any blood samples collected up until the time of withdrawal will be retained and included in the analysis.

Ancillary Studies

At centres participating in the fibrinolysis sub-study the consent form will specifically ask about whether the patient agrees to having additional blood samples taken. Blood samples will only be taken if the participant has given informed consent for this to occur.

The participants will also be informed that they have the right to withdraw from additional blood sampling at any time and this will not affect their future treatment in any way. Blood samples collected up until the time of withdrawal of consent will be retained and included in the analysis.

13.5. Confidentiality

The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.
Blood samples collected as part of the fibrinolysis sub-study will be stored in a secure facility that can only be accessed by authorised researchers. Samples will be code-labelled and the code-index will not be divulged to any parties outside of the local research group.

14. Indemnity

The NHS indemnity scheme applies to this trial when it is being conducted in the UK. Section 4 of the non-commercial clinical trial agreement 2008 describes the indemnity arrangements as follows:

As both sponsor and site are NHS bodies, i.e. NHS bodies / NHS Foundation Trusts in England, Wales or Northern Ireland and are indemnified by the same Indemnity Scheme (being one of the NHS Litigation Authority clinical negligence or the Welsh Risk Pool or the Clinical Negligence Fund in Northern Ireland) and the Party incurring any loss can recover such loss under one of the Indemnity Schemes, then such Party shall rely on the cover provided by the Indemnity Scheme and not seek to recover the Loss from the other Party(ies). Where the other Party (ies) caused or contributed to the Loss, it undertakes to notify the relevant Indemnity Scheme(s) to take this into account in determining the future levies of all Parties in respect of the indemnity schemes.
If:
The Parties are members of the same Indemnity Scheme in England, Wales or Northern Ireland and the Party incurring the Loss is not indemnified for that Loss by its Indemnity Schemes; or
All Parties are NHS bodies in Scotland; or
The Parties are NHS bodies/Foundation Trusts established in different jurisdictions within the United Kingdom;

Then the Parties shall apportion such Loss between themselves according to their respective responsibility for such Loss. Should the Parties be unable to agree the apportionment the matter shall be resolved in accordance with clause 16.5.
If one or more Parties are NHS Foundation Trusts and the Party incurring the Loss is not responsible for all or part of the Loss and is not indemnified in respect of the Loss by one of the Indemnity Schemes, then the Party incurring the Loss shall be entitled to recover the Loss from the other Party (ies) pursuant to the provisions of this Agreement.

15. Finance

15.1. Funding

Funding arrangements will be provided in the Trust agreement with the Sponsor.
This trial is funded in the UK by a grant from the NHSBT R&D Committee; Grant number 12-01-CSU.

15.2. Declaration of interests

None of the individuals named in this protocol have any competing interests to declare. The NHSBT CTU requires serving members of all Oversight Committees to sign a declaration of interests form on appointment and to declare any competing interests which may develop during the conduct of the trial to be declared at the start of every meeting

16. Oversight and Trial Committees

There are a number of committees involved with the oversight of the trial. These committees are detailed below.

16.1. Trial Management group (TMG)

A Trial Management Group (TMG) comprising the Chief Investigator, other lead investigators and members of the CTU. The TMG will be responsible for the day to day running and management of the trial. It will meet at least four times a year, more often during set up and close down phases of the trial. At least one face to face meeting will be held each year.

In the UK members include the CI, PIs from representative centres (UK), the Trial Manager, and a NHSBT CTU Clinical Operations Manager.

TMG (UK) Members:

- Dr Lise Estcourt — Chief Investigator
- Dr Simon Stanworth — Co-Chief Investigator
- Ms Gillian Powter — Trial Manager
- Mrs Claire Dyer — Clinical Operations Manager
- Ms Elinor Curnow — Trial Statistician
- Ms Siobhan Martin — Trial Data Manager
- Ms Katie Keen — Senior TREATT Data Manager
- Ms Alison Deary — Head of Clinical Operations
- Dr Graham Collins — Clinical Advisor
- Dr Gail Jones — Clinical Advisor

In Australia, the TMG members include the CI, local lead investigators, the local Trial Co-ordinator and PIs from local centres (Australia).

TMG (Australia) Members:

- Dr Erica Wood — Lead Australian investigator
- Dr Simon Stanworth — Chief Investigator
- Dr Zoe McQuilten — Co-lead Australian investigator
- Ms Amber Degelia — Australian Trial co-ordinator
- Ms Sharon Erb — Australian Trial co-ordinator

16.2. Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) has membership from the TMG and independent members, including the Chair. The role of the TSC is to provide overall supervision for the

trial and provide advice through its' independent chair. The ultimate decision on continuation of the trial lies with the TSC.

This trial protocol has been designed and developed in collaboration with international partners Dr Erica Wood (Australia) and Drs Terry Gernsheimer and Sherrill Slichter (US). With Australia joining the trial, the composition of the TSC has been adjusted. Should the US or other partners join this trial, the composition of the TSC may be further adjusted to reflect international recruitment.

TSC Members:

- Dr Ian Franklin — Independent Chair
- A/Prof Jake Shortt — Independent Member
- Dr Dan Hart — Independent Member
- Dr Lise Estcourt — Chief Investigator
- Dr Simon Stanworth — Co-Chief Investigator
- Ms Elinor Curnow — Trial Statistician
- Mr Cliff Gorton — Patient Representative
- Dr Charles van Heyningen — Patient Representative
- R&D Office — Sponsor Representative
- Dr Erica Wood — Lead Australian Investigator

16.3. Data Monitoring Committee (DMC)

The CTU has a core Data Monitoring Committee (DMC) for all of its trials, currently chaired by Professor Adrian Newland, Professor of Haematology at Barts and the London School of Medicine and a Consultant Haematologist at the Royal London. The group will act as DMC to this trial, provide advice to the Chair of the TSC and can recommend premature closure of the trial.

The conduct of the trial and the safety of patients accrued to the trial will be monitored by the DMC. The DMC will be guided by a DMC Charter that delineates the roles and responsibilities of the DMC, including delineation of the lines of communication between trial clinical investigators, trial data coordinating centre, and NHSBT.

The DMC will meet approximately every 6 months to review trial progress (recruitment, adherence to protocol) and safety data, including (serious) adverse events, bleeding events, and mortality. After an initial face-to-face meeting, meetings are envisioned to generally be by teleconference, though the DMC may request a face-to-face meeting as indicated. The DMC may also request more frequent meetings as necessary to protect trial integrity and trial safety.

16.4. Role of Trial Sponsor

The trial sponsor will have ultimate authority over the study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication. The trial sponsor will have a representative on the TSC. See section (16.2) for membership of the TSC.

16.5. Role of Trial Funder(s)

In the UK the trial sponsor and the trial funder are the same entity. The Australian funder, the National Health and Medical Research Council, has had no role in the design of the study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

17. Publication

17.1. Dissemination

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications.

17.2. Authorship

Authorship of all publications associated with this trial will be compliant with the International Committee of Medical Journal Editors criteria for authorship.

17.3. Approvals

The TSC will see and approve the final trial publication. The CIs will see and approve any supplementary publications, e.g. from a sub-study.

17.4. Identification

A trial identifier will be included on all presentations and publications (e.g. the ISCRTN)

17.5. Timing

No data may be made public before publication and never without agreement from the CIs.

17.6. Acknowledgements

All professionals who have participated in the TREATT trial for a minimum of one year will be listed in the acknowledgements section of the final trial report.

18. Protocol Amendments

Any modifications of the protocol which may impact on the conduct of the study, potential benefit of the participant or may affect participant safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed upon by the TREATT TSC, TMG, and NHSBT, and approved by the Ethics Committee and the Competent Regulatory Authority prior to implementation.

Administrative changes of the protocol are minor amendments that have no effect on the way that the study is conducted. These administrative changes will be agreed by the TREATT TMG and the Ethics Committee will be informed of the minor amendment.

Revision History:

Version	Author	Date	Reason for revision
1.0	Various.	10th September 2014	Version submitted to REC for ethical approval.

1.1	Various.	24th October 2014	Responding to the REC comments and to provide greater clarity.
1.2	Various	8th January 2015	Responding to the MHRA comments and to provide greater clarity
1.3	Various	13th February 2015	Minor changes following provisional approval from MHRA and to provide greater clarity. Additions with respect to the trial in Australia.
1.4	Various	5th June 2015	Minor textual amendments and changes to Trial team personnel. Amendment of dose adjustment table to bring it in line with Investigator Brochure.
2.0	Various	27 August 2015	• Trial Summary – Recruitment status updated: now open • Section 4.2 (and summary) Reordering of exclusion criteria and Clarification of Exclusion Criterion 9 (previously 12) • Sections 5.5 and 6.2.4 – Addition with regard to (potential) participants admitted to hospital with platelet counts ≤ 30 x 10^9/L. or ≤ 50 x 10^9/L. • Section 7 Proportion of participants changed to estimated proportion • Section 11.4 – Stopping Rules: Change to wording for clarification • 11.5 – Analysis Plan: proportion changed to Estimated proportion • Section 16.1 – Change in name of Australian Trial Coordinator • 16.3 – Reference to co-opted member of DMC removed as not relevant
2.1	Various	09 December 2015	• Amendment to 'Administration of Trial Treatment' (in summary and section 6.1) to allow for patients admitted with platelet counts already below 30 x 10^9/L • Clarification of definition of Day 1 with respect to Primary and Secondary Outcomes (In Summary and section 7) • Clarification of Day 1 with respect to Day 1 for Data Collection (In Summary and section 7) • Time boundaries added to define period when trial treatment can be started (6.2.4) • Typographical amendments to Trial Schema Flow Chart • Further detail added with respect to the daily bleeding assessment (section 8) • Additional analysis: A per-protocol analysis of the primary outcome which will exclude patients who did not follow the protocol (e.g. did not receive the trial treatment) section 11.4 • A secondary analysis of bleeding of grade 2 or above or death for the 30 days after treatment started (or when it should have

			started for patients that did not receive the treatment). (Section 11.5) • Clarification re bleeding grades in section 11.5.3 • Additional note re QoL questionnaires for participants who did not start treatment (Section 12.2) • Professor Stephen Morris added as Co-Investigator
3.0	Various	09 May 2018	• Changes/ updates to trial team, TMG and TSC personnel • Some laboratory values removed from the Schedule of Investigations • Post hospital discharge visits (GP and District nurse) removed from Health Economic analysis • Additions to the glossary • Total sample size revised to 616 and consequent changes to text relating to sample size in section 11.3 • Removal of anomalies, so that there is consistent reference to trial 'participants' rather than 'patients'. • Clarification that Day 1 is the first day of administration of trial treatment, albeit this may be a maximum of 72 hours from the first recorded platelet count of ≤ 30, or for patients admitted with a count already ≤ 30 a maximum of 72 hours from them starting treatment with chemotherapy. • Consequent to this changes to text in Section 7, (Trial Outcomes), 11.4 (Interim analysis), 11.5 (Analysis Plan) • Clarification of the methodology for the interim and main analyses in Section 7 (Trial Outcomes), Section 11.4 (Interim analysis), 11.5 (Analysis Plan) • Additional text section 6.2.4 re administration of IMP and dosing guidelines where participants have raised creatinine levels • Addition to section 6.2.2 on the nature of the oral IMP (tablets instead of capsules) • Addition to section 6.2.4 to note change of label on TREATT IMP • Expansion of text for exclusion criterion No 20 re PMH convulsions • Removal of footnotes to SAE table 9a as these contradict parts of text in this section • Addition of a new reference (validation of bleeding assessment tool)

3.1	Following comments from MHRA	30 July 2018	• Clarification that bilirubin & albumin required if VOD suspected or reported • Additional text to section 9.2.1 – Expectedness to clarify the Reference Safety Information

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20. Appendices

20.1. Adverse Reactions

20.1.1. Toxicities associated with Tranexamic Acid (TA)

Please refer to the Investigator Brochure Section 7 for a list of expected adverse reactions to the intravenous trial treatment, and to Section 4.8 of the Summary of Product Characteristics (found in Section 15 of the Investigator Brochure) for a list of expected adverse reactions to the oral trial treatment.

20.1.2. Toxicities Related to Platelet Transfusion

- **Viral Infections:**

With the transfusion of any blood product, a virus may be transmitted. All donor blood is routinely screened for the presence of hepatitis B and C, the AIDS virus (HIV 1 & 2), the HTLV viruses (1 & 2), West Nile virus (in the UK), and, on occasion, for cytomegalovirus. In spite of testing, infections with these or other viruses may rarely still result from a transfusion.

- **Bacterial Infections:**

Because platelets must be stored at room temperature and not in a refrigerator, overgrowth of bacteria may occur if there has been a break in the sterility of the system. This could result in a serious infection.

- **Transfusion Reactions:**

There also may be reactions to transfusion of any blood product such as chills, fever, drop in blood pressure, shortness of breath, and, very rarely, shock. On rare occasions, transfusions may be associated with a severe reaction that could result in lung injury, kidney failure, or heart failure. There may also be allergic reactions such as hives, rashes, or very rarely, a severe reaction that could result in death.

20.1.3. Additional access to central venous catheters

Administration of the trial treatment may lead to the central venous catheter being accessed more frequently. This may lead to a slight increase in the risk of infection. This will be minimised by staff trained in the use of the line minimising the number of times the line is accessed and using aseptic technique at all times.

20.1.4. Discomfort Related to Venesection

There may be some discomfort to subjects associated with the withdrawal of blood samples. Occasionally there may be soreness, bruise, light-headedness, and on rare occasions, infection or scarring damage to a vein.

20.2. WHO Grading System

General Definitions of WHO Grades

Grade 4
Any bleeding that is:

- Fatal
- Life-threatening. For example:
  - Bleeding that requires transfer to intensive care/treatment unit
  - Bleeding that is associated with haemodynamic instability and causes inadequate tissue perfusion
- Evidence of inadequate tissue perfusion could include:
  - Hypotension
  - Systolic blood pressure (BP) < 90mmHg
  - >40mmHg fall in systolic BP
  - Mean arterial pressure (MAP) <65mmHg
- In absence of hypotension, markers of inadequate tissue perfusion include increased blood lactate, increased base deficit, perfusion-related low pH (if other causes of metabolic acidosis (e.g. sepsis) are not present)

(Please also see organ-specific definitions)

Grade 3
Any bleeding that does not fulfil the criteria for grade 4 bleeding (general or organ-specific) BUT requires:

- Red cell transfusion specifically related to treatment of bleeding within 24 hours of onset of bleeding, for example:
  - Required to treat fall in haemoglobin of at least 2g/dl within preceding 24 hours without evidence of haemolysis
  - No haemoglobin increment within 24 hours of at least a 2 unit red cell transfusion without evidence of haemolysis
- A significant intervention, for example:
  - Endoscopy to treat the bleeding
  - Interventional radiography to treat the bleeding
  - Transfer to the operating theatre/room for treatment of bleeding

(Please also see organ-specific definitions)

Grade 2
Any bleeding that does not fulfil the requirements for grade 3 bleeding (general or organ-specific) BUT requires an intervention or treatment:

- Examples of Interventions
  - Nasal Packing
  - Bladder irrigation
- Examples of treatments
  - Platelet transfusion given to treat active bleeding and NOT given only because the platelet count is below the prophylactic platelet transfusion trigger
  - Medications prescribed to treat bleeding

(Please also see organ-specific definitions)

Grade 1
Any bleeding that does not fulfil the requirements for grade 2 bleeding (general or organ-specific). For examples of grade 1 bleeding please see the organ-specific definitions.

Organ-specific definitions of WHO Grades

	Grade 1	Grade 2	Grade 3	Grade 4
General	Bleeding that does not fulfil the requirements for grade 2 bleeding. Please see examples in organ-specific categories below.	Any bleeding that does not fulfil the requirements for grade 3 bleeding BUT requires an intervention or treatment: Examples of Interventions - Nasal Packing - Bladder irrigation Examples of treatments - Platelet transfusion given to treat active bleeding and NOT given only because the platelet count is below the prophylactic platelet transfusion trigger - Medications prescribed to treat bleeding	Any bleeding that does not fulfil the criteria for grade 4 bleeding BUT requires: Red cell transfusion specifically related to treatment of bleeding within 24 hours of onset of bleeding. OR A significant intervention, for example: - Endoscopy to treat the bleeding - Interventional radiography to treat the bleeding - Transfer to the operating theatre/ room for treatment of bleeding	Any bleeding that is fatal or life threatening. For example: - Bleeding that requires transfer to intensive care/treatment unit - Bleeding that is associated with haemodynamic instability and causes inadequate tissue perfusion (for further clarification see general guideline above).
Oral and nasal†	Spontaneous oropharyngeal bleeding - total duration of all episodes in previous 24 hours < 30 minutes* Traumatic oropharyngeal bleeding e.g. after bites to lips and tongue lasting > 10 minutes or interfering with daily activities Epistaxis - total duration of all episodes in previous 24 hours < 30 minutes*	Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes*		Any bleeding that requires intubation to protect the airway

	Petechiae of oral mucosa ≤ 25%	Petechiae of oral mucosa > 25%		
Skin†	Petechiae (< 3mm diameter), purpura (3mm to 10mm diameter) or bruising covering ≤ 25% of skin (1 arm = 9%; 1 leg = 18%; trunk = 36%; head = 9%; genitalia 1%)	Petechiae, purpura (3mm to 10mm diameter) or bruising covering > 25% of skin ((1 arm = 9%; 1 leg = 18%; trunk = 36%; head = 9%; genitalia 1%)		
Soft-tissue and musculoskeletal	Asymptomatic spontaneous soft-tissue haematoma less than 10cm in diameter. Traumatic haematoma of any size Traumatic joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	Asymptomatic spontaneous soft-tissue haematoma greater than 10cm in diameter. Symptomatic soft-tissue haematoma (e.g. causing pain or discomfort). Spontaneous joint bleeding (confirmed by aspiration, imaging study or other accepted technique)		Any bleeding that causes compartment syndrome.
Gastrointestinal	Faecal occult blood Rectorrhagia- visible red blood on tissue paper/not mixed with stool	Melaena Hematochezia – visible red blood mixed in stool, not requiring a transfusion Haematemesis – Grossly visible blood in emesis (vomit) or in nasogastric drainage tube (not related or secondary to swallowed blood)		

Genitourinary	Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle OR Bleeding heavier than normal OR Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting Microscopic haematuria/ dipstick positive haematuria	Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle OR Bleeding heavier than normal OR Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting Gross/visible haematuria	Any bleeding that causes: increase ≥1.5 X reference serum creatinine‡ or Serum creatinine rises by ≥ 26µmol/L (0.3mg/dl) within 48 hours or Urine output <0.5 mL/kg/hr for > 6 consecutive hrs	Any bleeding that causes: increase ≥3 X reference serum creatinine‡ or Serum creatinine rises by ≥354 µmol/L (4.0 mg/dl) or Commenced on renal replacement therapy or Urine output <0.3 mL/kg/ hr for > 24 hrs or Anuria for at least 12 hrs
Pulmonary		Haemoptysis – Visible blood Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding or mucositis).	Any bleeding requiring supplemental oxygen to maintain oxygen saturation above 93%.	Any bleeding requiring respiratory support (includes non-invasive (CPAP, BiPAP), or invasive ventilation)
Body cavity		Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	Grossly visible blood in body cavity fluids AND organ dysfunction with symptoms, AND/OR need to intervene (e.g. to aspirate).	
Eye†	Sub-conjunctival haemorrhage Traumatic retinal bleeding without visual impairment Traumatic vitreous bleeding without visual impairment	Diffuse sub-conjunctival haemorrhage in both eyes Spontaneous retinal bleeding without visual impairment Spontaneous vitreous bleeding without visual impairment	Retinal bleeding with temporary visual impairment ** (present for ≤ 7 days) Vitreous bleeding with temporary visual	Retinal bleeding with permanent visual impairment ** (present for > 7 days) Vitreous bleeding with permanent visual

			impairment *** (present for ≤ 7 days)	impairment ** (present for > 7 days)
Central nervous system		Lumbar puncture with blood (>5 RBC/μL in CSF on microscopic analysis and non-traumatic tap), no neurological symptoms and no visible red colour Traumatic CNS bleeding on imaging study without neurological dysfunction	Lumbar puncture with visible red colour in absence of neurological symptoms, and non-traumatic tap Spontaneous CNS bleeding on imaging study without neurological dysfunction	CNS symptoms with non-traumatic bloody lumbar puncture CNS bleeding on imaging study with neurological dysfunction
Invasive sites	Bleeding at invasive sites or sites of minor trauma (e.g. venepuncture sites, intravenous lines or catheter exit sites): active oozing at site for > 10 minutes	Bleeding at invasive sites (venepuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours.		

*Count actual bleeding (i.e. "running out" or need for basin, tissue, towel, etc.) not minor bleeding
**Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmological consultation
*** Visual impairment confirmed by ophthalmological consultation
† Petechiae of oral mucosa and skin, Subconjunctival haemorrhage, Haemorrhagic bullae/blisters in mouth, Purpura and ecchymoses
These are all documented as bleeding on the 1st day they are seen and any subsequent day that the bleeding is worse than the preceding day. If the bruising / petechiae is the same as or not as severe as the previous day, it will not be counted as bleeding [For discussion]. ǂ Reference serum creatinine is the baseline serum creatinine result taken on entry into the study

20.3. Definitions of Bleeding Signs

Definition of bleeding signs based on physical examination		
Site of bleeding	Sign	Definition
Skin (epidermis and dermis)		
	Petechiae	Red (recent) or purplish (a few days old) spot discoloration in the skin with a diameter between 0.5

		mm to < 3 mm, not blanching with pressure and not palpable
	Purpuric macule (purpura)	Differentiated from petechiae only for their larger size between 3 to 10 mm.
	Ecchymosis (bruise or contusion)	Larger than 10mm in size. Flat, rounded or irregular, red, blue, purplish or yellowish green patches, larger than a petechia or purpura. If elevated they represent superficial spreading of an underlying hematoma
Skin (subcutaneous tissue)		
	Haematoma	Bulging localized accumulation of blood often with discoloration of overlying skin
Visible mucous membranes		
	Petechia, purpuric macules and ecchymoses	As for skin
	Bulla/vescicle (Blister)	Visible raised, thin-walled, circumscribed lesions containing blood. Bullae (≥ 5mm) are larger than vescicles (< 5 mm). They should be counted together as bullae
	Epistaxis	Any bleeding from the nose, may be anterior or posterior and unilateral or bilateral
	Gingival bleeding	Any bleeding from the gingival margins
	Subconjunctival haemorrhage	Bright red discoloration underneath the conjunctiva at onset then same colour changes as ecchymoses
Muscles and soft tissues		
	Haematoma	Any localised collection of blood visible, or palpable or revealed by imaging. May be dissecting when spreading along fascial spaces

20.4. Other Definitions

20.4.1. Definition of DIC (ISTH) (43)

Score	Prolonged PT	Fibrinogen g/l	Platelet count	Elevated fibrin marker
0	< 3 s	> 1	> 100	Not ↑
1	> 3s but < 6s	< 1	< 100	
2	> 6s	-	< 50	↑
3	-	-	-	↑↑

Score greater than or equal to 5 is compatible with overt DIC

20.5.1 Definition of deep vein thrombosis

Diagnosis of deep-vein thrombosis (DVT) should follow the American Association of Chest Physician (ACCP) guidelines for diagnosis and treatment of DVT(57)

Confirmed Episodes

In patients with suspected first lower extremity DVT:

- Compression ultrasound of the proximal veins of the leg is positive for DVT
- Compression ultrasound of the whole leg is positive for DVT
- Venography2 (including CT, MRI, or MR direct thrombus imaging) is positive for DVT

In patients with suspected recurrent lower extremity DVT:

- Compression ultrasound (CUS) of the proximal veins of the leg shows a new non-compressible segment in the common femoral or popliteal vein, (a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result)
- Venography (including CT, MRI, or MR direct thrombus imaging) is positive for DVT

In patients with suspected upper extremity DVT:

- Combined modality ultrasound (compression with either Doppler or colour Doppler) is positive for DVT
- Venography (including CT, MRI, or MR direct thrombus imaging) is positive for DVT

Suspected Episodes

In patients with suspected first lower extremity DVT:

- Patients with negative scan results and a moderate or high pre-test probability of thrombosis should have additional testing with a highly sensitive D-dimer, whole-leg US or repeat proximal CUS in 1 week
- Patients with haematological malignancies are likely to have positive D-dimers for other reasons e.g. sepsis. Therefore, patients with a single negative proximal CUS and positive D-dimer should undergo whole-leg US or repeat proximal CUS in 1 week

ACCP recommend venography when ultrasound is impractical (e.g. when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic.

In patients with suspected recurrent lower extremity DVT:

- Compression ultrasound of the proximal veins of the lower leg shows a new non-compressible segment in the common femoral or popliteal vein, (<4 but ≥ 2-mm

increase in venous diameter during compression compared with that in the same venous segment on a previous result) should have additional testing with venography, if available, serial proximal CUS or testing with a moderately or highly sensitive D-dimer and serial proximal CUS if the test is positive.
- If no previous scan is available further testing with venography or a highly sensitive D-dimer is required.

In patients with suspected upper extremity DVT:
- Combined modality ultrasound (compression with either Doppler or colour Doppler) is negative or there is less than a complete evaluation and D-dimer is positive should undergo venography

DVT Excluded
- Negative serial proximal CUS
- Negative single proximal CUS and negative highly sensitive D-dimer
- Negative whole-leg US
- Negative venography
- Low or moderate pre-test probability of DVT and negative highly sensitive D-dimer
- Previous ipsilateral DVT, an abnormal US and negative highly sensitive D-dimer
- Negative combined-modality US and negative moderate or highly sensitive D-dimer
- Negative combined-modality US and negative CT or MRI venography

Pre-test Probability (PTP) (Well's Score) for DVT

Variable	Points
Active cancer (treatment on-going or within previous 6 months or palliative)	1
Paralysis or plaster cast	1
Bed > 3 days or surgery within 4 weeks	1
Tenderness along veins	1
Entire leg swollen	1
Calf swollen > 3cm	1
Pitting oedema	1
Collateral veins	1
Alternative diagnosis	-2
Add up points	
Low risk	0
Moderate risk	1 to 2
High risk	> 2

20.5.2 Definition of pulmonary embolism

Diagnosis of pulmonary embolism (PE) should follow the European Society of Cardiology (ESC) Guidelines on the diagnosis and management of acute pulmonary embolism(44).

Confirmed Cases

In patients with suspected high-risk pulmonary embolus (i.e. with shock or hypotension)

- Echocardiography shows RV overload and patient unstable or no other tests available
- A CT angiography showing a segmental or more proximal thrombus

In patients with suspected non-high-risk pulmonary embolus (i.e. without shock or hypotension)

- Pulmonary angiography showing PE
- A CT angiography showing a segmental or more proximal thrombus
- Compression ultrasound of the proximal veins of the lower leg is positive for DVT
- Moderate or high clinical probability of PE and high probability ventilation-perfusion lung scintigraphy (V/Q scan)

PE Excluded

- Normal pulmonary angiogram
- Normal V/Q scan
- Low or moderate clinical probability of PE and negative highly sensitive D-dimer
- Low or moderate clinical probability of PE and negative proximal leg CUS (+/- non-diagnostic V/Q scan; +/- negative single-detector CT angiography)
- Low or moderate clinical probability of PE and negative multi-detector CT angiography

Clinical Prediction Rules for PE

(Well's Score)

Variable	Points
Previous DVT or PE	1.5
Cancer	1
Bed > 3 days or surgery within 4 weeks	1.5
Haemoptysis	1
Heart rate > 100 beats/min	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Add up points	
Low risk	0 to 1
Moderate risk	2 to 6
High risk	> 6

(Geneva Score)

Variable	Points
Previous DVT or PE	3
Active malignancy	2
Surgery or fracture within 4 weeks	2
Age > 65yrs	1
Haemoptysis	2
Unilateral lower limb pain	3
Heart rate 75 to 94 beats/min	3
Heart rate ≥ 95 beats/min	5
Pain on lower limb deep vein at palpation and unilateral oedema	4
Add up points	
Low risk	0 to 3
Moderate risk	4 to 10
High risk	> 10