



FIBRINOGEN EARLY IN FEISTY II SEVERE TRAUMA STUDY

STATISTICAL ANALYSIS PLAN

VERSION 1.0

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Fibrinogen Concentrate vs. Cryoprecipitate in Traumatic Haemorrhage: A Randomised Controlled Trial

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1.0 OBJECTIVES

1.1 Aim

The primary aim of this study is to determine, in severely injured trauma patients with major haemorrhage and hypofibrinogenemia, whether early fibrinogen replacement using fibrinogen concentrate (FC) compared to cryoprecipitate (Cryo) increases the number of days alive and out of hospital (at home) within the first 90 days after randomization (DAH₉₀).

DAH₉₀ is a consumer-informed, patient-centred outcome which captures death and significant morbidity, both of which are associated with major bleeding in the setting of severe trauma.

‘Out of hospital’ refers strictly to days at home or in accommodation that is not health care related, but not to days in rehabilitation facilities or long-term care facility.

1.2 Hypothesis

In patients with severe trauma, major haemorrhage and hypofibrinogenaemia, the early replacement of fibrinogen with fibrinogen concentrate rather than with cryoprecipitate will increase the number of days alive at home within the first 90 days after randomization (DAH₉₀).

2.0 STUDY OUTCOMES MEASURES

2.1 Primary outcome – DAH₉₀

Number of days alive at home (in the participant's pre-admission living environment) by 90 days post-randomisation (DAH₉₀). Patients who die during the index admission or prior to day 90 will be assigned a DAH₉₀ value of zero. After consultation with consumer advisors, any living status other than that prior to admission (i.e. home or residential care) counts towards days not at home. Day 0 is the day of randomisation, with any day spent in a healthcare facility (acute or subacute hospital, rehabilitation facility or new admission to a residential care facility) defined as a day not at home. DAH₉₀ is 90 minus ‘days not at home’.

2.2 Secondary outcomes

- Number of RBC (red blood cell) units administered within 24 hours after randomisation
- All-cause mortality at 6 hrs and 24 hrs from randomisation
- Overall survival from randomisation (time to event), and all-cause mortality at 90 days
- Days at home at day 90 from randomization, amongst those still alive at 90 days from randomisation
- Death from haemorrhage at 6 hrs and 24 hrs from randomisation
- ICU and hospital (acute) free days up to day 28 from randomisation
- Ventilation-free days up to day 28 from randomisation
- Maximum (worst) Denver MOF (Multi Organ Failure) Score up to day 7 from randomisation
- Symptomatic thromboembolic (arterial and venous) complications

- EQ5D-5L at Day 90, and at 6 and 12 months from randomisation
- WHODAS-2.0 at Day 90, and at 6 and 12 months from randomisation
- GOS-E (Glasgow Outcome Score – Extended) at 12 months after randomisation amongst patients with moderate to severe TBI

3.0 OVERALL STUDY DESIGN

3.1 Study Design

Fibrinogen Early In Severe Trauma study II (**FEISTY II**) is a prospective, phase III, multi-centre, randomised two-arm parallel, open label trial.

3.2 Study Population

900 adult trauma patients with major haemorrhage.

3.3 Inclusion Criteria

Patients who are severely injured through trauma and satisfy all the following conditions:

- Adult patient (age ≥ 18 years) affected by trauma AND
- Judged to have active haemorrhage by treating clinician AND
- Activation of local MHP and/or Transfusion of Emergency Blood Products AND
- FITBEM A5 ≤ 10 mm or TEG FF A10 ≤ 15 mm or Clauss Fib ≤ 2 g/l

3.4 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria apply:

- Injury judged incompatible with survival
- Randomisation unable to occur within 6 hours of presentation to hospital
- Known pregnancy
- Known genetic or drug induced coagulation disorder
- Known objection to blood products
- Dedicated prior fibrinogen replacement (this presentation)
- Severe pre-existing physical or mental disability or severe co-morbidity that may interfere with the assessment of outcome
- Participation in a competing study

3.5 Co-enrolment

All co-enrolments in other trials/studies will be considered on a case-by-case basis by the management committee after receipt of Letter of Consideration.

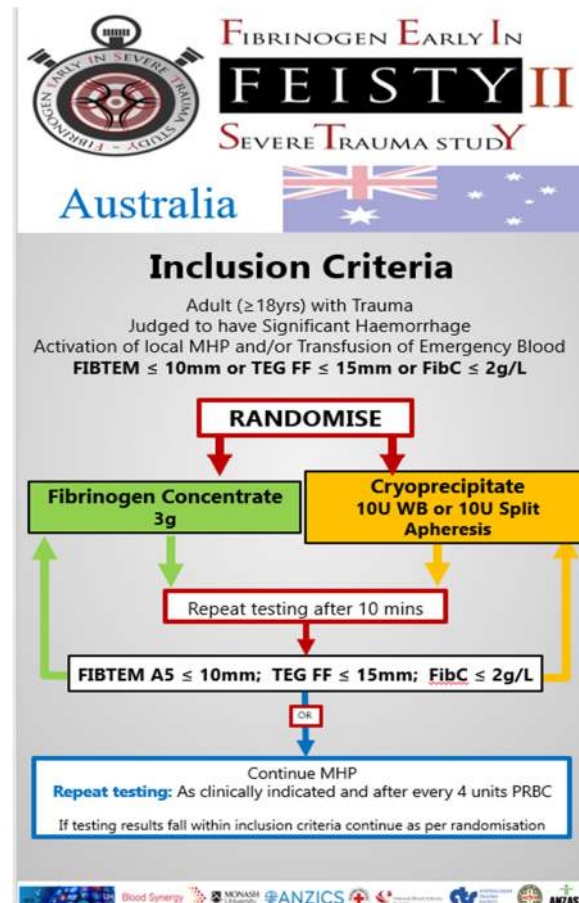
4.0 PARTICIPATING STUDY SITES

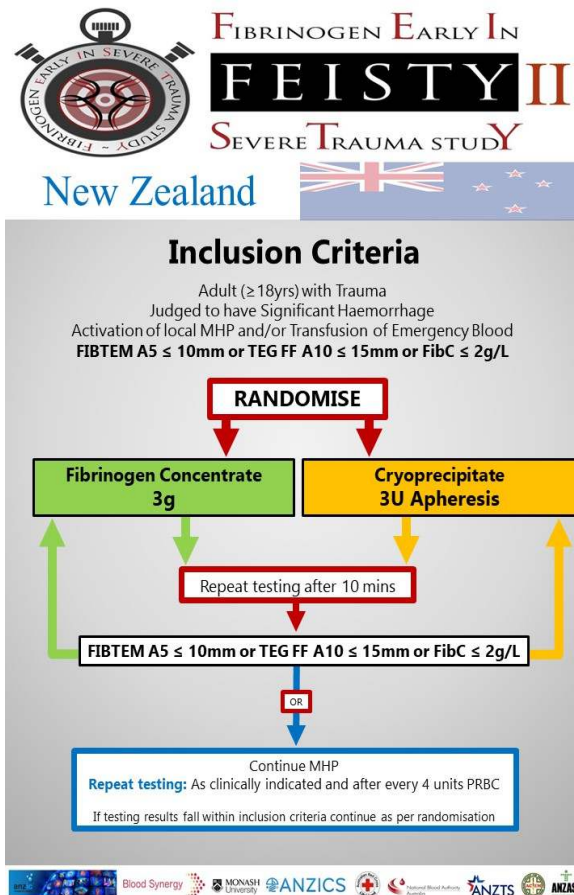
The trial recruits participants in the majority of trauma centres in Australia and New Zealand.

5.0 STUDY PROCEDURES

5.1 Randomisation

Patients will be randomized 1:1 in the ED or ICU or OT of the participating hospitals. Once confirmed that a patient is eligible, they will be randomised using a password protected, secure website using a central, computer-based randomisation program. Randomisation will be stratified by site and the presence/absence of TBI (GCS $\leq$ 8).





5.2 Baseline

Standard blood tests including coagulation tests; biochemistry; full blood count (FBC); Group and Hold and ROTEM or TEG and/or Clauss Fibrinogen will be conducted as part of standard practice for trauma patients shortly after arrival in hospital.

5.3 Follow up at day 90, 6 and 12 months

The participant or the person responsible (PR), if the participant has not regained capacity, will be contacted via telephone at 90 days, 6 and 12 months after randomisation for study follow up.

The day 90 follow up will be to establish 90-day survival and collect information on readmission and discharges to other hospitals, rehabilitation hospitals or long-term nursing care facilities. This data will be collected from the participant and/or PR as well as from hospital medical records and statewide hospitalisation data where available. This will inform the primary outcome of the study. Information on quality of life and functional outcome as measured by the EQ-5D-5L and WHODAS 2.0 surveys will also be collected at this follow up.

At 6 and 12 months after randomisation, the participant or PR will be contacted again via a phone call. These calls will collect information on quality of life and functional outcome information as measured

by the EQ-5D-5L and WHODAS 2.0 surveys. In patients with moderate to severe traumatic brain injury (Neuro AIS ≥ 3), at 12 months after randomisation the participant or PR will be contacted via phone and assessed using the GOS-E survey for functional outcome. GOS-E surveys will be performed by a trained centrally located outcome assessors.

6.0 DATA MANAGEMENT

6.1 Data Collection Methods

All data will be collected by study investigators and trained research at each site using a paper/electronic Case Report Form (CRF) developed by the coordinating centre. Coded data (identified by the unique participant study number only) will then be entered into a secure, password protected, web-based CRF (eCRF). All investigators and research staff will comply with the legislative requirements of their jurisdiction with regard to the collection storage, processing and disclosure of personal information.

Data collection will be restricted primarily to those variables necessary to define clinical characteristics including: baseline demographics, primary diagnoses, physiological parameters, diagnostic interventions, therapeutic interventions, and documentation of death. Adverse and serious adverse event data will be captured. Only the participant's sex and date of birth (for the purpose of calculating age) will be entered in the eCRF.

Randomised participants will be followed up to death or 12 months post-randomisation. Participants and/or their PR will be asked to provide three possible points of contact (home and close family contact details) to the research staff prior to discharge. Full protocol data will be collected in all participants including those excluded at any stage. Participants (or a proxy – generally a close family member) who are alive at 12 months after randomisation will be interviewed by a trained assessor/site research staff. A standardised structured approach will be used. Where the Investigational Products are withheld for any reason or the participant did not receive the Investigational Products, the participant will be followed up according to the study schedule and analysed on an-intention to treat-principle. Hospital medical records (paper or electronic medical records and statewide hospitalisation data where available) will be used in addition to participant and/or PR interviews to verify key clinical outcomes, including the primary outcome.

6.2 Data variables collected

Data collection will include:

Baseline

- Date of Birth
- Baseline demographics
- Date and time of injury
- Date and time of presentation to trauma centre
- Date and time of randomisation
- Arm randomised to FC or Cryo

Pre-Hospital

- Injury Type – Blunt / Penetrating / Burn / Other
- Baseline observations – Lowest GCS / Lowest BP / Highest HR
- Blood Product usage – RBC / FFP / TXA

Hospital Admission

- Hospital admission date and time
- Anticoagulation status
- Injury Severity Score

- Abbreviated Injury Scale
- Pre-injury WHODAS 2.0

In Trauma Unit

- Baseline observations – Lowest GCS / Lowest BP / Highest HR
- Baseline bloods – FBC / Plt / INR / FibC / pH / HCO₃ / BE / Cr
- Baseline VHA – ROTEM or TEG
- Blood product usage – RBC / FFP / Plt / FC / Cryo / TXA / PCC
- Date and time Trauma Unit Admission and Discharge (if patient did not go to ICU)

ICU Admission

- Date and time ICU Admission and Discharge
- Date and time MV initiation and ceasing
- Baseline observations – Lowest GCS / Lowest BP / Highest HR
- Baseline bloods – FBC / Plt / INR / FibC / pH / HCO₃ / BE / Cr
- Baseline VHA – ROTEM or TEG
- APACHE II
- Denver MOF Score

Daily Data (up to 7days)

- VHA – ROTEM / TEG
- Bloods - FBC / Plt / INR / FibC / pH / HCO₃ / BE / Cr
- Denver MOF Score
- SOFA Score

Daily up to day 28

- Thromboembolic complications
- Adverse Events
- Serious Adverse Events
- Protocol Deviations

6 Hours

- Mortality status
 - Cause of death

24 Hours

- Mortality status
 - Cause of death
- Blood Product Usage

Hospital Discharge

- Hospital Discharge date and time
- Mechanical ventilation duration
- Length of stay
- Discharge destination – location and date
- Vital status

90 Days

- Vital status
- Patient location
- Date of discharge home
- Hospital admissions – type of facility (acute care, rehabilitation, long-term high/low level care facility) and dates of admission and discharge up to day 90

- Pre-Injury WHODAS 2.0
- WHODAS 2.0
- EQ-5D-5L

6 months

- Vital status
- WHODAS 2.0
- EQ-5D-5L

12 Months

- Vital status
- WHODAS 2.0
- EQ-5D-5L
- GOS-E in TBI patients only

7.0 STATISTICAL CONSIDERATIONS

7.1 Sample Size Calculation

The FEISTY Pilot trial demonstrated that the primary endpoint (DAH₉₀) has a left-skewed distribution with an important spike at 0 (30-40%). The spike at 0 is due to the combined effect of deaths within 90 days and patients staying ≥ 90 days in hospital. The required sample size was obtained by simulation using 2,000 randomly generated datasets, analysed using quantile regression to avoid relying on a specific form for the endpoint distribution, using a quantile of 0.5 (the median). Quantile regression is a robust alternative to linear regression, which may be used for skewed or spiky data, and is commonly employed for DAH analysis. Simulation data were generated from a zero-inflated beta distribution, rescaled to obtain a distribution on 0-90 with appropriate mean and variance. The assumptions used for the control arm were that there will be 40% zeroes on average, with the non-zero component having beta distribution with a mean DAH₉₀ of 60 days and standard deviation of ~ 11.85 days. The simulation showed that a sample size of 850 evaluable patients is enough to provide $\geq 80\%$ power to detect an effect size of i) a 7-day difference in the mean of the non-zero component and a 1% difference in the zero component, or ii) a 5.5-day difference in the mean of the non-zero component and a 3% difference in the zero component or iii) a 4-day difference in the mean of the non-zero component and a 5% difference in the zero component. The type 1 error is well controlled at the nominal 5% level. After adjustment for an anticipated 5% of patients for whom no DAH₉₀ information is expected to be available and for whom missing data imputation (see below) is thus not practical, ('loss to follow-up'), $850/.95 \approx 900$ patients are required to maintain 80% power in the scenarios described above. The treatment effect, its 95% CI and corresponding p-value will be provided.

7.2 Analysis Methods

Independent senior statisticians at Monash University Department of Biostatistics, School of Public Health and Preventive Medicine will perform data analysis on an intention-to-treat basis for all endpoints.

Basic descriptive statistics

Key disease and demographic variables at baseline will be summarized by arm, including age, sex, mechanism of injury, time from injury to arrival at hospital, Injury Severity Score (ISS), systolic blood pressure, heart rate, Glasgow Coma Score (GCS) and prehospital blood products administered. Continuous valued variables will be summarized by mean and standard deviation, median and inter-quartile range, and number missing. Categorical

variables will be summarized by the number and percentage at each level of the categorical variable, and the number missing.

Main (Definitive) Analysis of the Primary Objective

In the definitive analysis of the primary objective, a difference in DAH₉₀ between arms will be tested for using quantile regression, controlling for the stratification variables (site and traumatic brain injury), as well as age, sex, type of injury (blunt vs. penetrating), ISS, systolic blood pressure at admission and GCS score at admission. The estimated treatment effect of FC (compared to Cryo), its 95% CI and the p-value for the hypothesis test of no effect will be reported.

A sensitivity analysis for the primary objective will repeat the definitive analysis, but controlling only for the stratification variables. As for the definitive analysis, the estimated treatment effect of FC (compared to Cryo), its 95% CI and the p-value for the hypothesis test of no effect will be reported.

Missing Data Imputation

It is expected that approximately 10% of patients will have incomplete DAH₉₀ follow-up data to 90 days. Of these, we further expect to have partial DAH₉₀ information (the duration of index hospitalisation will be known and the participant will be known to be alive at 90 days) for 5%-8%. Thus, only 2%-5% of patients will have DAH₉₀ completely missing. Multiple imputation will be applied to impute DAH₉₀ for the patients with partial DAH₉₀ information as follows. A zero-inflated negative binomial (ZINB) model will be built using those patients with complete DAH₉₀ information available (both duration of index hospitalisation and duration of re-hospitalisations known) with re-hospitalisation duration as the dependent (i.e., response) variable and with the index hospitalisation duration, the stratification factors (site and the presence/absence of TBI (GCS $\leq$ 8)), as well as age, sex, type of injury (blunt vs. penetrating), ISS, systolic blood pressure at admission and GCS score at admission as the independent variables (i.e., predictors). A separate ZINB model will be constructed for each treatment arm. Unknown values of the re-hospitalisation duration in each arm will then be imputed by stochastically drawing from the appropriate arm-specific model. The imputed re-hospitalisation durations will then be added to the known index hospitalisation durations to provide imputed values for the total time in hospital. This will then be subtracted from 90 to provide each participant's imputed DAH₉₀.

For the patients with partial DAH₉₀ information, missing values will be imputed by drawing stochastically from the appropriate arm-specific model described above. Twenty imputed datasets will be generated. The method of the definitive analysis of the primary objective (quantile regression) will be applied to each imputed dataset. The treatment effect estimates from the 20 imputed datasets will be combined using Rubin's rule.

Because the proportion of patients for whom the DAH₉₀ information is completely missing is expected to be very low (2% to 5%), and because in a case where the missingness is reasonably expected to be either missing at random (MAR) or missing completely at random (MCAR), there is no advantage in using multiple imputation over complete case analysis to impute an outcome variable where that outcome variable is completely missing, and the only covariates which are available to impute it are the same covariates that are available and that are planned to be used in a complete case analysis, these few patients will not have their DAH₉₀ values imputed, but rather will be omitted from analysis (complete case analysis).

Sensitivity Analysis for the Primary Objective

A sensitivity analysis will be conducted in which re-hospitalisations are ignored and only the index hospitalisation is subtracted from 90 to calculate the DAH₉₀. This analysis relies on the assumption that re-hospitalisations are rare and thus it is reasonable to ignore them for analysis. The few patients for whom the DAH₉₀ information is completely missing will be omitted from this analysis, (complete case analysis) as above.

In a second analysis method, a zero-inflated beta model will be fitted, including adjusting both the zero-inflated and non-zero components of the model for the stratification factors (site and the presence/absence of TBI (GCS ≤ 8)), as well as age, sex, type of injury (blunt vs. penetrating), ISS, systolic blood pressure at admission and GCS score at admission. A global effect of FC will be tested for using a likelihood ratio test (LRT) comparing the full parametric model above to a sub-model which omits the treatment effect from both the zero-inflated and non-zero components of the model. The LRT will compare $-2 \times$ the difference in log-likelihoods between the 2 models to the chi-squared distribution with 2 degrees of freedom, and report the corresponding p-value. It is expected that this will be more powerful than quantile regression if the model is well-specified. If the test result is significant, the effect of FC on the two components (spike/non-spike) will be tested separately using the corresponding Z-tests provided in the two-part (ZI) model. This will be a complete case analysis, and thus patients with partially or completely missing DAH₉₀ information will be omitted from the analysis. Overall treatment effect estimates, their 95% CI's and p-values will be provided.

Supportive Analysis of the Primary Outcome – Bayesian Analysis of DAH₉₀

The primary endpoint, DAH₉₀, will also be modelled using a Bayesian analysis using the BAMLSS (Bayesian Additive Models for Location, Scale and Shape) R-package, using the same two-part ZI parametric model as was used in the second step of the definitive analysis, above. This will allow us to make probabilistic statements of interest on the effect of treatment on the spike and the non-spike mean, which will be published in a secondary manuscript.

Secondary Objectives

- *Number of RBC (red blood cell) units administered within 24 hours after randomisation*

The ratio between treatment arms in the mean number of RBC units administered will be estimated using a Negative Binomial regression model, with the patient-level RBC unit count as the outcome (dependent) variable and treatment arm (FC vs. Cryo) as the independent variable of interest. In order to correctly account for patients who die within 24 hours, or who for any other reason, are not observed for the full 24 hours, the exposure time will be adjusted for by including the log of the exposure time as an offset term in the model. (It is expected that the number of patients for whom this will apply will be small: ~5%). The treatment effect will be reported as the ratio of the rates of RBC administration between arms and its 95% CI. The stratification variables (site and the presence/absence of TBI (GCS ≤ 8) at baseline) will be controlled for by including them as covariates in the analysis. The estimated mean RBC administration rate in each treatment arm considered separately will be provided using G-estimation, using the above Negative Binomial model to predict the counter-factual RBC count for each patient in the sample under each treatment separately, and summing these predicted counts within each treatment arm. The resulting treatment arm specific count predictions will be subtracted to estimate the average treatment effect.

- *All-cause mortality at 6 hours and 24 hours from randomisation*

A log-binomial regression model will be constructed with all-cause mortality as the binary dependent variable (response variable) and treatment arm as the independent variable (predictor variable). Adjustment will be made for the stratification variables by including them as covariates in the analysis. The proportion of patients lost to follow-up prior to the time point of interest (6 hours or 24 hours), is expected to be very small, justifying a complete case analysis. The treatment effect will be reported as the rate ratio between treatment arms and its 95% CI.

This analysis will be performed twice – once considering deaths by 6 hours as the response variable, and then considering deaths by 24 hours as the response variable.

- *Overall survival from randomisation*

Overall survival will be displayed using Kaplan–Meier curves. The treatment effect will be estimated using a Cox proportional-hazards model, accounting for the randomisation stratification variables, and reported as a hazard ratio with its 95% confidence interval. Site will be incorporated using an appropriate random-effect or frailty term, with TBI status included as a fixed effect. The proportional-hazards assumption will be assessed using graphical and model-based methods. Survival and mortality probabilities at 28 and 90 days will also be reported with 95% confidence intervals.

If the proportional-hazards assumption is materially violated, a log-rank test will be conducted in addition, and its p-value reported.

- *Death from haemorrhage at 6 hours and 24 hours from randomisation*

A log-binomial regression model will be constructed with death from haemorrhage as the dependent variable (response variable) and treatment arm as the independent variable (predictor variable). The proportion of patients who die from a cause other than haemorrhage prior to the time point of interest (6 hours or 24 hours), or are otherwise lost to follow-up before the time point of interest is expected to be very small – thus a complete case analysis will be performed. The rate ratio between treatment arms and its 95% CI will be provided. This analysis will be performed twice – once considering deaths from haemorrhage by 6 hours as the response variable, and then considering deaths from haemorrhage by 24 hours as the response variable.

- *Days at home at day 90 from randomisation, amongst those still alive at 90 days from randomisation*

The method for the definitive analysis of the primary objective (quantile regression) will be repeated amongst the subset of patients still alive at day 90. Patients with no days out of hospital within the first 90 days will score zero. The covariates to be controlled for will be the same as those controlled for in the definitive analysis of the primary objective. The difference in the median DAH₉₀ between treatment arms and its 95% CI will be provided.

- *ICU and hospital (acute) free days up to day 28 from randomisation*

This objective will be analysed using the same method as used for the definitive analysis for the primary objective (quantile regression). However, for this objective, re-admissions are ignored and thus do not detract from the ICU / hospitalization free time. All patients who die within the 28-day observation window will be considered to have had zero ICU / hospitalization free days for the purpose of this endpoint. The covariates to be controlled for will be those used as stratification factors in the randomization. This endpoint will involve a complete case analysis, rather than multiple imputation.

- *Ventilation-free days up to day 28 from randomisation*

This objective will be analysed using the same method as used for the definitive analysis for the primary objective (quantile regression). Patients who never receive any ventilation support will be assigned 28 ventilation-free days. All patients who die within the 28-day observation window will be considered to have had zero ventilation-free days for the purpose of this endpoint. The covariates to be controlled for will be the same as those used as stratification factors in the randomization. This endpoint will involve a complete case analysis, rather than multiple imputation.

- *Maximum (Worst) Denver MOF (Multi Organ Failure) Score by day 7 from randomisation*

The worst Denver MOF score per patient until 7 days will be compared between arms using a linear regression model with treatment arm as the independent variable of interest, and the worst Denver MOF score between randomization and day 7 inclusive as the response variable. Due to the high likelihood that there will be a lot of missing baseline data, Baseline Denver MOF score will not be controlled for. A variance stabilising transformation such as the log transformation will be applied to the data prior to modelling if graphical analysis suggests evidence of non-linearity.

- *Symptomatic thromboembolic (arterial and venous) complications within the first 28 days*

The difference between treatment arms in the mean number of complications within the first 28 days after randomisation will be modelled using a Negative Binomial regression model, with the patient-level count of the number of complications within the first 28 days after randomisation as the outcome (dependent) variable and treatment arm as the independent (predictor) variable of interest. Patients whose complication count is not observed for the full 28 days due to loss to follow-up within the 28-day period, will be adjusted for by including the log of the exposure period as an offset term in the model. The ratio of complication counts between arms and its 95% CI will be reported. The stratification variables and presence of a known history of Venous Thromboembolism (binary) will be controlled for by including them as covariates in the analysis.

As an additional method of analysis for the same objective, the probability of a patient experiencing at least one complication within the first 28 days after randomisation will be modelled using a complementary log-log regression model. Presence of at least one complication (binary) will be the outcome (dependent) variable, and treatment arm will be the independent variable of interest. Adjustment will be made for the stratification variables and presence of a known history of Venous Thromboembolism (binary), by including them as covariates in the analysis. In order to allow inclusion of patients who do not have complete follow-up for complications until 28 days, an offset term for the log of the exposure time will be included in the model. The ratio of the odds of at least one complication between arms and its 95% CI will be reported.

- *EQ5D-5L at Day 90, and at 6 and 12 months from randomisation*

A linear mixed effects model will be constructed with the post-baseline EQ5D-5L utility score as the outcome (dependent) measure, and treatment arm as the independent variable of interest. The value set used to calculate the utility scores will be the Norman et al Australian value set (2023). Time point (day 90, month 6 and month 12) will be included as a fixed factor, and patient will be included as a random factor in analysis. Since baseline (pre-injury) EQ5D-5L will likely be unavailable for many patients, and is also not likely to be highly predictive of post-baseline EQ5D-5L, it will not be controlled for in modelling. Post-hoc contrasts will be used to estimate the difference in EQ5D-5L between treatment arms at each time point. Patients who die before month 12 will be assigned a EQ5D-5L score of zero at all time points after their death.

Each of the 5 domains of the EQ5D-5L score ('mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression') will also be modelled separately, using a separate ordinal-outcome mixed effects model for each domain. Each domain consists of a single ordinal Likert scale question with 5 levels. Death will be added as a 6th level, being the worst of all outcomes. A separate model will be constructed for each of the five EQ5D-5L domains, with the ordinal valued EQ5D-5L domain score as the response. As above, treatment arm will be the independent variable of interest, time point will be included as a fixed factor, and patient will be included as a random factor in analysis. As for the overall EQ5D-5L analysis described above, the baseline (pre-injury) value of the domain level will not be controlled for.

For both the overall model and the domain specific models, the stratification variables will be controlled for in modelling.

For each model, the odds ratio corresponding to a one-level change in outcome will be provided, together with its 95% CI.

For both the composite and individual domain models, modelling will initially consider an unstructured covariance structure. However, for those endpoints where this model does not converge, an AR(1) covariance structure will be considered instead.

- *WHODAS-2.0 at Day 90, and at 6 and 12 months from randomisation*

The 12-item version of the WHODAS-2.0 score will be used, and the 12 individual responses, each of which takes values in the range 0 – 4, will be summed and then divided by 48 in order to convert them to a proportion

between 0 and 1 for each patient. Where a single WHODAS-2.0 item is missing, the mean value of the remaining 11 items is assigned to the missing item. The resulting WHODAS-2.0 score will be modelled using a linear mixed effects model, analogous to the model for the overall EQ5D-5L endpoint above. Patients who die before month 12 will be assigned a WHODAS-2.0 score of zero at all time points after their death. The stratification variables will be controlled for in modelling. A descriptive summary of the WHODAS-2.0 score at each time point will also be provided per treatment arm, treating the WHODAS-2.0 score both as a continuous variable, (in which case the descriptive summary will contain the mean and standard deviation, mean and IQR, and the range), and as a categorical variable, considering the following mutually exclusive disability categories: 1) no disability (0–4.5%); 2) mild disability (4.5–24.5%); 3) moderate disability (24.5–49.5%); 4) severe disability (49.5–95.5%); and 5) complete disability (95.5–100%). For analysis as a categorical variable, the descriptive summary will contain the count and percentage of patients at each level.

- *GOS-E (Glasgow Outcome Score – Extended) at 12 months after randomisation amongst patients with moderate to severe TBI at randomisation.*

The GOS-E is an 8-point scale used to assess global recovery. Amongst patients with moderate to severe TBI at randomisation, the difference between GOS-E between treatment arms will be tested for using an ordinal regression model with GOS-E as the outcome (dependent) variable and the treatment arm as the independent variable of interest. The stratification variables will be controlled for in modelling. (Baseline GOS-E will not be controlled for because it will be unknown for most participants. However, baseline GOS-E is likely to be fairly consistent amongst participants with moderate to severe TBI at randomization.) The odds ratio corresponding to a one-level change in GOS-E will be provided.

A descriptive summary of the GOS-E at 12 months will be provided per treatment arm, treating the GOS-E score as a continuous variable, (in which case the descriptive summary will contain the mean and standard deviation, median and IQR, and the range), as a categorical variable (in which case the descriptive summary will contain the count and percentage of patients at each level) and as a dichotomous variable, thresholded between 5 – 8 (favourable outcome) and 1 – 4 (unfavourable outcome).

Adverse Event Reporting

The trial will report the following pre-specified CTCAE v5.0 preferred terms

- Thromboembolic event (either Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)) requiring intervention
- Myocardial Infarction
- Ischaemic Stroke
- Any transfusion reaction, with all types of transfusion reaction reported collectively

Adverse Events (AE's) will be summarised descriptively by tabulating the worst grade of AE per patient per AE preferred term (PT) during the AE assessment time window. For each PT (rows), the number of patients with each grade (columns) as their worst grade for that PT will be shown.

Serious Adverse Event Reporting

Serious Adverse Events (SAE's) will be listed, showing start date, end date (where applicable, or 'ongoing' if there is no recorded end date), severity and relatedness to treatment.

Analysis Assumption Checking

For all continuous endpoints modelled using linear regression, normality of residuals will be assessed visually, and consideration will be given to performing a log-transformation of the response variable if significant non-normality is suspected.

Missing value imputation

The missing value imputation method for the primary objective is discussed in the relevant section. For secondary objectives, for all objectives except for those modelled using mixed effect models, unless otherwise stated, missing values for continuous valued covariates will be imputed with the mean, and missing values for categorical covariates will be imputed by creating an additional, 'unknown' category. Missing values for outcome variables will not be imputed and the participants for which this is relevant will be omitted from analysis for that objective.

Adjustment for multiple testing

No formal adjustment for multiple testing will be employed. Instead, all treatment effect estimates for secondary objectives should be interpreted as hypothesis generating only, and not definitive.

7.3 Interim Analysis

Following recruitment of 50% of the original target sample size (425 of an originally planned 850 patients), a review of recruitment rates, protocol compliance and mortality was undertaken. Additionally, at this point, a single interim analysis was conducted using all-cause patient mortality at 90 days after randomization as the main outcome. No signal of excessive mortality was observed in patients randomized to FC compared to those randomized to cryoprecipitate, and thus there was no need to stop for harm. The alpha spending function with power= 4 was used to determine the critical value of the z-test for proportions.

7.4 Subgroup Analysis

Heterogeneity of treatment effect across sub-groups will be assessed by considering a treatment-by-subgroup interaction term in the primary analysis model. Each interaction term will be considered in a separate model. The effect estimate and corresponding 95% CI for the interaction term will be reported. Results will be regarded as exploratory and presented in forest plots. The following subgroups will be considered:

- TBI severity (GCS ≤ 8 vs. >8)
- Age (≤ 65 vs. > 65)
- Injury severity score (ISS) (≤ 15 and > 15)
- Initial Fibrinogen ($\leq 1\text{g/L}$ vs. $> 1\text{g/L}$)
- Mechanism of injury (blunt vs penetrating) and
- Pre-hospital time (Time 000 call to Triage) (<120 minutes vs. ≥ 120 minutes)

8. Tables and Figures

Table 1: Baseline characteristics

Characteristic	Fibrinogen concentrate (N=x)	Cryoprecipitate (N=x)
Median age (IQR), years		
Male sex, no./total no. (%)		
Ethnicity, no./total no. (%)		
European		
Asian		
Australian Indigenous/Torres Strait Islander		
Māori		
Middle Eastern		
Latin American		
African		
Other		
Injuries		
Type of injury – no./total no. (%)		
Blunt		
Penetrating		
Burn		
Other		
Median time from injury to emergency arrival (IQR), mins		
Median time from injury to randomization (IQR), mins		
Median Injury Severity Score (IQR)		
Abbreviated Injury Scale score ≥ 3 - no./total no. (%)		
Head or neck		
Abdomen or pelvic contents		
Face		
Extremities or pelvic girdle		
Chest		
External		
Traumatic brain injury, no./total no. (%)		
Prehospital interventions		
Prehospital red cell transfusion, no./total no. (%)		
Prehospital fresh frozen plasma, no./total no. (%)		
Prehospital fibrinogen concentrate, no./total no. (%)		
Tranexamic acid, no./total no. (%)		
Median prehospital colloid (IQR), ml		
Median prehospital crystalloid (IQR), ml		
Physiology on emergency arrival		
Median Glasgow Coma Scale score (IQR)		
Median heart rate (IQR) – beats/min		
Median systolic blood pressure (IQR) - mmHg		
Systolic blood pressure < 90 mm Hg, no./total no. (%)		
Intubated before randomization, no./total no. (%)		
Median haemoglobin (IQR) - g/L		
Median platelet count (IQR) – $\times 10^9/L$		
Median fibrinogen concentration (IQR) - g/L		
Median FIBTEM A5 (IQR) - mm		
Median lactate concentration (IQR) – mmol/L		

Table 2. Fibrinogen replacement administered (24-hour intervention period)

Variable	Fibrinogen concentrate (N=x)	Cryoprecipitate (N=x)
Received assigned product for first two doses, no./total no. (%)		
Median time from randomization to administration of first dose (IQR) - min		
Median number of study doses administered (IQR)		
Cross-over to alternate product, no./total no. (%)		
Received one or more fibrinogen concentrate doses in first 24 hours, no./total no. (%)		
Received one or more cryoprecipitate units in first 24 hours, no./total no. (%)		
Median fibrinogen concentrate dose administered in first 24 hours (IQR), g		
Median number of cryoprecipitate units administered in first 24 hours (IQR), units		

Table 3: Primary Outcome Summary Statistics – Number of days alive and at home from randomization to day 90 (DAH₉₀)

Outcome Measure	Statistic	Fibrinogen concentrate (n=x)	Cryoprecipitate (n=x)	Total (n=x)
DAH ₉₀	Median [IQR]	xx.x [xx – xx]	xx.x [xx – xx]	xx.x [xx – xx]
DAH ₉₀ considering the index hospitalization only	Median [IQR]	xx.x [xx – xx]	xx.x [xx – xx]	xx.x [xx – xx]
DAH ₉₀	Mean of non-zero component (95% CI)	xx.x (xx – xx)	xx.x (xx – xx)	xx.x (xx – xx)
	Proportion Zeroes (95% CI)	xx.x (xx – xx)	xx.x (xx – xx)	xx.x (xx – xx)

Table 4: Primary Outcome Modelling Results – Number of days alive and at home from randomization to day 90 (DAH₉₀)

Analysis Method	Adjustment covariates	Effect estimate (95% CI)	P-value
Quantile Regression	Stratification variables and others*	xx.x (xx – xx)	x.xx
Quantile Regression	Stratification variables only	xx.x (xx – xx)	x.xx
Quantile Regression**	Stratification variables and others*	xx.x (xx – xx)	x.xx
Zero-inflated Beta Regression	Stratification variables and others*	xx.x (xx – xx)	x.xx
		xx.x (xx – xx)	

* Adjustment covariates include other important covariates, listed as above

** DAH₉₀ outcome values consider the index hospitalization only

Table 5: Key secondary outcomes

Outcome	Fibrinogen concentrate (N=x)	Cryoprecipitate (N=x)	Effect estimate (95% CI)
All-cause mortality			
at 6 h – no./total no. (%)			
at 24 h – no./total no. (%)			
At 28 d – no./total no. (%)			
at 90 d – no./total no. (%)			
Mortality from haemorrhage			
at 6 h – no./total no. (%)			
at 24 h – no./total no. (%)			
Number of days free of intensive care unit admission at day 28			
Number of days free of hospital admission at day 28			
Number of days free of invasive ventilation at day 28			
Number of days at home at day 90			
Number of red cell units administered within 24 hours			
Number of thromboembolic events up to day 28			
Denver Multiorgan Failure score up to day 7			

All figures quoted are median and IQR unless otherwise specified.

Figure 1 Consort diagram

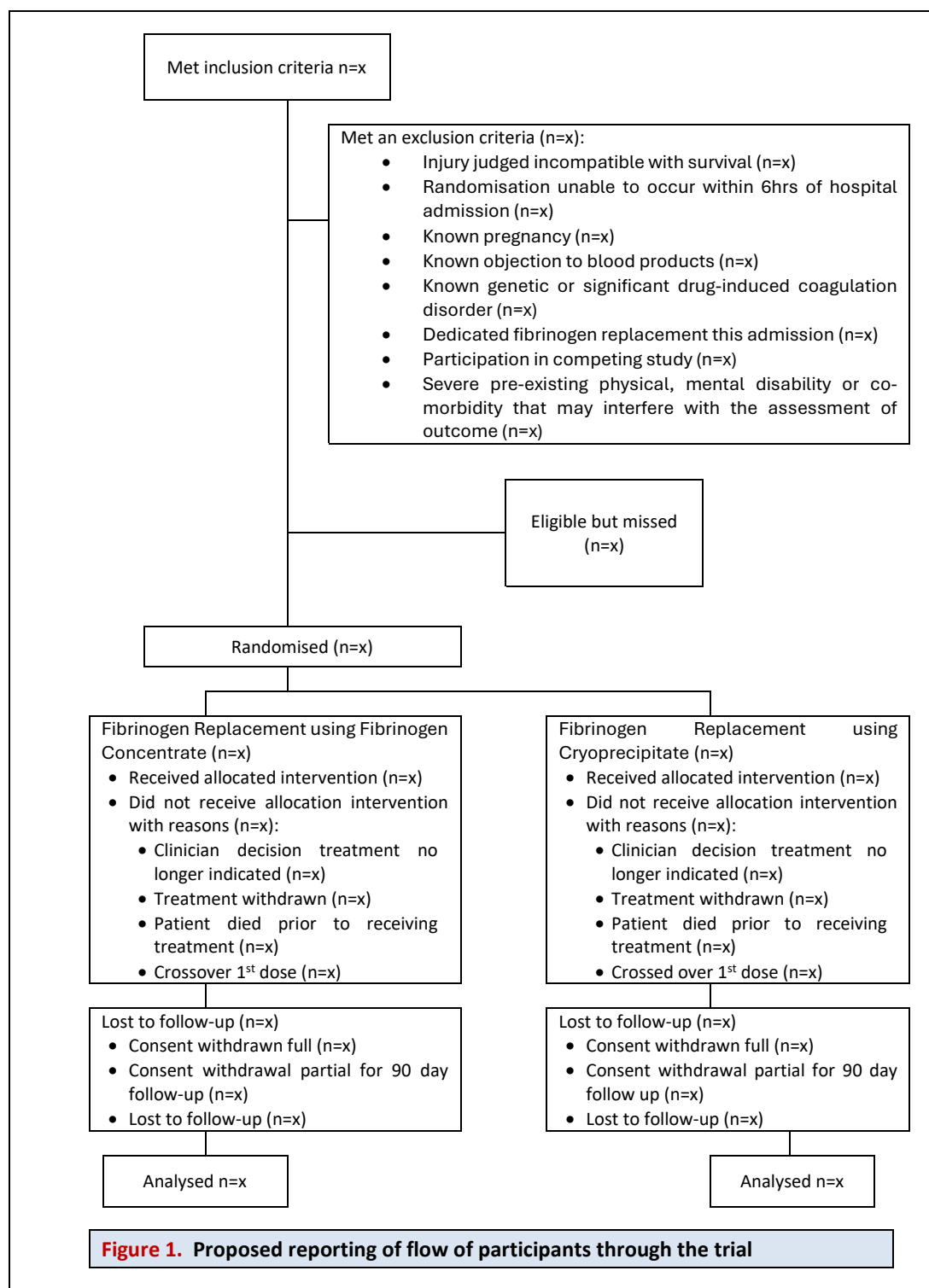


Figure 2a Distribution of days alive and at home at 90 days by treatment allocation

Figure 2b Forest plot of primary outcome by prespecified subgroups

Figure 3 Kaplan-Meier survival through 90 days by treatment allocation

Figure 4 Fibrinogen concentration over time by treatment allocation

Secondary manuscript

EQ5D and WHODAS at day 90, 6 months and 12 months and GOS-E (for participants with TBI) at 12 months to be reported in a secondary manuscript.