NHS Blood and Transplant

CRYOSTAT-2

A multi-centre, randomised, controlled trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring major haemorrhage protocol (MHP) activation

Early cryoprecipitate in trauma

Queen Mary University of London

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Statistical Analysis Plan

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1. Background and Design

The main characteristics of this trial have been summarised using the CRYOSTAT-2 Protocol v4.0 from 15/02/2022. 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

This is a multi-centre, randomised, controlled trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring major haemorrhage protocol (MHP) activation. The study will be run and conducted in the UK and USA.

The ultimate goal of this trial is to investigate the effects of transfusing early high dose cryoprecipitate (which is a concentrated source of fibrinogen), to adult trauma patients with severe bleeding within 90 minutes of admission to hospital. This study will evaluate whether early cryoprecipitate (equivalent of 6g fibrinogen replacement) during major traumatic haemorrhage will reduce mortality.

1.2 Patient Eligibility Criteria

Patients are eligible for this trial if:

1. The participant is judged to be an adult (according to local practice, e.g. 16 years or older in UK) and has sustained severe traumatic injury
2. The participant is deemed by the attending clinician to have on-going active haemorrhage
   AND REQUIRES:
3. Activation of the local major haemorrhage protocol for management of severe blood loss
   AND HAS STARTED or HAS RECEIVED:
4. At least one unit of any blood component

A patient will not be eligible for this trial if they fulfil one or more of the following criteria:

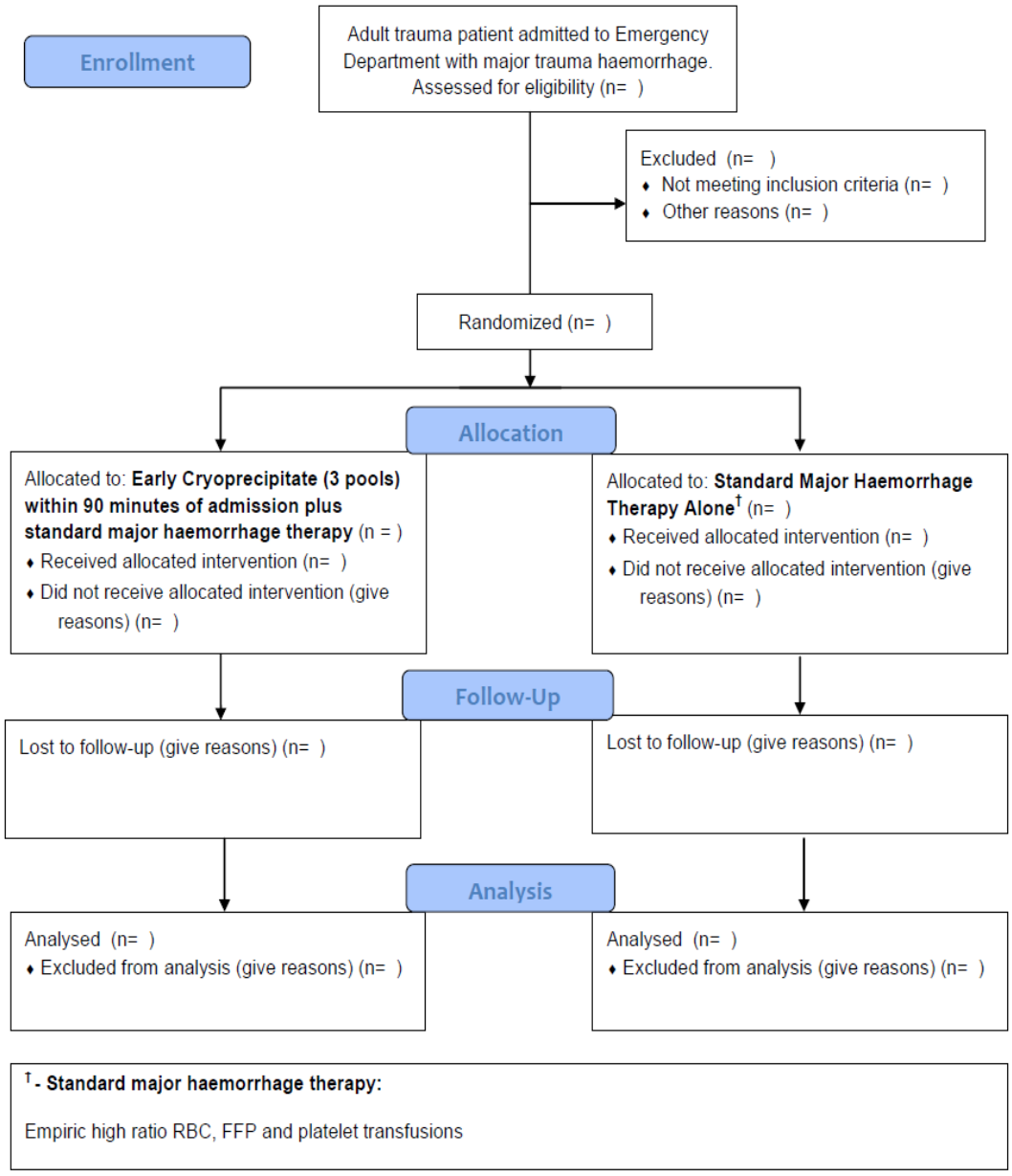
1. The participant has been transferred from another hospital
2. The trauma team leader deems the injuries incompatible with life
3. More than 3 hours have elapsed from the time of injury (taken as time of the 999 call if unknown by medical team).

1.3 Trial Intervention

Intervention arm:
Early intravenous infusion of cryoprecipitate (3 pools of cryoprecipitate – the equivalent to 15 single units of cryoprecipitate or 6g fibrinogen), within 90 minutes of admission to hospital in addition to standard major haemorrhage therapy.

Comparator arm:
Major haemorrhage therapy alone.

Figure 1 Summary of trial entry, randomisation and treatment



1.4 Randomisation and Blinding Procedures

Participants will be allocated in a 1:1 ratio to either intervention (early cryoprecipitate) or comparator (standard MHP) arm. The allocation sequence will be produced by the trial statistician using SAS statistical software. It will have a varying block size that will not be disclosed, and will be stratified by centre.

Allocation cards will be prepared independently and in advance by the CTU and provided to participating sites. Each envelope will contain a randomisation number and the allocated treatment. Envelopes will be opened in sequential order.

Members of the trauma team and study research personnel will enrol participants and assign them to the randomised treatment.

1.5 Sample size calculation

Initial recruitment plans were based on the initial sample size of 1568 patients. An estimate of 380 participants at UK sites and 140 participants at international sites per year, allows around 1568 to be recruited over 3 years, with approximately 1142 from UK and 426 from international sites.

The sample size has been calculated to use 90% power to detect a reduction in 28 day all-cause mortality of 7% (from 26% to 19%) using a 5% level of significance and a two tailed test. An initial blinded analysis after the first 300 participants have been recruited and followed-up to 28 days will allow us to reassess sample size requirements and recruitment rates, and if necessary modify the design of the study. A group sequential design has been used to allow for the Data Monitoring Committee reviewing the primary outcome for evidence of harm or benefit after 500 and 1000 participants have been followed-up for 28 days.

Allowing for the interim analyses in this way, the required sample size to meet specified power requirements is 1530 participants in total. We initially increased this by 2.5% to allow for drop out, but drop out was higher than anticipated, so this was later increased (in protocol 3.1) to 4.4% leading to a total of 1600 participants. This is a target sample size of 800 participants per arm. Opening US sites was also extremely challenging so in protocol v2.0 the recruitment target was set across the whole trial, rather than specific targets for each country separately. A larger proportion of patients will therefore be recruited in the UK.

2. Data Handling

2.1 CRF descriptions and data collection schedule

CRF	Completion requirement
Form 1: Screening: eligibility checklist	Compulsory, enrolment
Form 2: Pre-hospital information	Compulsory, enrolment
Form 3: Randomisation	Compulsory, randomisation
Form 4: Cryoprecipitate administration in Emergency department	Compulsory, 90mins from arrival at hospital
Form 5: 6 and 24 hours from arrival in emergency department	Compulsory, 6 hours, 24 hours
Form 6: Study completion form	Compulsory, to be either completed at either study day 28 (± 4 days), day of discharge or death (whichever is sooner)
Form 7: Hospital stay form	Compulsory, to be either completed at either study day 28 (± 4 days), day of discharge or death (whichever is sooner)
Form 8: Health questionnaire	Complete if applicable, EQ-5D-5L at discharge or day 28 (± 4 days) whichever is sooner
Form 9: Health questionnaire: EQ-5D-5L	Complete if applicable, at discharge or day 28 (± 4 days) whichever is sooner
Form 10: Glasgow outcome scale	Complete if applicable at discharge or day 28 (± 4 days) whichever is sooner

Form 11: Serious adverse event (SAE)	Complete if applicable, record from randomisation until discharge or Study day 28 and if death occurs
Form 12: Serious adverse event (SAE) narrative form	Complete if SAE reported on Form 11
Form 13: Serious transfusion related adverse event	Complete if applicable
Form 14: Serious transfusion related adverse event narrative from	Complete if serious transfusion related adverse event is reported on Form 11
Form 15: Study withdrawal form	Complete if applicable- any participant who was withdrawn from the trial prior to study day 28

Timepoint*	***On arrival at hospital***	***Enrolment***	***Post randomisation***					
		T_0	T_1	T_2	T_3	T_4	T_5	T_6
ENROLMENT								
Eligibility Screen		*X*						
Emergency waiver		*X*						
Randomisation/allocation		*X*						
INTERVENTION			◄►					
Cryoprecipitate (3 pools, 15 units) in addition to MHP			*X*					
Major haemorrhage protocol (MHP) alone			*X*					
ASSESSMENTS								
Participant characteristics		*X*						
Clinical assessment		*X*						
TXA administration			*X*					
RBC, FFP, cryo, platelets (including given pre-hospital)	*X*				*X*			
Mortality			*X*	*X*	*X*	*X*	*X*	*X*
Serious Adverse Events					*X*	*X*		
Participant destination at discharge						*X*		
Glasgow Outcome Score						*X*	*X*	
EQ5D-5L						*X*	*X*	
**Timepoints are:*	*T_0 – Enrolment & allocation of early cryoprecipitate, must be within 90 minutes of arrival at hospital* *T_1 – cryoprecipitate administered, must be started within 90 minutes of arrival at hospital* *T_2 – 6 h (± 1 h) from arrival at hospital* *T_3 - 24h (± 4 h) from arrival at hospital* *T_4 – date of discharge or day 28 (± 4 days) from arrival at hospital whichever is the sooner* *T_5 - 6 months (± 14 days)* *T_6- ≥12 months (mortality data post discharge to be captured by flagging with the ONS)*							

2.2 Procedures for recording and reporting outcomes

The Principal Investigator has overall responsibility for data collection at Sites on designated paper Case Report Forms. Participant data will be sent to NHSBT CTU for data entry onto the trial database, MACRO™, a commercially available FDA 21 CRF Part 11 compliant clinical trial database system produced by Elsevier. Data will be recorded on paper CRFs which will be compiled by the CTU. Three participant identifiers (Participant ID allocated at enrolment, initials and site number) will be captured on the CRF. 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.

If a participant has been discharged prior to day 28 (±4 days) – centralised mortality data will be captured via the Office for National Statistics (ONS), specifically at six- and twelve-months. Participants' health records enrolled at MTCs in England will be flagged for death up to 1 year from date of admission. In the unlikely event that mortality data are not available, or a participant is considered lost to follow up, the research team at the study centre will be asked to contact the participant's GP to confirm their survival status, and if appropriate, contact the patient. Patients will be fully informed of this mechanism and asked to consent to being contacted in such circumstances via written informed consent.

Quality of life data at hospital discharge and 6 months from the time of injury (± 14 days) will be collected via the Trauma and Audit Research Network (TARN).

2.3 End-point Review Panel assessments/SAE Review

All SAEs will be adjudicated by at least one clinical member of the central trial team. They will adjudicate the categorisation (including cause of death for deaths) and causality of the SAE and their judgements will be used for the analysis, if they differ from centre reporting. Any differences in adjudication between reviewers on the same SAE will be resolved by the Chief Investigator.

2.4 Other assessments

Hospital resource use up to discharge or day 28 (whichever is the sooner) will be calculated from information provided as part of the study CRF.

2.5 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 extracted into a statistical software package and used for final analysis.

3. Detailed Analysis Plan

3.1 Interim analysis and sample size re-estimation (if applicable)

An internal pilot phase will be completed 12 months from the date of the first site opening. Our enrolment criteria for progression to the full trial will be i) stop if fewer than 200 participants are recruited at 12 months, ii) recruit additional centres if between 200-300 participants, iii) continue if at or above target (300 participants) at 12 months. There will be no statistical modelling for this pilot phase, just a comparison of the number of randomised participants 12 months after the first site opened against these different thresholds.

If the pilot determines the trial continues, an interim blinded analysis will be performed after 300 participants have been recruited and been followed up to Day 28. The primary purpose will be to confirm the sample size for the primary efficacy outcome of all-cause mortality. The overall 28-day mortality rate across both arms will be calculated for these 300 participants to maintain blinding. If 28-day mortality is not definitively known for at least 80% of participants, the sample size re-estimation will be repeated at the next interim analysis when the information is available using all participants for whom NHS Digital matching was possible. This is because the inferences used will tend towards underestimating the mortality rate which would underestimate the required sample size. Following review of the sample size re-estimation, the Data Monitoring Committee recommended that a second sample size re-estimation is conducted when around 750 participants have been recruited, but at a time to fit in with any request to the funder for an extension to the trial recruitment period.

Any increase or decrease in the 28-day mortality rate from rates used in the sample size calculation (26% in the standard arm, 19% in the control arm, 22.5% overall) will be assumed to apply equally to both arms to maintain a treatment difference of 7% and used to re-estimate the sample size required for the overall study. The proportion of drop-out will also be summarised and compared against the 2.5% drop-out rate allowed for in the sample size calculation. If the re-evaluated sample size is appreciably larger than 1568 in total (>5% larger), detailed consideration, involving the Trial Steering Committee and the funding agencies will be given to whether it is clinically important, cost-effective and feasible to continue the study. Such detailed consideration will include the level of uncertainty in the overall mortality rate based on 300 observations (approx. ±5%), and consequent uncertainty in the required sample size.

If the pilot and first interim analysis determine the trial continues, further interim analyses will be performed after 500 and 1000 participants have been recruited and followed-up for 28 days, with outcomes available for at least 90% of participants. At these recruitment points, the treatment effect observed will be compared against O'Brien-Fleming boundaries for harm or benefit. Results will be passed to the DMC to guide their review of the primary outcome data. The stopping rules will be used as a guideline, alongside the other safety data available to the DMC, and used as part of their overall assessment of the trial. They will have overall oversight and can recommend terminating the trial early for these or any other safety concerns.

3.2 Analysis principles

This analysis plan includes analysis of all outcomes up to 28 days. The analysis of later outcomes will follow in a second analysis plan.

The main analysis will be by intention to treat. Intention to treat analysis will include all randomised participants on whom values of a response variable have been obtained. The data will be analysed according to the treatment arm to which the participant was randomised.

Participants who did not meet all the inclusion criteria and/or met at least one of the exclusion criteria, or those who were co-enrolled in other trials without approval, will be considered as randomised in error. Participants who were randomised to the early cryoprecipitate arm, and did not receive at least 3 pools of cryoprecipitate, or did not start their first infusion of cryoprecipitate within 90 minutes of admission or more than 3 hours from injury will be considered as protocol deviations, together with any other significant deviations from the protocol. The CIs will review all other deviations and advise on which are clinically significant and affect the analysis and should be removed from per protocol analysis. Participants randomised in error, participants with protocol deviations and those withdrawn will be included in the intention to treat analysis where possible. Participants lost to follow up will also be included in the analysis where possible. Those who consented to and were enrolled and randomised in the trial will be analysed, even if they did not receive the assigned intervention, to understand reasons for failure to complete the assigned strategy.

Per protocol definition: Per protocol analysis will be conducted as a sensitivity analysis. As there is no placebo used in the study, per protocol analysis which excludes participants who do not receive trial treatment would differentially exclude those in the intervention arm. Per protocol analysis will therefore focus on the cohort of participants who could have benefitted from the intervention and only exclude significant protocol deviations unrelated to the details of cryoprecipitate administration (timing, number of pools), randomisations in error, those who died within 90 minutes of admission and those who did not receive any blood products after arrival at hospital (an indication of those who had already stopped bleeding). A summary of the number of patients excluded in each category, overall and by arm, will be presented with counts and percentages. Per protocol analysis will be presented for all mortality endpoints up to 28 days (6h, 24h and 28d), transfusion requirements, hospital stay and thrombotic events. Per protocol analysis will be conducted according to the treatment arm to which the participant was randomised.

Recruitment by centre will be presented to show the proportion of screened patients who were eligible then randomised into the trial, the number of patients randomised at each site and the proportion of these who were included in the per protocol analysis. Details of participants withdrawn, randomised in error and any protocol deviations will be presented, describing the reason and circumstances in each case and whether or not they were included in per protocol primary outcome analysis. The key demographics and clinical condition of the participants randomised will be presented for each arm of the trial to describe the intention to treat and per protocol cohorts. A CONSORT diagram will be presented to show how participants progressed through the trial.

Primary and secondary outcomes will be presented by treatment arm as numbers, percentages, means, medians and rates as appropriate. Standard deviations, interquartile ranges and ranges will also be presented to describe the uncertainty in the estimates and the spread of the data. Where there is interest in differences between treatment arms, statistical tests will be performed and these will be indicated in the tables. This study has been powered to detect a difference between treatment arms in the primary outcome of 28 day all-cause mortality only. There may not be sufficient power to detect differences between arms for the secondary outcomes.

For all analyses, participants reported alive on the Day 28 form (which can be completed between days 24 and 32), will be assumed to be alive on day 28. If 28-day mortality is not definitively known, data from the ONS will be used to determine the primary outcome wherever possible (assuming the absence of a death record means the patient was alive 2 weeks before the trace was conducted), otherwise any participant discharged from the major trauma centre will be inferred to be alive at 28 days. Participants with missing primary outcome data will be excluded.

The primary outcome will be presented as counts and percentages, and after adjustment for centre and then any other statistically significant participant factors. All other analyses will be unadjusted for participant factors. Where odds ratios and relative risks are reported, they will be adjusted for centre through the inclusion of a random effect term in a mixed model, as centre is used in the randomisation process. Marginal effect models will be used to allow for this clustering and p-values for these models will relate to the Wald test for the treatment term in the model. For any other models where marginal effects are not used, p-values will be obtained by comparing -2 x log-likelihood value for models with and without the treatment term. Risk-adjusted odds ratios will be estimated using a logistic regression model. Risk-adjusted relative risks will initially be estimated using a binomial log-linear model. If the model has issues with convergence a Poisson model with robust variance estimator will be used as an alternative.

All descriptive statistics will be unadjusted. All tests will be two-sided and p-values of less than 0.05 will be considered as statistically significant. The exception to this is the primary outcome analysis where the p-value threshold for the final stage of the sequential design will be used. At the time of sample size calculation this was anticipated to be 0.0453, but the final value used will be stated in the Data Analysis Report as it will depend on the final sample size and exactly when interim analyses were conducted. All odds ratios and relative risks will be presented for the early cryoprecipitate arm relative to the standard MHP arm. A ratio which is greater than 1 indicates that the odds or risk of the event is greater in the early cryoprecipitate arm. Two-sided 95% confidence intervals will be presented with all ratios. P-values will be reported to four decimal places with p-values less than 0.0001 as <0.0001. The statistical package SAS will be used to conduct analyses.

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 as all analyses have been pre-specified.

3.3 Analysis of primary outcome measures

The analysis of all-cause mortality at 28 days from arrival at hospital will include all randomised participants where this outcome is known. The proportion of participants for whom 28 day vital status was not available from any source will be summarised by treatment arm.

The proportion of participants who died on or before day 28 from admission will be presented by treatment arm. The relative risk and odds ratio for death within 28 days for those in the early cryoprecipitate arm, relative to the standard arm, with 95% confidence intervals, will also be presented, adjusted for centre using a random effect term. This odds ratio adjusted for centre will be the primary analysis of the outcome, and the p-value for the treatment arm term in this mixed logistic regression model will be presented. A Kaplan-Meier plot of survival to day 28 by treatment arm will be presented.

For US participants only, the primary outcome will be presented separately for participants of different races and ethnicities. Due to the small number of US participants, there will no hypothesis testing for the treatment effect in each group and no subgroup analysis will be conducted to describe race by treatment arm or ethnicity by treatment arm interactions.

Logistic regression analysis for death within 28 days will be performed, to assess the effect of treatment arm after adjusting for other relevant factors. The factors to be considered for inclusion in the model are: age, type of injury (blunt/penetrating), SBP, GCS, early bolus of TXA (pre-hospital or in the ED), ISS and sex. Factors will only be added to the logistic regression model if they are statistically significant in improving the model fit at the 10% level. A random effect term for centre will be included in the model. Multiple imputation based on full conditional specification will be used to impute any missing values for these potential risk adjustment factors. The set of variables used in the multiple imputation models will be: age, type of injury (blunt/penetrating), SBP, GCS, early bolus of TXA, ISS, sex, heart rate and treatment arm. The same risk factors identified for the intention to treat analysis will be applied for the per protocol analysis.

The adjusted odds ratio for death within 28 days for the early cryoprecipitate arm, relative to the standard arm, with 95% confidence interval, following adjustment for any significant participant factors and centre will be presented. The adjusted odds ratio for death within 28 days, 95% confidence interval and p-value will be presented for each factor in the logistic regression model.

28 day mortality will also be presented for the early cryoprecipitate arm according to the following categories of cryoprecipitate administration timing (when first cryoprecipitate was started): ≤45 mins from admission, 46-60 mins, 61-90 mins and over 90 mins. Participants randomised to the early cryoprecipitate arm who did not receive cryoprecipitate, or where the timing was unknown, will be excluded. Relative risks and odds ratios with 95% confidence intervals, adjusted for centre, will also be presented for each time category relative to the standard treatment arm, together with p-values from the Wald test which tests the null hypothesis each odds ratio is 1 given other terms in the model. A Kaplan-Meier plot of survival to day 28 for the standard MHP arm and each of the four categories of cryoprecipitate timing in the early cryoprecipitate arm will be presented. Histograms of time from admission to first cryoprecipitate will be presented by arm for those with timing of first cryoprecipitate reported.

To assess the effect of timing of cryoprecipitate administration on 28 day mortality, after adjustment for other significant factors, in the subgroup of participants who were randomised to early cryoprecipitate and received it with the timing reported, time from admission to cryoprecipitate administration will be added to the logistic regression analysis described above as a linear term. Evidence of non-linearity in the relationship between cryoprecipitate timing and the log odds ratio of death within 28 days will be assessed by examining the model residuals. If there is evidence of non-linearity, cryoprecipitate timing will instead be fitted as a spline term in the model.

28-day mortality will also be presented for the early cryoprecipitate arm according to the whether they did or did not receive any cryoprecipitate as the trial intervention. Relative risks and odds ratios with 95% confidence intervals, adjusted for centre, will also be presented for each group relative to the standard treatment arm, together with p-values from the Wald test which tests the null hypothesis each odds ratio is 1 given other terms in the model. A Kaplan-Meier plot of survival to day 28 for the standard MHP arm and those who did or did not receive cryoprecipitate in the early cryoprecipitate arm will be presented.

Cause of death will be summarised for all patients that died, by treatment arm, with counts and percentages.

3.4 Analysis of secondary outcome measures

For each of the secondary outcome measures, the data presented and any statistical tests performed are described below. In all cases data will be presented for each arm of the trial separately, and overall.

All-cause mortality (including death from bleeding) at 6 hours and 24 hours from admission
The proportion of participants who died from any cause at 6 hours and 24 hours from admission will be presented. The adjusted relative risk and odds ratio, with 95% confidence intervals, will be presented for 6 and 24 hour mortality for the early cryoprecipitate arm relative to the standard arm.

Death from bleeding at 6 hours and 24 hours
The proportion of participants who died from bleeding at 6 hours and 24 hours from admission will be presented by treatment arm. The adjusted relative risk and odds ratio, with 95% confidence intervals, will be presented for each outcome for the early cryoprecipitate arm relative to the standard arm, utilising exact regression models if the number of events is small, if separation occurs or if the standard regression model does not converge. Death from bleeding will be defined as those cases where cause of death is reported as 'uncontrolled bleeding' on the CRF. For those who died from bleeding, median (IQR) time to death from bleeding will be reported.

Transfusion requirements, in numbers of units, for RBC, platelets, FFP & cryoprecipitate at 24 hours from admission, including pre-hospital transfusion
The number of RBC, platelets, FFP, cryoprecipitate units and total blood products transfused per participant from injury to 24 hours after admission will be summarised as a median and interquartile range, first for all participants and then for those who survived at least 24 hours. The mean number of RBC, platelets, FFP, cryoprecipitate units and total blood products transfused per participant per hour from injury to 24 hours will also be summarised, adjusted for centre, and compared using a negative binominal regression model. Box and whisker plots will be used to summarise the number of units of each product type administered up to 24 hours from admission by treatment arm.

The proportion of participants who received cryoprecipitate at any time will be summarised by treatment arm. For those who received cryoprecipitate, the time from admission to the time the first cryoprecipitate was started will be described for each arm using median, interquartile range and range. Median time to first cryoprecipitate infusion will be compared between arms using the Mann-Whitney test. The proportion of participants who received their first infusion within 90 minutes of admission, adjusted for centre, will be presented by treatment arm and compared using a logistic regression model. The proportion will also be presented by study year, to assess whether there is any contamination over time of early cryoprecipitate being used more as part of standard therapy. A logistic regression model will be used to examine any such trend in the standard arm by adding a linear term for study year to the model. If any participants in the early cryoprecipitate arm did not receive cryoprecipitate at all, or within 90 minutes, the reasons will be summarised.

The proportion of participants in the early cryoprecipitate arm who received 3 or more early pools will also be summarised together with the proportion of participants in each arm who received 3 or more pools of cryoprecipitate within 24 hours. If any participants in the early cryoprecipitate arm received < 3 early pools, the reasons will be summarised.

Destination of participant at time of discharge from hospital
The number and percentage of participants discharged from hospital will be summarised by arm. The location the participants were discharged to will be summarised as number and percentage for each arm of the trial.

Quality of life measures: EQ5D-5L and Glasgow Outcome Score at discharge
For the EQ-5D-5L descriptive systems questionnaire, the number and percentage of participants who have completed the index value questions and health today question will be presented by arm. In addition, median (IQR) and mean (standard deviation) index value will be calculated, along with Cohen's d and a 95% confidence interval for the standardised difference in mean index values between arms. The index value allows the five health dimensions to be converted into a single numeric measure, with higher values reflecting better health. 1 relates to 'perfect health' and 0 to 'dead', but some index values can be negative. The Mann-Whitney test will be used to examine whether the difference in median index values is significant between the two treatment arms. For EQ Visual Analogue Scale (VAS), median (IQR) and mean (standard deviation) self-evaluated health score will be calculated, along with Cohen's d and a 95% confidence interval for the standardised difference in mean self-evaluated health score between arms. This score has a range of 0-100, with higher values reflecting better health. The Mann-Whitney test will be used to examine whether the difference in median self-evaluated health score is significant between the two treatment arms.

For the Glasgow Outcome Scale (GOS) at discharge or Day 28, the number and percentage of participants who have completed the questionnaire will be presented by arm. The number and percentage of participants in each of the five categories will be presented and compared between treatment arms using ordinal regression with a random effect for centre.

Hospital resource use up to discharge or day 28, including ventilator days, hours spent in critical care and in-patient stays
The median and interquartile range of ventilator days and ventilator free days for each arm will be presented. These analyses do not take account of any differential follow-up due to death, therefore comparison between arms will be conducted using competing risks analysis. Extubation will be considered as the event and death prior to extubation will be considered as the competing risk. As there is no standard method for modelling the cumulative incidence function which allows for random effects, this analysis will be unadjusted for centre. The impact of this will be explored through the inclusion of a fixed effect term for centre and the analysis amended if required. The Fine and Gray model will be used to assess any association between treatment arm and ventilator days.

The median and interquartile range of hospital stay, including Level 2 and/or Level 3 stay, will be presented for each arm. As this does not take account of differential follow-up due to death, comparison between arms will be conducted using competing risks analysis. Discharge from hospital will be considered as the event and death prior to discharge will be considered as the competing risk. As there is no standard method for modelling the cumulative incidence function which allows for random effects, this analysis will be unadjusted for centre. The impact of this will be explored through the inclusion of a fixed effect term for centre and the analysis amended if required. The Fine and Gray model will be used to assess any association between treatment arm and hospital stay. First critical care stay (defined as days requiring Level 2 or 3 care) will be assessed using the same methodology, and median (IQR) critical care free days will be reported.

3.5 Other outcome measures

The total number of symptomatic thrombotic events from randomisation up to day 28, death or discharge from hospital of each type will be summarised for participants in each arm of the trial, along with the number of participants affected and the mean number of thrombotic events experienced per participant per week. The cumulative incidence of thrombotic events at day 28 in each arm of the trial will be estimated from a competing risks analysis with death as the competing risk. As there is no standard method for modelling the cumulative incidence function which allows for random effects, this analysis will be unadjusted for centre. The impact of this will be explored through the inclusion of a fixed effect term for centre and the analysis amended if required. The Fine and Gray model will be used to assess the effect of early cryoprecipitate treatment on incidence of thrombotic events.

The volume of crystalloids and colloids infused per participant from injury to 24 hours after admission will be summarised as a median and interquartile range first for all participants and then for those who survived at least 24 hours. The mean volume infused per participant per hour from injury to 24 hours will also be summarised and compared using a linear regression model. The volume of colloids and crystalloids administered from injury to 24 hours from admission will be summarised on a box and whisker plot.

Serious transfusion related adverse events will be summarised by treatment arm and compared using Fisher's exact test, as they are anticipated to be rare.

The use of thromboprophylaxis measures, anticoagulants and their antidotes will be summarised by treatment arm.

The proportion of participants who received tranexamic acid at any point from injury up to 24 hours from admission will be presented by treatment arm. The proportion of participants who receive tranexamic acid from injury up to 24 hours from admission will also be presented for UK and international centres separately. The difference between treatment arms overall and the difference in overall use within 24 hours between countries will be assessed using logistic regression.

3.6 Sub-Group analyses

The main primary outcome analysis (Table 9) will be repeated to assess the heterogeneity of treatment effects for the following subgroups:

a) UK participants vs non-UK participants
b) head AIS <4 vs ≥4
c) participant sex
d) participant age <70 vs ≥70 years
e) injury type blunt vs penetrating

The secondary outcome analysis of 6 and 24 hour mortality will also be repeated for subgroup analysis b) head AIS < 4 vs ≥4.

One main effect term and one interaction term for each of the treatment arm by subgroup categories will be added to the logistic regression model containing only the treatment arm and centre terms, with no risk adjustment for other factors. The statistical significance of adding each interaction term will be reported, along with the odds ratio and 95% confidence interval.

It is hypothesised that cryoprecipitate may have a different impact on reducing 28 day mortality in UK participants than non-UK participants due to different patterns of care and in patients of different ages. It is hypothesised that cryoprecipitate will have a greater impact

on reducing mortality in participants with head AIS <4 than head AIS ≥4, in men rather than women and in blunt rather than penetrating injuries.

Kaplan-Meier plots will be presented for each subgroup analysis.

Details of the intervention delivery will also be summarised for the UK vs non-UK participant subgroups.

3.7 Sensitivity analyses

Missing data for the primary outcome is expected to be minimal due to the hard endpoint and additional data provision from ONS in England and Wales. However, to assess the impact of missing data, two sensitivity analyses will be performed. The first will assess the inference that any participant discharged from the major trauma centre is alive at 28 days. It will assess how the results would change if the inference were incorrect for 2% of those participants inferred (a national audit of major haemorrhage in trauma showed that only 2.2% of patients died between hospital discharge and 1-year[1]). 2% of inferred cases will be randomly selected, without regard for treatment arm, and instead inferred as deceased at 28 days and the primary outcome reproduced. The second sensitivity analysis will use multiple imputation based on full conditional specification if 28-day mortality is missing (after inference) for more than 5% of the participants enrolled. Variables will be included in the imputation model if they have a completeness of ≥65% and these variables are age, type of injury (blunt/penetrating), SBP, GCS, early bolus of TXA, ISS, sex and country. Forty imputations will be used and the average across the imputations will be calculated. The analysis model will include a random effect term for centre. If the proportion of participants with missing 28-day mortality is less than or equal to 5% then this sensitivity analysis will not be performed.

Cases where the only available survival information reports the participant alive between days 24 and 27 will be summarised by arm, and if this exceeds 2% of participants included in the intention to treat analysis, the event rates and odds ratio for the primary outcome analysis will be repeated excluding these participants to see if the assumption of surviving to 28 days affected the analysis.

To assess the treatment effect without risk-adjustment for centre, the unadjusted odds ratio for the primary outcome will also be presented.

If there is a statistically significant difference in the 28-day mortality rate between the two treatment arms, the fragility index will be calculated. This calculates the number of additional deaths needed in the arm with the lowest mortality rate in order to render the result non-significant in unadjusted analysis.

3.8 Procedures for handling Missing Data

Any missing primary and secondary outcome data will be summarised. Primary and secondary outcome measures will not be imputed for primary analyses and these will be treated as missing data and excluded from the relevant analyses. If outcome data is missing for more than 25% of participants, outcomes will not be reported.

Section 3.3 describes the multiple imputation that will be conducted for the secondary risk-adjusted analysis of the primary outcome.

Section 3.7 describes a sensitivity analysis that will be conducted if the primary outcome is missing for more than 5% of participants enrolled.

4. Data Analysis Tables

Data analysis will be based on the following tables. Further tables/rows/columns may be added in the Data Analysis Report if deemed necessary.

4.1 Screening, Recruitment and Follow-up tables

4.1.1 Recruitment by Centre

Table 1 Recruitment by centre

Sites	Total number screened	% Eligible from screened	% Randomised from eligible	Total number randomised	% in per protocol analysis[1]
Royal London Hospital					
John Radcliffe Hospital					
University Hospital Southampton					
St George's Hospital					
St Mary's Hospital, London					
Kings College Hospital, London					
Derriford Hospital, Plymouth					
Addenbrooke's Hospital, Cambridge					
Southmead Hospital, Bristol					
James Cook University Hospital, Middlesbrough					
Leeds General Infirmary, Leeds					
Queen's Medical Centre, Nottingham					
Royal Victoria Infirmary, Newcastle					
Hull Royal Infirmary, Hull					
Northern General Hospital, Sheffield					
Queen Elizabeth Hospital, Birmingham					
Royal Preston Hospital, Preston					
Royal Sussex County Hospital, Brighton					
University Hospital, Coventry					
Royal Stoke University Hospital					
Manchester Royal Infirmary					

Sites	Total number screened	% Eligible from screened	% Randomised from eligible	Total number randomised	% in per protocol analysis[1]
Salford Royal Hospital					
Aintree University Hospital, Liverpool					
University Hospital of Wales, Cardiff					
Royal Victoria Hospital, Belfast					
Houston					
Overall					
[1] Percentage of those randomised					

4.1.2 Participants withdrawn

Table 2 Participants withdrawn

Participant ID	Treatment arm	Reason for withdrawal	Timing of withdrawal (days from admission)	Included in PP primary outcome analysis?

4.1.3 Participants randomised in error

Table 3 Participants randomised in error

Participant ID	Treatment arm	Description of error	Included in PP primary outcome analysis?

4.1.4 Protocol Deviations

Table 4 Summary of protocol deviations - n/N (% of all randomised)Protocol deviation	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
No cryoprecipitate given			
<3 pools cryoprecipitate given			
First cryoprecipitate given >90 mins after admission			

First cryoprecipitate given >3 hours after injury			
Other reason A			
Other reason B			
Other (see next Table)			
Total participants with one or more protocol deviations			

[1] These protocol deviations were considered clinically significant, in addition to those indicated in the 'Other protocol deviations' table (this footnote will only be used if there are any relevant categories)

Note that participants may have had more than one protocol deviation.

Participants with protocol deviations were included in intention to treat analysis wherever possible. The 'Exclusions from per protocol cohort' table summarises the patients that were excluded from per protocol analysis.

Table 5 Other participant protocol deviations

Participant ID	Treatment arm	Description of protocol deviation	Clinically significant?

Participants with protocol deviations were included in intention to treat analysis wherever possible. The 'Exclusions from per protocol cohort' table summarises the patients that were excluded from per protocol analysis.

4.2 Missing Data tables

Table 6 Missing primary outcomes data table – n/N (%)

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Missing data for 28 day vital status			
Missing data for cryoprecipitate timing			
Missing data for cryoprecipitate administered			
Missing race (US participants only)			
Missing ethnicity (US participants only)			
Missing cause of death (for those who died within 28 days)			

Table 7 Missing secondary outcomes data table – n/N (%)

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Missing data for participants who died from any cause			
Mortality at 6 hours from admission			
Mortality at 24 hours from admission			

Missing data for participants who died from bleeding			
Mortality at 6 hours from admission			
Mortality at 24 hours from admission			
Missing data for recording of time to death from bleeding (for those who died from bleeding)			
Missing data for blood product units transfused per participant from injury to 24 hours, for those who survived at least 24 hours			
RBC			
Platelets			
FFP			
Cryoprecipitate			
Total blood products			
Crystalloids			
Colloids			
Missing data for time from admission to first cryoprecipitate (for those who received it)			
Missing data for participants who received their first infusion within 90 mins of admission[1]			
Study year 1 (Jul 17 - 18)			
Study year 2 (Jul 18 - 19)			
Study year 3 (Jul 19 - 20)			
Study year 4 (Jul 20 - 21)			
Study year 5 (Jul 21 – Nov 21)			
Missing data for reason cryoprecipitate not given (where not given)			
Missing data for reason first cryoprecipitate given after 90 minutes (where given >90mins)			
Missing data for reason 1-2 pools of cryoprecipitate were given (where given 1-2 pools)			
Missing data for recorded destination of participant at time of discharge from hospital (for those discharged)			
Missing data for EQ-5D-5L questionnaire needed for index value, completion at discharge or day 28 (where alive)			
Missing data for self-evaluated health score on EQ-5D-5L at discharge or day 28 (where alive)			
Missing data for Glasgow Outcome Scale, completion at discharge or day 28 (where alive)			
Missing data for ventilator days			
Missing data for hospital stay			

Missing data for first critical care stay			

4.3 Baseline Characteristics tables

Table 8 Baseline characteristics – data are number/total number (%) for categorical variables, and median (IQR) for continuous variables

	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Subjects			
Male			
Age (years)			
Time from injury to admission to emergency department (mins)			
Injuries and physiology at admission to emergency department			
Blunt injury			
Injury Severity Score			
Systolic blood pressure (mm Hg)			
Heart rate (per min)			
In cardiac arrest			
Glasgow Coma Score			
Pre hospital			
RBC (units)			
FFP (units)			
Crystalloids (ml)			
Colloids (ml)			
TXA administered			
Race and ethnicity (US participants only)			
White			
Black			
Other race			
Hispanic ethnicity			
Not Hispanic ethnicity			
Unknown ethnicity			

Summary of missing data

4.4 Primary Outcome table(s)

Table 9 All-cause mortality at 28 days by arm

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[2] (95% CI)				
Odds ratio also adjusted for participant factors[3] (95% CI)				
Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] Early Cryo arm relative to Standard arm, adjusted for centre, p-value for treatment term in mixed logistic regression model.

[3] Early Cryo arm relative to Standard arm adjusted for centre and significant participant factors.

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 10 All-cause mortality at 28 days by arm for different races and ethnicities (US participants only)

Participants who died on or before day 28 from admission – n/N (%)	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Black race			
White race			
Other race			
Hispanic ethnicity			
Not Hispanic ethnicity			
Unknown ethnicity			

Table 11 All-cause mortality at 28 days in the standard arm and in the early cryoprecipitate arm by first cryoprecipitate timing

Cryoprecipitate administered at	Mortality rate n/N (%)	Relative risk (95% CI)[1]	Odds ratio (95% CI)[1]	P-value[2]
Standard MHP arm				
Early cryo arm ≤ 45 mins from admission				
Early cryo arm 46-60 mins from admission				
Early cryo arm 61-90 mins from admission				
Early cryo arm > 90 mins from admission				

[1]Cryoprecipitate administered in the time period relative to standard arm overall, adjusted for centre
[2] Wald test p-value from logistic regression model, adjusted for centre

Effect of timing of first cryoprecipitate administration on 28 day mortality

A table or figure to summarise how the first cryoprecipitate timing affects 28 day mortality.

Table 12 All-cause mortality at 28 days in the standard arm and in the early cryoprecipitate arm for those who did or did not receive any cryoprecipitate

Cryoprecipitate group	Mortality rate n/N (%)	Relative risk (95% CI)[1]	Odds ratio (95% CI)[1]	P-value[2]
Standard MHP arm				
Early cryo arm - no cryoprecipitate received				
Early cryo arm - some cryoprecipitate received				

[1] Relative to standard arm overall, adjusted for centre
[2] Wald test p-value from logistic regression model, adjusted for centre

Table 13 Risk-adjusted model for all-cause mortality at 28 days

Risk Factor	Odds ratio[1] (95% CI)	P-value
Risk factor A		
Risk factor B		
.		
.		
.		
Early cryoprecipitate arm		

[1]Adjusted odds ratio from logistic regression model, also adjusted for centre

Table 14 Causes of death for all-cause mortality at 28 days - n/N (% of those who died)

Cause of death	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Total deaths within 28 days – n/N (% of those randomised)			
Multi-organ failure			
Multiple injury			
Myocardial infarction			
Pulmonary embolism			
Sepsis			

Stroke			
Traumatic brain injury			
Uncontrolled bleeding			
Other			
Not reported			
All			

4.5 Secondary Outcome table(s)

Table 15 Mortality data

Outcome	**Std MHP arm (n=)**	**Early cryo arm (n=)**	**Overall (n=)**	**P-value**
Mortality at 6 hours from admission - n/N (%)				
Relative risk (95% CI) for mortality at 6 hours from admission[1]				
Odds ratio (95% CI) for mortality at 6 hours from admission[1]				
Mortality at 24 hours from admission - n/N (%)				
Relative risk (95% CI) for mortality at 24 hours from admission[1]				
Odds ratio (95% CI) for mortality at 24 hours from admission[1]				
Death from bleeding at 6 hours from admission - n/N (%)				
Relative risk (95% CI) for death from bleeding at 6 hours from admission[1]				
Odds ratio (95% CI) for death from bleeding at 6 hours from admission[1]				
Death from bleeding at 24 hours from admission - n/N (%)				
Relative risk (95% CI) for death from bleeding at 24 hours from admission[1]				
Odds ratio (95% CI) for death from bleeding at 24 hours from admission[1]				
Median (IQR) time to death from bleeding in those who bled				
[1] Early Cryo arm relative to Standard arm adjusted for centre, from mixed logistic regression model				

Table 16 Transfusion requirements

Outcome	**Std MHP arm (n=)**	**Early cryo arm (n=)**	**Overall (n=)**	**P-value**

Median (IQR) products transfused per participant from injury to 24 hours				
RBC (units)				
Platelets (units)				
FFP (units)				
Cryoprecipitate (units)				
Total blood products (units)				
Crystalloids (ml)				
Colloids (ml)				
Median (IQR) products transfused per participant from injury to 24 hours, for those who survived at least 24 hours				
RBC (units)				
Platelets (units)				
FFP (units)				
Cryoprecipitate (units)				
Total blood products (units)				
Crystalloids (ml)				
Colloids (ml)				
Mean products transfused per participant per hour over the first 24 hours				
RBC (units)[1]				
Platelets (units)[1]				
FFP (units)[1]				
Cryoprecipitate (units)[1]				
Total blood products (units)[1]				
Crystalloids (ml)[2]				
Colloids (ml)[2]				
Participants who received cryoprecipitate – n/N (%)				
Median time from admission to start of first cryoprecipitate for those who received it[3] (mins)				
IQR				
Range				
Participants who received their first infusion within 90 mins of admission – n/N (%)				
Overall[4]				
Study year 1 (Jul 17 - 18)				

Study year 2 (Jul 18 - 19)				
Study year 3 (Jul 19 - 20)				
Study year 4 (Jul 20 - 21)				
Study year 5 (Jul 21 – Nov 21)				
p-value for change over time[5]				
Participants who received 3 or more pools of early cryoprecipitate– n/N (%)				
Participants who received 3 or more pools of cryoprecipitate in 24h – n/N (%)				
Participants who received tranexamic acid from injury up to 24 hours from admission – n/N (%)				
Overall[4]				
UK centres[6]				
International Centres[6]				

[1] P-value from negative binomial regression model, adjusted for centre

[2] P-value from linear regression model, adjusted for centre

[3] P-value from Mann-Whitney test

[4] P-value from logistic regression model, adjusted for centre

[5] P-value for linear study year term in logistic regression model, adjusted for centre, standard MHP participants only

[6] P-value from logistic regression, adjusted for centre, for difference in overall use between countries

Table 17 Reasons for participants in the early cryoprecipitate arm not being administered cryoprecipitate – n/N (% of those not administered cryoprecipitate)

Reason	**Early cryo arm (n=)**
Total not administered cryoprecipitate – n/N (% of those randomised to early cryo)	
No active bleeding identified	
Patient died	
Reason A	
Reason B	
.	
All	

Table 18 Reasons for participants in the early cryoprecipitate arm receiving first cryoprecipitate after 90 minutes from admission – n/N (% of those administered first cryoprecipitate after 90 minutes)

Reason	**Early cryo arm (n=)**

Total received first cryoprecipitate after 90 minutes – n/N (% of those randomised to early cryo)	
Reason A	
Reason B	
.	
All	

Table 19 Reasons for participants in the early cryoprecipitate arm receiving 1-2 pools of cryoprecipitate – n/N (% of those who received 1-2 pools of cryoprecipitate)

Reason	**Early cryo arm (n=)**
Total received 1-2 pools of cryoprecipitate – n/N (% of those randomised to early cryo)	
Reason A	
Reason B	
.	
All	

Table 20 Quality of life

Outcome	**Std MHP arm (n=)**	**Early cryo arm (n=)**	**Overall (n=)**	**P-value**
Participants who completed EQ-5D-5L index value questions at discharge or day 28 of those alive - n/N (%)				
Participants who completed EQ-5D-5L health today question at discharge or day 28 of those alive - n/N (%)				
Median (IQR) index value at discharge[1]				
Mean (sd) index value at discharge				
Cohen's d for index value at discharge (95% CI)				
Median (IQR) self-evaluated health score at discharge[1]				
Mean (sd) self-evaluated health score at discharge				
Cohen's d for self-evaluated health score at discharge (95% CI)				

Participants who completed GOS questionnaire at discharge of those alive - n/N (%)				
GOS at discharge (N, %)[2]				
Low disability				
Moderate disability				
Severe disability				
Persistent vegetative state				
Death				

[1] P-value for Mann-Whitney test

[2] P-value for ordinal regression, adjusted for centre

Table 21 Hospital Stay

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value
Median (IQR) ventilator days[1,2]				
Median (IQR) ventilator free days[1]				
Median (IQR) hospital stay[1,2] (days)				
Median (IQR) first critical care stay[1,2] (days)				
Median (IQR) critical care free days[1]				
Participants discharged from hospital – n/N (%)				
Destination – n/N (% of those discharged)				
Home				
Nursing home/rehab facility				
Another hospital				
Other				

[1] Crude median and IQR which make no allowance for differential follow up due to death.

[2] P-value from Fine and Gray model to compare cumulative incidence curves which allows for differential follow up due to death.

4.6 Other Outcome summary tables

Table 22 Other outcomes

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value
Thrombotic events – N				
Venous thromboembolism Pulmonary embolus DVT				
Participants affected – n/N (%)				

Mean number of events per participant per week				
Arterial thrombotic events Myocardial infarction Stroke Other occlusion of any other artery				
Participants affected – n/N (%)				
Mean number of events per participant per week				
Cumulative incidence of thrombotic events at day 28 – % (95% CI) [1]				
Serious transfusion related adverse events - n/N (%) [2]				
Thromboprophylaxis measures used – n/N (%)				
Anticoagulants given – n/N (%)				
Antidotes administered for those on anticoagulants – n/N (%)				

[1] P-value from Fine and Gray model

[2] P-value for Fisher's exact test

4.7 Safety data summary tables

N/A – presented in other tables.

4.8 Sub-group analysis table

Table 23 All-cause mortality at 28 days by arm - UK participants vs Non-UK participants

	UK		**Non-UK**	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				
Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] P-value for interaction, adjusted for centre and UK vs non-UK

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 24 All-cause mortality at 28 days by arm - head AIS < 4 vs head AIS ≥ 4

	Head AIS < 4		Head AIS ≥ 4	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				
Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] P-value for interaction, adjusted for centre and AIS < 4 vs AIS ≥ 4

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 25 All-cause mortality at 6 hours and 24 hours by arm - Head AIS < 4 vs Head AIS ≥ 4

	Head AIS < 4		Head AIS ≥ 4	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Mortality at 6 hours from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				
Mortality at 24 hours from admission– n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] P-value for interaction, adjusted for centre and AIS < 4 vs AIS ≥ 4

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 26 All-cause mortality at 28 days by arm – participant sex

	Male		Female	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				

Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] P-value for interaction, adjusted for centre and sex

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 27 All-cause mortality at 28 days by arm – participant age < 70 vs ≥ 70 years

	<70		**≥ 70**	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				
Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] P-value for interaction, adjusted for centre and <70 vs ≥ 70 years

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 28 All-cause mortality at 28 days by arm – injury type blunt vs penetrating

	Blunt		**Penetrating**	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[1] (95% CI)				
P-value for interaction term[2]				
Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] P-value for interaction, adjusted for centre and blunt vs penetrating injury

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 29 Delivery of intervention - UK participants vs Non-UK participants

	UK		**Non-UK**	
Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Std MHP arm (n=)	Early cryo arm (n=)
Participants who received cryoprecipitate – n/N (%)				

Median time from admission to start of first cryoprecipitate for those who received it				
IQR				
Range				
P-value[1]				
Participants who received their first infusion within 90 mins of admission – n/N (%)				
Overall				
P-value[2]				
Study year 1 (Jul 17 - 18)				
Study year 2 (Jul 18 - 19)				
Study year 3 (Jul 19 - 20)				
Study year 4 (Jul 20 - 21)				
Study year 5 (Jul 21 – Nov 21)				
P-value for change over time[2]				
Participants who received 3 or more pools of early cryoprecipitate – n/N (%)				
Participants who received 3 or more pools of cryoprecipitate in 24h – n/N (%)				

[1] P-value for Mann-Whitney test
[2] P-value from logistic regression, adjusted for centre

4.9 Sensitivity analysis tables

Table 30 Exclusions from per protocol cohort, by arm – n/N (%)

Reason for exclusion	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Randomised in error			
Clinically significant protocol deviation[1]			
Died within 90 minutes of arrival			
No blood products after arrival			
Included in per protocol analysis			

[1] As indicated in 'Summary of protocol deviations' or 'Other protocol deviations' tables

Table 31 Baseline characteristics – data are number/total number (%) for categorical variables, and median (IQR) for continuous variables, per protocol

	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Subjects			
Male			
Age (years)			
Time from injury to admission to emergency department (mins)			
Injuries and physiology at admission to emergency department			
Blunt injury			
Injury Severity Score			
Systolic blood pressure (mm Hg)			
Heart rate (per min)			
In cardiac arrest			
Glasgow Coma Score			
Pre hospital			
RBC (units)			
FFP (units)			
Crystalloids (ml)			
Colloids (ml)			
TXA administered			
Race and ethnicity (US participants only)			
White			
Black			
Other race			
Hispanic ethnicity			
Not Hispanic ethnicity			
Unknown ethnicity			
Summary of missing data			

Table 32 All-cause mortality at 28 days by arm, per protocol

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value
Participants who died on or before day 28 from admission – n/N (%)				
Relative risk[1] (95% CI)				
Odds ratio[2] (95% CI)				
Odds ratio also adjusted for participant factors[3] (95% CI)				
Participants for whom 28 day vital status was not available from any source – n/N (%)				

[1] Early Cryo arm relative to Standard arm, adjusted for centre

[2] Early Cryo arm relative to Standard arm, adjusted for centre, p-value for treatment term in mixed logistic regression model.

[3] Early Cryo arm relative to Standard arm adjusted for centre and significant participant factors.

Note: Participants for whom 28 day vital status was not available were not included in this analysis in addition to x participants excluded due to x, y and z.

Table 33 All-cause mortality at 28 days by arm for different races and ethnicities (US participants only), per protocol

Participants who died on or before day 28 from admission – n/N (%)	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Black race			
White race			
Other race			
Hispanic ethnicity			
Not Hispanic ethnicity			
Unknown ethnicity			

Table 34 All-cause mortality at 28 days in the standard arm and in the early cryoprecipitate arm by first cryoprecipitate timing, per protocol

	Mortality rate n/N (%)	Relative risk (95% CI)[1]	Odds ratio (95% CI)[1]	P-value[2]
Standard MHP arm				
Early cryo arm ≤ 45 mins from admission				
Early cryo arm 46-60 mins from admission				
Early cryo arm 61-90 mins from admission				
Early cryo arm > 90 mins from admission				

[1]Cryoprecipitate administered in the time period relative to standard arm overall, adjusted for centre

[2] Wald test p-value from logistic regression model, adjusted for centre

Table 35 All-cause mortality at 28 days in the standard arm and in the early cryoprecipitate arm for those who did or did not receive any cryoprecipitate, per protocol

	Mortality rate n/N (%)	Relative risk (95% CI)[1]	Odds ratio (95% CI)[1]	P-value[2]
Standard MHP arm				
Early cryo arm - no cryoprecipitate received				
Early cryo arm - some cryoprecipitate received				

[1] Relative to standard arm overall, adjusted for centre

[2] Wald test p-value from logistic regression model, adjusted for centre

Table 36 Causes of death for all-cause mortality at 28 days, per protocol

Cause of death	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)
Total deaths within 28 days – n/N (% of those randomised)			
Multi-organ failure			
Multiple injury			
Myocardial infarction			
Pulmonary embolism			
Sepsis			
Stroke			
Traumatic brain injury			
Uncontrolled bleeding			
Other			
Not reported			
All			

Table 37 Mortality data, per protocol

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value
Mortality at 6 hours from admission - n/N (%)				
Relative risk (95% CI) for mortality at 6 hours from admission[1]				
Odds ratio (95% CI) for mortality at 6 hours from admission[1]				
Mortality at 24 hours from admission - n/N (%)				
Relative risk (95% CI) for mortality at 24 hours from admission[1]				
Odds ratio (95% CI) for mortality at 24 hours from admission[1]				

Death from bleeding at 6 hours from admission - n/N (%)				
Relative risk (95% CI) for death from bleeding at 6 hours from admission[1]				
Odds ratio (95% CI) for death from bleeding at 6 hours from admission[1]				
Death from bleeding at 24 hours from admission - n/N (%)				
Relative risk (95% CI) for death from bleeding at 24 hours from admission[1]				
Odds ratio (95% CI) for death from bleeding at 24 hours from admission[1]				
Median (IQR) time to death from bleeding in those who bled				
[1] Early Cryo arm relative to Standard arm adjusted for centre in mixed logistic regression model				

Table 38 Transfusion requirements, per protocol

Outcome	**Std MHP arm (n=)**	**Early cryo arm (n=)**	**Overall (n=)**	**P-value**
Median (IQR) products transfused per participant from injury to 24 hours				
RBC (units)				
Platelets (units)				
FFP (units)				
Cryoprecipitate (units)				
Total blood products (units)				
Crystalloids (ml)				
Colloids (ml)				
Median (IQR) products transfused per participant from injury to 24 hours, for those who survived at least 24 hours				
RBC (units)				
Platelets (units)				
FFP (units)				
Cryoprecipitate (units)				
Total blood products (units)				
Crystalloids (ml)				
Colloids (ml)				
Mean products transfused per participant per hour over the first 24 hours				
RBC (units)[1]				

Platelets (units)[1]				
FFP (units)[1]				
Cryoprecipitate (units)[1]				
Total blood products (units)[1]				
Crystalloids (ml)[2]				
Colloids (ml)[2]				
Participants who received cryoprecipitate – n/N (%)				
Median time from admission to start of first cryoprecipitate for those who received it[3] (mins)				
IQR				
Range				
Participants who received their first infusion within 90 mins of admission – n/N (%)				
Overall[4]				
Study year 1 (Jul 17 - 18)				
Study year 2 (Jul 18 - 19)				
Study year 3 (Jul 19 - 20)				
Study year 4 (Jul 20 - 21)				
Study year 5 (Jul 21 – Nov 21)				
p-value for change over time[5]				
Participants who received 3 or more pools of early cryoprecipitate– n/N (%)				
Participants who received 3 or more pools of cryoprecipitate in 24h – n/N (%)				
Participants who received tranexamic acid from injury up to 24 hours from admission – n/N (%)				
Overall[4]				
UK centres[6]				
International Centres[6]				

[1] P-value from negative binomial regression model, adjusted for centre
[2] P-value from linear regression model, adjusted for centre
[3] P-value from Mann-Whitney test
[4] P-value from logistic regression model, adjusted for centre
[5] P-value for linear study year term in logistic regression model, adjusted for centre, standard MHP participants only
[6] P-value from logistic regression, adjusted for centre, for difference in overall use between countries

Table 39 Hospital Stay, per protocol

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value

Median (IQR) ventilator days[1,2]				
Median (IQR) ventilator free days[1]				
Median (IQR) hospital stay[1,2] (days)				
Median (IQR) first critical care stay[1,2] (days)				
Median (IQR) critical care free days[1]				
Participants discharged from hospital – n/N (%)				
Destination – n/N (% of those discharged)				
Home				
Nursing home/rehab facility				
Another hospital				
Other				

[1] Crude median and IQR which make no allowance for differential follow up due to death.

[2] P-value from Fine and Gray model to compare cumulative incidence curves which allows for differential follow up due to death.

Table 40 Other outcomes, per protocol

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n=)	P-value
Thrombotic events – N				
Venous thromboembolism Pulmonary embolus DVT				
Participants affected – n/N (%)				
Mean number of events per participant per week				
Arterial thrombotic events Myocardial infarction Stroke Other occlusion of any other artery				
Participants affected – n/N (%)				
Mean number of events per participant per week				
Cumulative incidence of thrombotic events at day 28 – % (95% CI) [1]				
Serious transfusion related adverse events - n/N (%) [2]				
Thromboprophylaxis measures used – n/N (%)				
Anticoagulants given – n/N (%)				
Antidotes administered for those on anticoagulants – n/N (%)				

[1] P-value from Fine and Gray model
[2] P-value for Fisher's exact test

4.10 Missing data analysis table

Table 41 Sensitivity analyses for primary outcome

Outcome	Std MHP arm (n=)	Early cryo arm (n=)	Overall (n =)	Odds ratio[1] (95% CI)	P-value
Participants who died on or before day 28 from admission (switching 2% of outcomes inferred based on discharge from MTC)					
Participants who died on or before day 28 from admission (multiple imputation)[2]					
Participants reported alive between day 24 and day 27 – n/N (%)					
Participants who died on or before day 28 from admission – n/N (%) (excluding participants only reported alive between day 24 and 27)[3]					
Participants who died on or before day 28 from admission (unadjusted for centre)					
Fragility index[4]					

[1]Early cryo arm relative to Standard arm, adjusted for centre
[2] Only if 28-day mortality is missing for more than 5% of the participants enrolled
[3] Only if proportion reported alive between day 24-27 is more than 2% of the participants in the ITT analysis
[4] Number of additional deaths in the arm with the lowest mortality rate, to render the result non-significant in unadjusted analysis

4.11 Figures

Figure	Description
Figure 1	Participant flow chart (CONSORT diagram)
Figure 2	Kaplan-Meier survival plot up to 28 days from admission by treatment arm, intention to treat
Figure 3	Kaplan-Meier survival plot up to 28 days from admission by treatment arm and time of first cryoprecipitate administration, intention to treat
Figure 4	Histogram of time from admission to first cryoprecipitate administration by arm, intention to treat
Figure 5	Optional figure of effect of timing of first cryoprecipitate administration on 28 day mortality

Figure 6	Kaplan-Meier survival plot up to 28 days from admission by treatment arm and whether any cryoprecipitate given, intention to treat
Figure 7	Box and whisker plots to summaries the number of units of RBC, platelets, FFP, cryoprecipitate, total blood products, colloids and crystalloids administered up to 24 hours from admission split by treatment arm, intention to treat
Figures 8 - 12	Kaplan-Meier survival plots up to 28 days from admission by treatment arm and for each subgroup in turn, intention to treat
Figure 13	Kaplan-Meier survival plot up to 28 days from admission by treatment arm, per protocol
Figure 14	Kaplan-Meier survival plot up to 28 days from admission by treatment arm and time of first cryoprecipitate administration, per protocol
Figure 15	Histogram of time from admission to first cryoprecipitate administration by arm, per protocol
Figure 16	Kaplan-Meier survival plot up to 28 days from admission by treatment arm and whether any cryoprecipitate given, per protocol
Figure 17	Box and whisker plots to summarise the number of units of RBC, platelets, FFP, cryoprecipitate, total blood products, colloids and crystalloids administered up to 24 hours from admission split by treatment arm, per protocol
Figure 18	Forest plot of odds ratios and confidence intervals for main intention to treat and per protocol analyses of the primary outcome, subgroup analyses and sensitivity analyses

5. Statistical Analysis Plan Amendments

Revision History:

Version	Author	Date	Reason for revision
1.1	Helen Thomas	25/07/2019	Amending inference for 28-day mortality to include any patient discharged and adding second sample size re-estimation recommended by DMC. Clarifying in the text that p-value for treatment arm term in mixed logistic regression model will be presented. Adding reference.
2.0	Helen Thomas	20/05/2022	Updated to latest CTU SAP template and to match protocol v4.0. Correction of SAE adjudication process. Amendments to per protocol analysis plans including addition of a table of which participants were excluded and why. Unapproved co-enrolments treated as randomisations in error not protocol deviations. Addition of primary outcome by whether or not cryoprecipitate was given, by race and by ethnicity. Removal of summaries of those who became ineligible after randomisation. Tables added to summarise causes of death, protocol deviations and reasons why intervention not given, rather than being summarised in text. Use of TXA in first 24 hours moved from Other outcomes table to Transfusion table. Further detail added on how risk-adjustment will be implemented. Further detail on p-value used for primary outcome. Further detail on

			QoL scoring measures. Forest plot, histograms and K-M plots for subgroup analyses added.

6. References

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1 S J Stanworth, R Davenport, N Curry, F Seeney, S Eaglestone, A Edwards, K Martin, S Allard, M Woodford, F E Lecky, K Brohi Mortality from Trauma Haemorrhage and Opportunities for Improvement in Transfusion Practice *British Journal of Surgery (2016) 357:365*