Statistical Analysis Plan

TREATT

Trial to EvaluaAte Tranexamic acid therapy in Thrombocytopenia

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Prepared by:

Name	Role	Signature	Date
Elinor Curnow	Trial Statistician		13/03/2020

Approved by:

Name	Role	Signature	Date
Simon Stanworth	Chief Investigator	Approved electronically	13/05/2020
Lise Estcourt	Chief Investigator	Approved electronically	13/05/2020
Ian Franklin	TSC Chair	Approved electronically	02/07/2020
Helen Thomas	Lead Statistician	Approved electronically	17/06/2020

Statistical Analysis Plan

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Statistical Analysis Plan

1. Background and Design

The main characteristics of this trial have been summarised using the TREATT Protocol v3.1 from 09/08/2018. Please refer to this Protocol for full details. All essential documents for the trial are held in the Trial Master File.

1.1 Trial Summary and Objective

Background

Platelet transfusions are commonly administered as prophylaxis to reduce the risk of bleeding in patients with haematological malignancies. Two recent randomised controlled trials of prophylactic platelet transfusions have directly evaluated the benefit of prophylactic platelet transfusions more directly; both found a no-prophylaxis approach led to greater rates of World Health Organization (WHO) grade 2-4 bleeding overall. However although patients who received prophylactic platelet transfusions had fewer bleeds, a high baseline bleeding rate remained (43% of patients had WHO grade 2-4 bleeding in TOPPS[1]). This suggests that factors other than those addressed by the use of platelet transfusions are important in determining bleeding risk.

A recent systematic review of clinical trials of tranexamic acid (TXA) in patients with haematological disorders to prevent bleeding identified 4 trials (published in 5 papers). All studies were small and of poor quality; all but one of the trials were conducted and published well over 10 years ago. The results suggest a reduction in bleeding, but it was not possible to combine the data. All studies reported a reduction in platelet usage. The trials were too small to assess the effect of TXA on thromboembolic events. For all these reasons, we believe that the effectiveness and safety of TXA in haematology is uncertain and that a high quality randomised controlled trial is needed.

Aim of study

To assess whether TXA reduces bleeding in haematology patients. Secondary outcomes include safety (thrombotic events) and platelet use.

1.2 Patient Eligibility Criteria

Patient inclusion criteria:

Patients are eligible for this trial if:

- Aged ≥ 18 years of age
- Confirmed diagnosis of a haematological malignancy
- Undergoing, or planning to undergo, chemotherapy or haematopoietic stem cell transplantation
- Anticipated to have a hypoproliferative thrombocytopenia resulting in a platelet count of ≤ $10x10^9$/L for ≥ 5 days
- Able to comply with treatment and monitoring

Patient exclusion criteria:

A patient will not be eligible for this study 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

1.3 Trial Intervention

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,

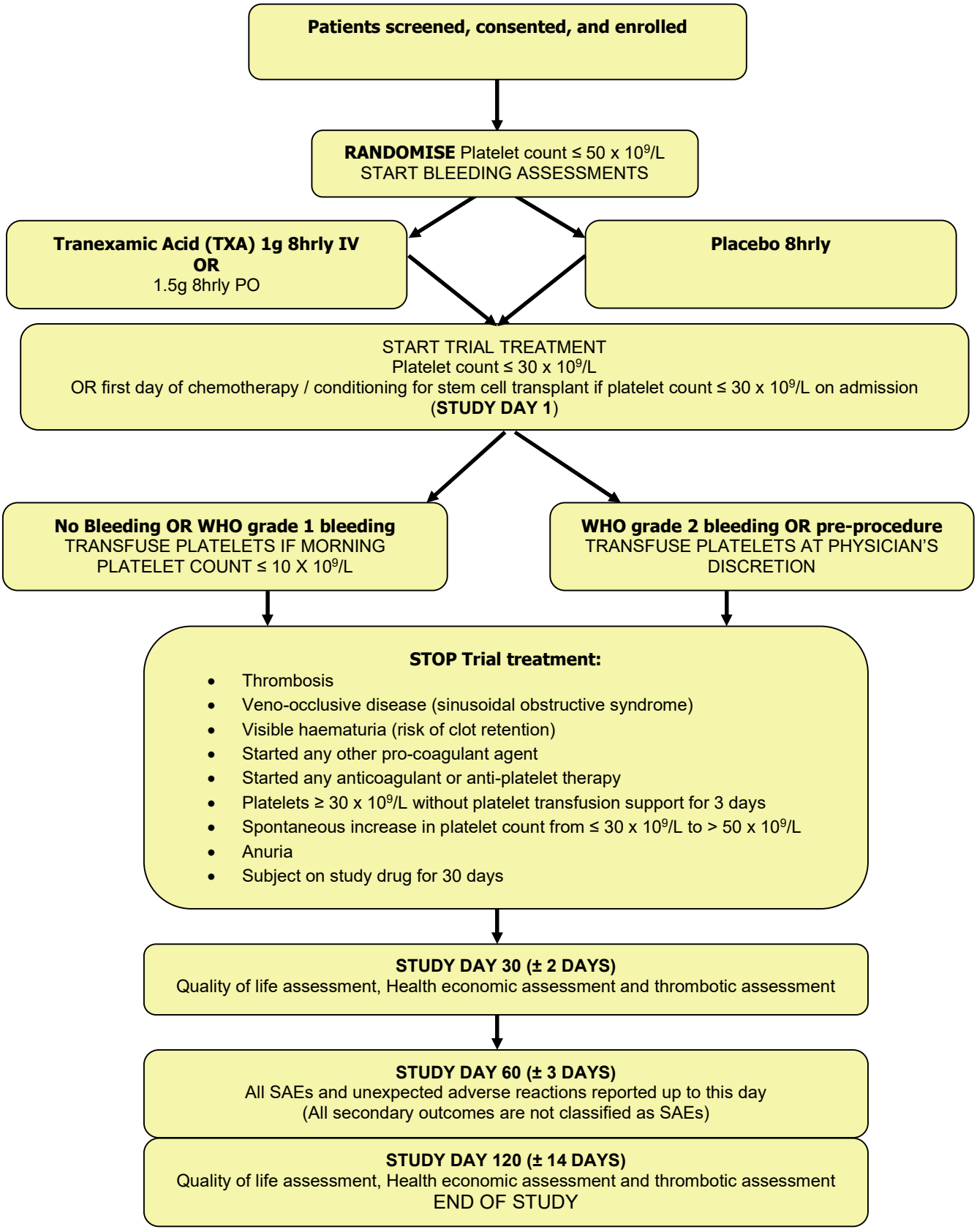
All participants will start with Intravenous administration

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 a capsule/tablet every 8 hours.

Figure 1 Summary of trial entry, randomisation and treatment



1.4 Randomisation and Blinding Procedures

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. Randomisation lists will be created using computed-generated random numbers.

1.5 Sample size calculation

1.5.1 Minimal Clinically Important Difference (MCID)

Based on the experience of similar patients in the TOPPS trial[1], 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.

1.5.2 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 participants 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[2].

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 the study intervention. In the recent TOPPS trial, completeness of bleeding outcome documentation was

excellent. A bleeding assessment was completed on 93% (8405/9030) of days for participants in the no-prophylaxis group, and 97% (8733/8970) of days in the prophylaxis group. The majority of participants 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 participants) while on the trial.

1.5.3 Safety outcomes

This trial is not powered to definitively establish the safety of the treatment with respect to the frequency of venous thromboembolism (VTE). However, with the planned enrolment of 616 participants, 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.

2. Outcome Measures

2.1 Primary outcome measures

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 administration of the study intervention.**

2.2 Secondary outcome measures

2.2.1 Secondary Efficacy Outcomes

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

- 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 up to 30 days without a platelet transfusion
- Proportion of participants surviving up to 30 days without a red cell transfusion
- Quality of life

2.2.2 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

2.2.3 Other Outcomes

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

- 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

2.3 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 (participant decided to stop taking trial treatment vs. participant did not decide to stop taking trial treatment)

3. Data Handling

3.1 CRF descriptions and data collection schedule

Table 1 CRF completion requirement

CRF	Completion requirement
Form 1a- Eligibility & consent	Mandatory at consent
Form 2- Demography	Mandatory at consent
Form 3- Diagnosis & treatment plan	Mandatory at consent
Form 4- Medical history	Mandatory at consent
Form 5a- Laboratory data	Mandatory at consent
Form 5b- Laboratory data	Days between consent and randomisation
Form 6- Randomisation	Mandatory at randomisation
Form 7- Daily bleeding and Temperature assessment	From day R up to study day 30
Form 8- Non-severe bleeding assessment	From day R up to study day 30, if non-severe bleeding is reported on form 7b

Form 9a- Severe bleeding assessment (initial report)	From day R up to study day 30, if severe bleeding is reported on form 7b
Form 9b- Severe bleeding assessment (follow-up report)	When form 9a has been completed
Form 10- Transfusion data form	From day R up to study day 30, if transfusion reported on form 6, form 7, form 12 or form 13
Form 11- Interventions & procedures for daily bleeding	From day R up to study day 30, if indicated on form 7
Form 12- Daily assessments	After day R, up to day 1
Form 1b- Eligibility re-check	Mandatory on day 1
Form 13- Daily assessments	From day 1 to day 30
Form 14- Change to trial treatment administration	From day 1 to day 30, if indicated on form 13
Form 15- Discontinuation of trial treatment	Mandatory for all consented participants
Form 16- Completion of 30 day study observation period	Mandatory for all consented participants
Form 17a- Day 60 (+/- 3 days): follow- up assessments	Mandatory for all consented participants who completed the first 30 days (indicated on form 16)
Form 17b- Day 120 (+/- 14 days): follow-up assessments	Mandatory for all consented participants who completed the first 60 days (indicated on form 17a)
Form 18- Adverse event	From day 1 up to day 60, if applicable
Form 19- Safety outcome: thrombotic events or veno occlusive disease	From consent up to study day 120, if applicable
Form 20- Health questionnaire: EQ-5D-5L	At randomisation, study day 12 (+/- 2 days), study day 30 (+/-2 days), study day 120 (+/- 14 days)
Form 21- Health questionnaire: FACT-Th18	At randomisation, study day 12 (+/-2 days), study day 30 (+/- 2 days)
Form 22a- Health economics	Study day 30 (+/- 2 days)
Form 22b- Health economics	Study day 120 (+/-14 days) or last day of follow-up

Table 2 Trial Schedule (Assessments)

Trial Assessment	Consent	Days between consent and random-isation	Day R Day of random-isation platelet count ≤ $50x10^9/l$	Days between Day R and study day 1	Day 1 1st day of trial treatment	Day 2	Days 3 - 11	Day 12 (± 2)	Days 13 - 29	Day 30 (± 2)	Day 60 (± 3)	Day 120 (± 7)
Demographics and medical history	X											
Eligibility Assessment	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 Tele-phone follow-up
Highest recorded temperature each day			X		X	X	X	X	X			
SAE Assessment					X	X	X	X	X	X	X	

Table 3 Trial Schedule (Investigations)

Trial Assessment	Consent	Days between consent and randomis-ation	Day R Day of randomisation; platelet count ≤ $50x10^9/l$	Days between Day R and study day 1	Day 1 1st day of trial treatment	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	Required three times a week	X	Required three times a week	X
Liver function tests:bilirubin and albumin	X		X			X	Required if VOD is reported 3 times a week	X	Required if VOD is reported 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

3.2 Procedures for recording and reporting outcomes

CRFs will be used to collect data from study entry. Two participant identifiers (trial number allocated at consent and initials) will be used on all CRFs. Data will be recorded by electronic data capture (EDC). Prime responsibility for the complete collection of data for each centre will reside with the local Principal Investigator but may be delegated (for example to a research nurse). Overall responsibility for collating data from all centres will reside with the Trial Manager.

3.3 SAE Review

As part of pharmacovigilance procedures, all blinded SAEs will be reviewed by the Chief Investigators in real-time.

3.4 Other assessments

None.

3.5 Trial Data Management and Verification

Quality control of data entered and data cleaning will be performed by the trial data manager and will be detailed in the Data Management Plan (FRM4727). This will include performing range, data completeness and consistency checks. Once this stage is finished, the trial dataset will be declared frozen and exported from the MACRO database for final data review and validation checks by a statistician, who will raise data queries with the trial manager or data manager. Once the trial statistician, data manager, and trial manager are satisfied that all queries have been resolved, the database will be locked. The locked database will be exported to the Statistical Master File and then imported into SAS and used for final analysis.

4. Detailed Analysis Plan

4.1 Interim analysis

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 participants, it is similarly judged important that any deleterious effect of anti-fibrinolytic therapy with respect to bleeding in thrombocytopenic participants be documented at a level that would be clinically and statistically credible. The Data Monitoring Committee will have overall oversight and can recommend terminating the trial early for these or any other safety concerns.
An interim analysis will be performed after 300 participants have been in the trial for 30 days. A summary of SAEs, UARs, thrombotic events, veno-occlusive disease and death, by treatment arm, will be provided to the Data Monitoring Committee. This summary will be performed by the independent statistician, and will remain inaccessible to the trial statistician, to ensure the trial statistician remains blinded. 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. 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 consent until 120 days after first administration of trial treatment.
In addition, a multivariate test for heterogeneity of UK and Australian baseline participant characteristics will be performed by the trial statistician. The population used for this analysis will be a modified intention to treat population including all eligible randomised participants whose platelet count falls to $30x10^9$/L or below. Sex, diagnosis (acute leukaemia or not) and treatment plan (autograft or not) will be analysed as binary outcomes. The normal approximation to the binomial will be applied for each binary variable and sex, diagnosis (acute leukaemia or not), treatment plan (autograft or not) and haemoglobin at randomisation will be compared using Hotelling's T-squared test, as long as the following criteria are fulfilled: (i) the estimated proportions are not close to the [0,1] boundaries; (ii) the number of participants in each binary outcome category is > 5; (iii) for each binary variable, 3 standard deviations above and below the expected proportion is within the range [0,1]. If not all the criteria are fulfilled, an alternative test will be considered: a logistic regression of participant country (UK or not) on sex, diagnosis (acute leukaemia or not), treatment plan (autograft or not) and haemoglobin at randomisation will be performed and the concordance statistic and its 95% confidence interval will be calculated. A confidence interval that does not include 0.5 would indicate evidence of a difference between UK and Australian participants. A summary of the multivariate test will be provided to the Data Monitoring Committee. 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.

4.2 Analysis principles

Unless otherwise specified, all tests will be two-sided and p-values of less than 0.05 will be considered as evidence of a difference between treatment arms.

Multiple comparisons will be performed and this may increase the probability of observing a statistically significant result by chance. No adjustments will be made to account for multiple testing.

P-values will be reported to four decimal places with p-values less than 0.00005 as <0.0001. SAS or R will be used to conduct analyses.

All analyses will be adjusted for the stratification variable (recruitment site). Recruitment site will be accounted for by including a random effect in each model.

All hazard, odds and rate ratios will be presented as active treatment versus placebo. A ratio which is greater than 1 indicates that the hazard, odds or rate is greater in the active treatment arm. 95% confidence intervals will be presented with all ratios. P-values for regression models will be obtained by comparing -2 x log-likelihood values for models with and without the treatment term.

The key demographics and clinical condition of the participants at consent will be presented for each arm of the trial to describe the cohort. A CONSORT diagram will be presented to show how participants progressed through the trial.

4.2.1 Efficacy population

The population used for efficacy analyses will be a modified intention to treat population (mITT) including all randomised participants whose platelet count falls to $30x10^9$/L or below. Data are gathered for 30 days from the day the first dose of trial treatment is administered or is planned to be administered for those participants who did not receive treatment. Participants will be analysed in the arm that they were randomised to. 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 after randomisation and 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 participants 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. Subjects whose platelet count falls to $30x10^9$/L or below will be included in the analyses, even if they were randomised in error, did not receive trial treatment, stopped trial treatment "early", or received prophylactic transfusions not in accordance with the protocol.

Rationale: Owing to the emergent nature of treatment of thrombocytopenic participants, 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 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 protocol-adherence 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 $\leq 30 \times 10^9$/L, OR if the participant was admitted with a platelet count already below 30×10^9/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 trial eligibility criteria and/or met at least one of the trial exclusion criteria will be considered as randomised in error. Participants who were randomised in error and received study intervention will be considered a protocol deviation. Participants who withdrew from the trial after starting trial treatment, who missed a dose of trial treatment or who chose to stop trial treatment "early" *are* included in the per protocol analysis.

4.2.2 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.

4.2.3 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 consent until 120 days after first administration of trial treatment.

4.3 Analysis of primary outcome measures

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 day the first dose of trial treatment is administered, will be estimated by the Kaplan-Meier method and compared by treatment arm 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. Participants withdrawn or lost to follow up before day 30 will be censored at the time that they withdrew/were lost to follow up. Any missing bleeding assessments during the 30-day follow up period or to the last point of contact, whichever is first, will be assumed to be grade 1 or below.

If there is evidence of a difference in the primary outcome between treatment arms, the number needed to treat (NNT) (for benefit) will be presented. NNT is the number of participants who need to be treated with tranexamic acid in addition to standard care in order for one additional participant to benefit. It is calculated as 1 / (difference in proportion experiencing the primary outcome in each treatment arm as a decimal).

4.4 Analysis of secondary outcome measures

Secondary efficacy outcomes

- Proportion of days with bleeding up to study day 30 will be compared by treatment arm using binary logistic regression analysis (bleeding or not on any given day). Correlation 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. Median, IQR will be reported by treatment arm. To accommodate a random centre effect, Cox regression analysis will be used to compare time to first episode of bleeding of WHO grade 2 or greater between treatment arms. 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. The estimate of the hazard of bleeding of WHO grade 2 or greater from this model should be interpreted with caution because it does not properly account for the competing risk of death. However, since the number of deaths are predicted to be small, the impact of the competing risk is likely to be negligible. This will be explored by examining the cumulative incidence function for death prior to bleeding of WHO grade 2 or greater.
- Highest grade of bleeding up to study day 30 will be compared by treatment arm 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 by treatment arm 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 or to the last point of contact, whichever is first. In addition, unadjusted median, IQR number of platelet transfusions per day in hospital will be reported.
- Number of red cell transfusions/participant up to study day 30 will be compared by treatment arm 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. In addition,

unadjusted median, IQR number of red cell transfusions per day in hospital will be reported.

- Proportion of participants surviving up to 30 days without a platelet transfusion will be estimated by the Kaplan-Meier method and compared by treatment arm using Cox regression analysis. The event of interest is time to first platelet transfusion or death. Participants withdrawn or lost to follow up before day 30 will be censored at the time that they withdrew/were lost to follow up.
- Proportion of participants surviving up to 30 days without a red cell transfusion will be estimated by the Kaplan-Meier method and compared by treatment arm using Cox regression analysis. The event of interest is time to first red cell transfusion or death. Participants withdrawn or lost to follow up before day 30 will be censored at the time that they withdrew/were lost to follow up.
- Quality of life at study days 12 and 30 will be assessed using FACT-G and FACT-Th health questionnaires. For the FACT-G subscale scores (physical well-being, social/family well-being, emotional well-being, functional well-being), FACT-G total score and FACT-Th total score, mean (SD) will be calculated and compared by treatment arm using normal regression analysis. For each normal linear regression model, residual plots will be examined. If there is substantial evidence of skew or non-constant variance, log-transformed values will be used instead.

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 estimated by the Kaplan-Meier method and compared using Cox regression analysis. Participants withdrawn or lost to follow up before day 30/day 120 will be censored at the time that they withdrew/were lost to follow up.
- 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. To accommodate a random centre effect, 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 other causes 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. To accommodate a random centre effect, Cox regression analysis will be used to compare death due to bleeding 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 other causes will be censored at the time of death. If numbers of deaths due to bleeding are very small, the number of deaths will simply be described by arm.
- 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 deaths.

4.5 Other outcome measures

- Proportion of days with thrombocytopenia (platelet count <10x10^9/L) from consent up to study day 30 will be compared by treatment arm using binary logistic regression analysis (thrombocytopenic or not on any given day). Correlation at participant level will be accounted for by including a random participant effect. If the number of thrombotic events is very small, the proportions will simply be described by arm.
- Proportion of days with thrombocytopenia (platelet count <30x10^9/L) from consent up to study day 30 will be compared by treatment arm using binary logistic regression analysis (thrombocytopenic or not on any given day). Correlation at participant level will be accounted for by including a random participant effect. If the number of thrombotic events is very small, the proportions will simply be described by arm.
- Proportion of days with thrombocytopenia (platelet count <50x10^9/L) from consent up to study day 30 will be compared by treatment arm using binary logistic regression analysis (thrombocytopenic or not on any given day). Correlation at participant level will be accounted for by including a random participant effect. If the number of thrombotic events is very small, the proportions will simply be described by arm.
- 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 binary logistic regression analysis (fever or not on any given day). Correlation at participant level will be accounted for by including a random participant effect.
- Reasons for platelet and red cell transfusions will be described by arm.
- A plot depicting median, IQR platelet count over time from consent up to study day 30, by arm, will be produced. Where consent, randomisation and/or treatment occurred on the same day, the participant's platelet count will only be included in the median calculation for the last of the concurrent events.
- A plot depicting overall survival from randomisation up to study day 120, by arm, will be produced.
- Trial treatment will be summarised by arm, including number of participants who changed route or frequency, number of participants who missed a dose, reasons for discontinuation of treatment. Median, IQR number of days on trial treatment and on oral trial treatment, from the first day of treatment administration until discontinuation of trial treatment, for participants who received at least one dose of trial treatment, will be estimated using competing risks analysis. Death prior to discontinuation of trial treatment will be considered as the competing risk.
- Number of granulocyte transfusions/participant up to study day 30 will be summarised by treatment arm..
- Location of bleeding up to study day 30 will be summarised, by treatment arm
- Number of participants requiring interventions and procedures for bleeding up to study day 30 will be summarised by treatment arm. This may be sub-categorised by type of intervention or procedure if there are large numbers of participants requiring interventions and procedures.
- Number of participants requiring concomitant medication (categorised as medication increasing risk of bleeding, medication decreasing risk of bleeding, no concomitant medication) up to study day 30 will be summarised by treatment arm. This may be sub-categorised by type of concomitant medication if there are large numbers of participants requiring concomitant medication.
- Number of participants on Mylotarg during the first 30 days of the trial will be summarised by treatment arm.

4.6 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 covariate and 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 (participant decided to stop taking trial treatment vs. participant did not decide to stop taking trial treatment). Although participants may decide to stop taking trial treatment for many reasons, the main reason is thought to be an unwillingness to take the large, over-encapsulated oral trial treatment. The over-encapsulated oral trial treatment is to be replaced with smaller tablets in the UK and Australia. Therefore, an additional analysis of treatment compliance will be performed using four mutually-exclusive categories: participant decided to stop taking trial treatment during the period of over-encapsulated oral treatment; participant decided to stop taking trial treatment during the period of oral treatment as tablets; participant did not decide to stop taking trial treatment during the period of over-encapsulated oral treatment; participant did not decide to stop taking trial treatment during the period of oral treatment as tablets. The number of UK participants who discontinued IV trial treatment during the period in September 2018 when oral treatment was unavailable will be described by arm.

4.7 Sensitivity analyses

- The key demographics and clinical condition of participants at consent will be described for each arm of the trial, comparing all randomised participants with the mITT population to ensure that excluded participants are similar across the arms.
- Per-protocol analysis of the primary outcome. This analysis will exclude all participants who did not adhere to a set of minimum protocol-adherence criteria during the first 30 days of the trial. Participants who were randomised in error will be excluded from this analysis. The per-protocol analysis will be performed using the same method as for the mITT analysis. Protocol-adherence will be summarised by treatment arm. In addition, since the per-protocol analysis may lead to an over-estimation of the difference in the proportion experiencing the primary outcome in each treatment arm, which may be explained by differing levels of protocol-adherence in each treatment arm, an instrumental variable analysis will be performed. The randomisation arm will be used as the instrument. The instrumental variable estimate will be calculated as the mITT estimate of the difference in the proportion experiencing the primary outcome in each treatment arm / proportion adhering to the minimum compliance criteria in the active treatment arm. The standard error of the instrumental variable estimate will be calculated using two-stage least squares.
- Some participants may withdraw or be lost to follow up during the conduct of the trial. In addition, some participants who are followed up for the full 30 days may be missing some bleeding assessments. In these cases, it is impossible to know whether such participants would be either less or more likely to experience bleeding if they had complete bleeding assessments for the full 30-day follow up period. Sensitivity of the primary outcome to incomplete follow up and missing bleeding assessments will be assessed by re-calculating the primary outcome, by arm, for all participants included in the mITT analysis, after imputing all missing bleeding assessments up to study day 30.

Imputation will be performed using multiple imputation by fully conditional specification (Van Buuren, 2007), with the number of imputations equal to the percentage of missing data.

- Number of days between platelet count first 30 x 10^9/L or below OR if the participant was admitted with a platelet count already below 30 x 10^9/L, number of days between the start of chemotherapy or conditioning for a stem cell transplant, and start of trial treatment, or planned start for those participants who did not receive treatment, will be summarised by treatment arm, for all participants included in the mITT analysis. It is important to monitor this since the 30-day analysis period only begins at the start of study treatment.
- Number of bleeds between platelet count first 30 x 10^9/L or below and start of trial treatment or planned start for those participants who did not receive treatment will be summarised by treatment arm, for all participants included in the mITT analysis. It is important to monitor whether any bleeds occurred prior to the start of the 30-day analysis period.

4.8 Procedures for handling Missing Data

For all outcomes, the volume of missing data will be summarised by treatment arm.

Participants withdrawn or lost to follow up before day 30 will be included in the primary outcome analysis (and in secondary outcome analyses where possible), censoring at the time that they withdrew/were lost to follow up.

It is expected that deaths and other safety outcomes, other than for participants withdrawn or lost to follow up, will be fully reported.

For the main analysis of the primary outcome, any missing bleeding assessments during the 30-day follow up period or to the last point of contact, whichever is first, will be assumed to be grade 1 or below. Sensitivity of the primary outcome to missing data will be assessed as per the sensitivity analysis described above.

Missing values for secondary and baseline characteristics will not be imputed. Missing data will be excluded from the relevant analyses.

5. Data Analysis Tables to be Completed

Data analysis will be based on the following tables.

5.1 Interim analysis tables

Table 1 Baseline characteristics for UK vs. Australian participants – data are number (%) for categorical variables, and mean (SD) for continuous variables

	UK (n=)	Australia (n=)	P value
Sex: Male			
Diagnosis: Acute leukaemia			
Treatment plan: Autograft			
Haemoglobin at randomisation (G/L)			

'Other' diagnosis includes xxx and 'other' treatment plan includes xxx.

Sex is missing for xxx participants, of which xxx are not available.

Diagnosis is missing for xxx participants, of which xxx are not available.

Treatment plan is missing for xxx participants, of which xxx are not available.

Haemoglobin at randomisation is missing for xxx participants, of which xxx are not available.

Table 2 Safety data summary - data are numbers

Outcome	Arm A (n=)	Arm B (n=)	Overall (n=)
Total number of serious adverse events (SAE) up to day 60			
Sepsis			
Organ failure			
GvHD			
Transfusion reaction			
Fever			
Other SAEs			
Number of participants experiencing at least one SAE			
Symptomatic thrombotic events up to day 120			
Venous thromboembolisms			
Arterial ischaemic events			
Veno-occlusive disease up to day 120			
Unexpected adverse reactions up to day 60			
Deaths up to day 120			

5.2 Screening, Recruitment and Follow-up tables

5.2.1 Recruitment by Centre

Table xx Recruitment by centre

Centre	Number of participants screened	Number of eligible participants	% eligible of those screened	Number of participants approached	Number of participants consented	Number of randomisations	% randomised of those eligible
Birmingham Heartlands Hospital							
Derriford Hospital, Plymouth							
Kings College Hospital, London							
Churchill Hospital, Oxford							
Freeman Hospital, Newcastle							
University Hospital, Coventry							
St James's Hospital, Leeds							
Bristol Haematology & Oncology Centre							
Victorian Comprehensive Cancer Centre (formerly Peter MacCallum Cancer Centre), Melbourne,							
St. Vincent's Hospital, Melbourne							
The Beatson Oncology Centre, Glasgow							
Royal Adelaide Hospital							

The Alfred Hospital, Melbourne							
Andrew Love Cancer Centre, Barwon Health, Geelong							
Salisbury District Hospital, UK							
Royal Devon and Exeter Hospital							
University College London Hospital							
Lincoln County Hospital							
Belfast City Hospital							
Queen Elizabeth Hospital, Birmingham							
Royal United hospital, Bath							
Royal North Shore Hospital, Sydney							
Westmead Hospital, Sydney							
Canberra Hospital							
St Vincent's, Sydney							

5.2.2 Participants withdrawn

Table xx Participants withdrawn

Participant ID	Arm	Reason for withdrawal	Stage of withdrawal

5.2.3 Participants randomised in error

Table xx Participants randomised in error

Participant ID	Arm	Detail of error

5.2.4 Participants entered in trial more than once (if relevant) or co-enrolled in other trials

Table xx Participants co-enrolled in other trials

Participant ID	Arm	Detail of co-enrolment

5.2.5 Protocol Deviations

Table xx Protocol deviations

Participant ID	Arm	Detail of protocol deviation

5.3 Baseline Characteristics tables

Table xx Baseline characteristics- data are number (%) for categorical variables, and mean (SD) for continuous variables

	Active arm (n=)	Placebo arm (n=)	Overall (n=)

Male			
Age (years)			
Ethnicity White Asian Black African Black Caribbean Arab/other Middle East ancestry Aboriginal Other Mixed ethnic group: White/Black Caribbean White/Black African White/Asian White/Aboriginal White/Other Other mixed ethnic group			
Height (cm)			
Weight (kg)			
Diagnosis AML ALL APL CML CLL Hodgkins Lymphoma Non-Hodgkins Lymphoma Myeloma MDS Other			
Treatment plan Induction chemotherapy Consolidation chemotherapy Autograft Allograft Other			
Platelet count at consent (x 10^9/L)			
Platelet count at randomisation (x 10^9/L)			
Haemoglobin at consent (G/L)			
Haemoglobin at randomisation (G/L)			
FACT-G subscale score at randomisation			
Physical well-being			
Social/family well-being			
Emotional well-being			
Functional well-being			
FACT-G total score at randomisation			

FACT-Th total score at randomisation			
Medical history			
Diabetes requiring treatment			
Hypertension requiring treatment			
Renal impairment requiring treatment			
Confirmed invasive fungal infection			
Other malignancy			
HLA antibodies			

'Other' diagnoses were xxx and 'other' treatment plans were xxx.

5.4 Primary Outcome table(s)

Table xx Primary outcome table

	Active arm (n=)	**Placebo arm (n=)**	**Overall (n=)**	**P value**
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - % (95% CI)				
Hazard ratio (95% CI)				
Risk difference (95% CI)				
Number needed to treat[1] – N				
Proportion of missing bleeding assessments from day 1 up to study day 30 – n/N (%)				
Proportion of participants missing vital status at study day 30 – n/N (%)				
All primary outcome analyses are adjusted for centre. [1] For benefit. Calculated as 1/risk difference.				

5.5 Secondary Outcome table(s)

Table xx Secondary efficacy outcomes table

Outcome	**Active arm (n=)**	**Placebo arm (n=)**	**Overall (n=)**	**P value**
Proportion of days with WHO grade 2 bleeding or above – % (95% CI)				
Odds ratio[1] (95% CI)				

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Time to first episode of bleeding of WHO grade 2 or greater (days) (median[2], IQR[2])				
Hazard ratio (95% CI)				
Highest grade of bleeding a participant experiences				
Grade 0 – n/N (%)				
Grade 1 – n/N (%)				
Grade 2 – n/N (%)				
Grade 3 – n/N (%)				
Grade 4 – n/N (%)				
Grade unassigned – n/N (%)				
Proportional odds ratio (95% CI)				
Grades 2, 3 or 4 – n/N (%)				
Number of platelet transfusions/participant (units) up to study day 30 (median, IQR)				
Rate ratio (95% CI)				
Number of red cell transfusions/participant (units) up to study day 30 (median, IQR)				
Rate ratio (95% CI)				
Proportion of participants surviving up to 30 days without a platelet transfusion – % (95% CI)				
Hazard ratio (95% CI)				
Proportion of participants surviving up to 30 days without a red cell transfusion – % (95% CI)				
Hazard ratio (95% CI)				
All secondary efficacy outcome analyses are adjusted for centre. [1] Odds ratio from logistic regression model, also adjusted for participant. [2] Lower quartile will be reported. Median and upper quartile will be reported if achieved.				

Table xx Quality of life

Outcome	**Active arm (n=)**	**Placebo arm (n=)**	**Overall (n=)**	**P-value**
FACT-G subscale score at study day 12				
Physical well-being - mean (SD)				
Social/family well-being - mean (SD)				
Emotional well-being - mean (SD)				
Functional well-being - mean (SD)				

FACT-G total score at study day 12 - mean (SD)				
FACT-Th total score at study day 12 - mean (SD)				
FACT-G subscale score at study day 30				
Physical well-being - mean (SD)				
Social/family well-being - mean (SD)				
Emotional well-being - mean (SD)				
Functional well-being - mean (SD)				
FACT-G total score at study day 30 - mean (SD)				
FACT-Th total score at study day 30 - mean (SD)				
All quality of life outcome analyses are adjusted for centre.				

Table xx Safety outcomes table

Outcome	Active arm (n=)	Placebo arm (n=)	Overall (n=)	P value
All-cause mortality during the first 30 days after the first dose of trial treatment is administered – % (95% CI)				
Hazard ratio (95% CI)				
All-cause mortality during the first 120 days after the first dose of trial treatment is administered – % (95% CI)				
Hazard ratio (95% CI)				
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 (N)				
Number of participants developing Veno-occlusive Disease within 60 days of first administration of trial treatment (N)				
Death due to thrombosis during the first 120 days after the first dose of trial treatment is administered – % (95% CI)				
Hazard ratio (95% CI)				
Death due to bleeding during the first 30 days after the first administration of trial treatment is received – % (95% CI)				
Hazard ratio (95% CI)				

Table xx Safety data summary - data are numbers

Outcome	Active arm (n=)	Placebo arm (n=)	Overall (n=)
Total number of serious adverse events (SAE) up to day 60			
Sepsis			
Organ failure			
GvHD			
Transfusion reaction			
Fever			
Other SAEs			
Number of participants experiencing at least one SAE			
Symptomatic thrombotic events up to day 120			
Venous thromboembolisms			
Arterial ischaemic events			
Veno-occlusive disease up to day 120			
Unexpected adverse reactions up to day 60			
Deaths up to day 120			

All SAEs, unexpected adverse reactions, thrombotic events and veno-occlusive disease are reported in full in Appendix 1.

5.6 Missing Data tables

Table xx Missing secondary efficacy outcomes data table – n/N (%)

	Active arm (n=)	Placebo arm (n=)	Overall (n=)
Missing data for platelet transfusions up to study day 30			
Missing data for red cell transfusions up to study day 30			
Missing data for FACT-G subscale score at study day 12			
Missing data for FACT-G total score at study day 12			
Missing data for FACT-Th total score at study day 12			
Missing data for FACT-G subscale score at study day 30			
Missing data for FACT-G total score at study day 30			
Missing data for FACT-Th total score at study day 30			

5.7 Other Outcome summary tables

Table xx Proportion of days with thrombocytopenia

Outcome	Active arm (n=)	Placebo arm (n=)	Overall (n=)	P value
Proportion of days with thrombocytopenia (<10x10^9/L) from randomisation up to study day 30 - % (95% CI)				
Odds ratio (95% CI)				
Proportion of days with thrombocytopenia (<30x10^9/L) from randomisation up to study day 30 - % (95% CI)				
Odds ratio (95% CI)				
Proportion of days with thrombocytopenia (<50x10^9/L) from randomisation up to study day 30 - % (95% CI)				
Odds ratio (95% CI)				
Proportion of missing platelet counts from randomisation up to study day 30 – n/N (%)				
All analyses are adjusted for centre and participant.				

Table xx Proportion of days with fever

Outcome	Active arm (n=)	Placebo arm (n=)	Overall (n=)	P value
Proportion of days with fever (highest daily temperature ≥ 38.1°C) of days spent in hospital, up to study day 30 - % (95% CI)				
Odds ratio (95% CI)				
Missing fever data up to study day 30 – n/N (%)				
All analyses are adjusted for centre and participant.				

Table xx Reasons for transfusions – n/N (%)

Outcome	Active arm (n=)	Placebo arm (n=)	Overall (n=)
Reasons for platelet transfusions			
Prophylaxis for platelet count ≤10x10^9/L			
Prophylaxis and platelet count >10x10^9/L			
Invasive procedure			
Active bleeding			

Missing data for reasons for platelet transfusions			
Reasons for red cell transfusions			
Low haemoglobin			
Active bleeding			
Other			
Missing data for reasons for red cell transfusions			

Table xx Summary of trial treatment

	Arm A (n=)	Arm B (n=)	Overall (n=)
Number of participants ever on treatment – n/N (%)			
Number of days on treatment – median (IQR)			
Number of participants ever on oral treatment – n/N (%)			
Number of days on oral treatment – median (IQR)			
Number of participants who changed route or frequency (N only)* From oral to IV From IV to oral Reduced frequency Increased frequency Reason for frequency change[1] Renal impairment Other			
Missing data for route or frequency change – n/N (%)			
Number of participants who have missed a dose in a 24 hour period – n/N (%)			
Number of participants who have discontinued treatment – n/N (%) >30 days since started treatment Spontaneous increase in platelet count >50 x 10^9/L 3 consecutive days with morning platelet count >30 x10^9/L Received open label TXA, other antifibrinolytic agent or procoagulant drug Started anticoagulant or antiplatelet therapy Visible haematuria Diagnosis of thrombosis Anuric			

Developed sinusoidal obstructive syndrome			
Clinical decision			
Unacceptable adverse reaction to trial treatment			
Change in participant's condition			
Participant's decision			
Missing data for reason for discontinuation of treatment – n/N (%)			

* Participants may appear more than once

[1] Reason for frequency change not reported for 1 participant.

Table xx Location of bleeding – n/N (%)

Location of bleeding	Active arm (n=)	Placebo arm (n=)	Overall (n=)
Skin			
Oropharyngeal			
Epistaxis			
Gastrointestinal			
Blood in urine			
Soft tissue and musculoskeletal			
Haemoptysis			
Invasive procedure			
Abnormal vaginal bleeding			
Retinal or vitreous			
Body cavity/other			
Subconjunctiva of the eye			

Table xx Other outcomes – n/N (%)

Outcome	Active arm (n=)	Placebo arm (n=)	Overall (n=)
Number of participants on Mylotarg up to study day 30			
Missing Mylotarg data up to study day 30			
Number of granulocyte transfusions/participant up to study day 30			
Missing granulocyte transfusion data up to study day 30			
Number of participants requiring interventions and procedures for bleeding up to study day 30			
Missing data for interventions and procedures for bleeding up to study day 30			

Number of participants requiring concomitant medication up to study day 30			
Missing data for concomitant medication up to study day 30			

5.8 Sub-group analysis tables

Table xx Primary outcome - UK participants vs Australian participants [table will only be produced if evidence of heterogeneity at the interim analysis]

	UK		**Australia**	
	Active arm (n=)	**Placebo arm (n=)**	**Active arm (n=)**	**Placebo arm (n=)**
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - n/N (%)				
Hazard ratio (95% CI)				
P-value for interaction term				
All primary outcome analyses are adjusted for centre.				

Table xx Primary outcome - Platelet count at consent (≤30x10^9/L vs. >30x10^9/L)

	≤30x10^9/L		**>30x10^9/L**	
	Active arm (n=)	**Placebo arm (n=)**	**Active arm (n=)**	**Placebo arm (n=)**
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - n/N (%)				
Hazard ratio (95% CI)				
P-value for interaction term				
All primary outcome analyses are adjusted for centre.				

Table xx_a Primary outcome - Treatment compliance during first 30 days of the trial (participant decided to stop taking trial treatment vs. participant did not decide to stop taking trial treatment)

	Participant decided to stop trial treatment	**Participant did not decide to stop trial treatment**

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	Active arm (n=)	Placebo arm (n=)	Active arm (n=)	Placebo arm (n=)
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - n/N (%)				
Hazard ratio (95% CI)				
P-value for interaction term				
All primary outcome analyses are adjusted for centre.				

Table xx_b Primary outcome - Treatment compliance during first 30 days of the trial (participant decided to stop taking trial treatment during the period of over-encapsulated oral treatment; participant decided to stop taking trial treatment during the period of oral treatment as tablets; participant did not decide to stop taking trial treatment during the period of over-encapsulated oral treatment; participant did not decide to stop taking trial treatment during the period of oral treatment as tablets)

	Participant decided to stop trial treatment during the period of over-encapsulated oral treatment		Participant decided to stop taking trial treatment during the period of oral treatment as tablets		Participant did not decide to stop taking trial treatment during the period of over-encapsulated oral treatment		Participant did not decide to stop taking trial treatment during the period of oral treatment as tablets	
	Active arm (n=)	Placebo arm (n=)	Active arm (n=)	Placebo arm (n=)	Active arm (n=)	Placebo arm (n=)	Active arm (n=)	Placebo arm (n=)
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - n/N (%)								
Hazard ratio (95% CI)								
P-value for interaction term								
All primary outcome analyses are adjusted for centre.								

5.9 Sensitivity and missing data analysis tables

Table xx Baseline characteristics for all randomised participants vs. all randomised participants with platelet count ≤30x10^9/L – data are number (%) for categorical variables, and mean (SD) for continuous variables

	Randomised participants		Randomised participants with platelet count ≤30x10^9/L	
	Active arm (n=)	Placebo arm (n=)	Active arm (n=)	Placebo arm (n=)
Male				
Age (years)				
Ethnicity White Asian Black African Black Caribbean Arab/other Middle East ancestry Aboriginal Other Mixed ethnic group: White/Black Caribbean White/Black African White/Asian White/Aboriginal White/Other Other mixed ethnic group				
Height (cm)				
Weight (kg)				
Diagnosis AML ALL APL CML CLL Hodgkins Lymphoma Non-Hodgkins Lymphoma Myeloma MDS Other				
Treatment plan Induction chemotherapy Consolidation chemotherapy Autograft Allograft Other				
Platelet count at consent (x 10^9/L)				

Platelet count at randomisation (x 10^9/L)				
Haemoglobin at consent (G/L)				
Haemoglobin at randomisation (G/L)				
FACT-G subscale score at randomisation				
Physical well-being				
Social/family well-being				
Emotional well-being				
Functional well-being				
FACT-G total score at randomisation				
FACT-Th total score at randomisation				
Medical history				
Diabetes requiring treatment				
Hypertension requiring treatment				
Renal impairment requiring treatment				
Confirmed invasive fungal infection				
Other malignancy				
HLA antibodies				

Table xx Per protocol analysis

	Active arm (n=)	**Placebo arm (n=)**	**Overall (n=)**	**P value**
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - n/N (%)				
Hazard ratio (95% CI)				
Risk difference (95% CI)				
Protocol adherence[1] – n/N (%)				
Risk difference[2] (95% CI) – instrumental variable analysis				
All primary outcome analyses are adjusted for centre. [1] Participants included in the mITT analysis who adhered to the minimum compliance criteria.				

[2] Calculated as the mITT risk difference/proportion adhering to the minimum compliance criteria in the active treatment arm

Table xx Primary outcome analysis with imputation of missing bleeding assessments

	Active arm (n=)	Placebo arm (n=)	Overall (n=)	P value
Proportion of participants who die or have bleeding of WHO grade 2 or above from day 1 up to study day 30 - n/N (%)				
Hazard ratio (95% CI)				
Risk difference (95% CI)				

Table xx Bleeding between platelet count first ≤30 x 10^9/L and start of trial treatment – n/N (%)

	Active arm (n=)	Placebo arm (n=)	Overall (n=)
Number of days between platelet count first ≤30 x 10^9/L and start of trial treatment - mean (SD)			
Number of bleeds between platelet count first ≤30 x 10^9/L and start of trial treatment - mean (SD)			
Number of bleeds of grade 2 or above between platelet count first ≤30 x 10^9/L and start of trial treatment - mean (SD)			

5.10 Figures

- CONSORT diagram
- Median platelet count from consent up to study day 30, by treatment arm
- Overall survival from randomisation to study day 120, by treatment arm
- Highest grade of bleeding a participant experiences, by treatment arm

6 Statistical Analysis Plan Amendments

Revision History:

Version	Author	Date	Reason for revision
1.1	EC	13/03/2020	• Added summary of numbers of participants who discontinued trial treatment during the period oral treatment was unavailable in the UK. • Added footnote to interim analysis. • Added minor changes to correct typos suggested by Ian Franklin. • Agreed by TMG to include ineligible participants randomised in error in the ITT analysis.

7 References

1. MPD998 Statistical Analysis and Reporting
2. TREATT bleedgrades v1.2 03_11_2017
3. Collett D. Modelling survival data in medical research. Florida: Chapman & Hall/CRC, 2003.
4. Stanworth SJ, Estcourt LJ, Powter G, Kahan B, Dyer C, Choo L, et al. A no-prophylaxis platelet transfusion strategy for hematologic cancers. N Engl J Med. 2013;368(19):1771-80.
5. Van Buuren, S. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical Methods in Medical Research* 2007; 16: 219–242.

Appendix 1

Table xx Reported SAEs

Pt ID	Treatment arm	Description	Serious criterion	TREATT Classification

Table xx Unexpected adverse reactions

Pt ID	Treatment arm	Description	TREATT Classification	Causality

Table xx Thrombotic events

Pt ID	Treatment arm	Type of thrombotic event	Serious criterion

Table xx Veno-occlusive disease

Pt ID	Treatment arm	Bilirubin at diagnosis	Serious criterion