Statistical Analysis Plan

Individual participant data meta-analysis of the CLIP-II and CLIPNZ-II trials

Cryopreserved versus liquid-stored platelets for the treatment of surgical bleeding

SAP version	Version 2
Date	15 October 2026
Constituent trials	CLIP-II (NCT03991481) and CLIPNZ-II (ACTRN12621000271808)
Analysis framework	One-stage individual participant data meta-analysis
Primary analysis population	All randomised participants who received at least one unit of allocated study platelets
Statistical software	SAS version 9.4 or later

Role	Name	Date/signature
Chief investigator, CLIP-II	Professor Michael Reade	
Lead statistician	Professor Michael Bailey	

Status and purpose. This SAP supplements the published protocol and CLIP-II SAP update. It was written before harmonisation, with knowledge of the constituent-trial results, as anticipated in the published protocol (Version 1, 13 October 2026). The post-harmonisation update (Version 2, 15 October 2026) is limited to the source corrections below and their implications for pooled analyses. The planned analyses are unchanged. The primary non-inferiority analysis is the sole confirmatory analysis; all other analyses are exploratory.

Source corrections identified after harmonisation

BARC4 classification (JAMA Table 2 and Supplement 3, eTable 8). Consistent application of the transfusion-window criterion changes events from 33/104 versus 19/98 to 35/104 versus 20/98 (cryopreserved versus liquid-stored platelets). The reproduced adjusted risk difference changes from 9.8 percentage points (95% CI, −0.6 to 20.3) to 11.2 percentage points (95% CI, 2.1 to 20.4). In the adherence population, events change from 18/78 versus 18/95 to 19/78 versus 19/95; the unadjusted risk difference changes from 4.1 percentage points (95% CI, −8.1 to 16.4) to 4.4 percentage points (95% CI, −8.1 to 16.8).

Blood-loss labelling (Supplement 3, eTable 3). “Volume of intraoperative bleeding” should read “Postoperative 24-hour blood loss including ICU-arrival blood”. This label is corrected in eTable 5. The primary outcome continues to exclude ICU-arrival blood.

Cell-saver transcription (Supplement 3, eTable 3). The median volume returned in the liquid-stored platelet group is 68 mL, rather than the published 8 mL; the IQR is unchanged.

Implications for pooled analyses. The corrected BARC4 derivation will be applied consistently across both trials in the primary and adherence sensitivity populations. Pooled reporting will use the corrected blood-loss label and cell-saver value.

1. Background and rationale

CLIP-II and CLIPNZ-II are harmonised, blinded, multicentre, randomised non-inferiority trials comparing cryopreserved with conventional liquid-stored platelets for the treatment of bleeding in cardiac surgery. The trials used near-identical protocols, outcomes and follow-up schedules, but were conducted as separate studies because the Australian and New Zealand blood services used different cryopreserved platelet preparation and reconstitution methods.[1,2]

The overarching protocol prospectively stated that harmonisation would facilitate an individual participant data meta-analysis (IPDMA), including exploration of platelet dose, preparation method and possible differences in adverse effects. This SAP prespecifies the combined analyses while preserving the randomised comparison within each constituent trial.

2. Objectives and hypotheses

2.1 Primary objective

To determine whether cryopreserved platelets are non-inferior to liquid-stored platelets for postsurgical chest-drain blood loss during the first 24 hours after ICU admission, using combined individual participant data from CLIP-II and CLIPNZ-II.

2.2 Secondary objectives

- To estimate pooled treatment effects for the prespecified secondary, tertiary and safety outcomes from the constituent trials. These analyses will be exploratory and will be reported using effect estimates and 95% confidence intervals without P values.
- To explore the treatment effect on a modified CHIPS-adapted haemostatic efficacy score derived from the bleeding and transfusion data available in the CLIP studies.
- To assess whether treatment effects differ between CLIP-II and CLIPNZ-II, recognising that study is inseparable from country and cryopreserved platelet preparation method.
- To assess treatment-effect heterogeneity across clinically prespecified participant and treatment subgroups.
- To evaluate the robustness of the primary result to protocol adherence and alternative modelling assumptions.
- To describe treatment delivery, including study platelet dose, use of early open-label platelets and time from platelet order to transfusion.

2.3 Primary hypothesis

Let R denote the ratio of geometric mean 24-hour postsurgical blood loss for cryopreserved relative to liquid-stored platelets. Cryopreserved platelets will be declared non-inferior if the upper bound of the two-sided 95% confidence interval for R is less than 1.20. This is equivalent to a one-sided test at alpha=0.025. Values of R below 1 favour cryopreserved platelets.

No formal superiority hypothesis will be tested. Any estimate favouring cryopreserved or liquid-stored platelets will be interpreted from its magnitude, direction and precision and will not support a confirmatory superiority claim.

3. Study design and data sources

This is a one-stage IPDMA of two independently randomised trials. Treatment allocation was stratified by hospital within each study. CLIP-II randomised participants before surgery, whereas CLIPNZ-II randomised participants at the time of the first platelet request. Both trials compared up to three units of allocated study platelets, with open-label liquid-stored platelets permitted according to protocol-defined criteria.

Study	Country	Planned transfused sample	Randomisation timing	Cryopreserved preparation	Study indicator
CLIP-II	Australia	202	Preoperative	Platelet concentrate reconstituted in separately thawed compatible plasma	CLIP
CLIPNZ-II	New Zealand	229	At first platelet request	Platelets and plasma frozen in one bag separated before freezing	NZ

4. Analysis populations

4.1 Primary analysis population

The primary analysis population will include all randomised participants in either trial who received at least one unit of their allocated study platelet product. Participants will be analysed according to randomised allocation, irrespective of the number of study units received, subsequent open-label platelet use, treatment discontinuation or other protocol deviations. This population corresponds to the prespecified primary analysis populations used in the constituent trials.

4.2 Adherence sensitivity population

A sensitivity analysis will exclude participants who received open-label platelets before completion of the intended maximum of three study units without meeting protocol-defined withholding criteria. Participants who received fewer than three study units because no further platelets were clinically indicated will remain eligible.

4.3 Randomised cohort description

For transparency, patient flow will describe all consented and randomised participants, including those who did not receive study platelets and the reason for non-treatment. Comparative effectiveness analyses will not include randomised participants who received no study platelets.

5. General statistical principles

- The primary pooled analysis will use a one-stage IPDMA model.
- All treatment effects will be reported with 95% confidence intervals. The primary non-inferiority test will use one-sided alpha=0.025.
- The primary non-inferiority analysis is the sole confirmatory analysis. All secondary, tertiary, safety, subgroup, treatment-by-study interaction and other ancillary analyses are exploratory. They will be reported using effect estimates and 95% confidence intervals without P values, and no multiplicity adjustment will be applied.
- Constituent study will be included as a fixed effect in pooled continuous and binary comparative models. Site and EuroSCORE II adjustment will follow the outcome-specific CLIP-II approach: supporting adjustment applies to the primary and prespecified secondary outcomes, rather than automatically to every tertiary outcome. Hospital site will be nested within study. The time-to-event and modified CHIPS models are specified separately below.
- For median-regression, hospital site nested within study will be included as a fixed categorical effect. This directly adjusts for the finite set of recruiting hospitals and avoids assumptions about the distribution and variance of an underlying site population. Prespecified contingency procedures for sparse data or non-estimable models are described in Sections 10.7 and 14.
- Adjusted primary and secondary analyses will include total EuroSCORE II as the patient-severity covariate.[3] Additional and tertiary outcomes will follow the outcome-specific analyses reported in CLIP-II; they will not automatically receive EuroSCORE II or site adjustment. Study will be accounted for in pooled comparative estimates. The modified CHIPS-adapted score will use the separate exploratory model in Section 10.8.
- Ratios will compare cryopreserved with liquid-stored platelets. Absolute differences, including binary risk differences, will be cryopreserved minus liquid-stored; risk differences will be expressed in percentage points.
- Model assumptions, convergence and influential observations will be evaluated. Any deviations from the prespecified model will be documented and justified.

6. Data harmonisation and derivations

The trials were prospectively harmonised. Common source variables will be used directly after checking their definitions and coding. Source reconciliation was completed on 15 October 2026. Corrections identified during that process are recorded at the start of this document.

Date and time variables will be converted to common SAS date, time or datetime formats. Durations will use the same origin, event definition, censoring rule and unit in both trials. Where a source variable is unavailable in one trial, the outcome will not be pooled unless a clinically equivalent derivation can be prespecified and verified.

7. Participant flow and baseline characteristics

A combined flow diagram will present participants by trial and treatment group from consent and randomisation through study platelet receipt, inclusion in the primary analysis, adherence sensitivity population and 90-day follow-up.

Baseline characteristics will be summarised by treatment group overall and separately by study. Continuous variables will be presented as mean (SD) or median (IQR), as appropriate; categorical variables as count (percentage). Baseline significance testing will not be performed.

8. Outcomes

8.1 Primary outcome

Volume of postsurgical chest-drain blood loss during the first 24 hours from ICU admission, expressed in millilitres. Blood already present in the chest drains at ICU arrival will be excluded.

8.2 Prespecified secondary outcomes

- Total postsurgical chest-drain blood loss from ICU admission until drain removal, death or day 28, whichever occurs first.
- BARC4 bleeding, defined by the original Bleeding Academic Research Consortium consensus as any perioperative intracranial bleeding within 48 hours; reoperation after sternotomy closure to control bleeding; transfusion of at least 5 units of allogeneic whole blood or packed red blood cells within a 48-hour period, excluding cell-saver blood; or chest-tube output of at least 2 L within a 24-hour period.[9] Application to the broader CLIP cardiac-surgery population is an adaptation of the original CABG definition. The reconciled transfusion-window derivation will be applied consistently in both studies and in both analysis populations. The collection intervals used to implement the 48-hour transfusion criterion and any limitations in identifying rolling periods will be retained in the harmonisation record. Corrected CLIP-II event counts are recorded at the start of this document.
- Number of red blood cell units transfused during the first 24 hours after ICU admission.
- Total number of red blood cell units transfused from operation commencement until ICU discharge, death or day 7, whichever occurs first.
- Occurrence of venous thromboembolism, arterial occlusion, acute coronary syndrome or acute respiratory distress syndrome from operation commencement until hospital discharge or death.

8.3 Prespecified tertiary and additional exploratory outcomes

Tertiary and additional outcomes include bleeding, transfusion, laboratory, adverse-event, organ-support, resource-use and mortality outcomes. All analyses of these outcomes are exploratory. Appendix 2 provides the planned mock tables, listings and figures and distinguishes outcomes prespecified in the published protocol from those subsequently added or derived in the CLIP-II SAP update and those added for this IPDMA.

8.4 Exploratory tertiary outcome: modified CHIPS-adapted haemostatic efficacy score

A five-level haemostatic efficacy score will be derived using the CHIPS adaptation of the Universal Definition of Perioperative Bleeding[4,5,6], modified to reflect the variables and assessment windows available in CLIP-II and CLIPNZ-II. Scores range from 1 (insignificant bleeding) to 5 (massive bleeding), with higher scores indicating worse haemostatic outcomes. Each participant will be assigned the highest severity level triggered by any

component. The CHIPS-adapted score was not available when the IPDMA was conceived and has only recently been published. Consequently, it was not specified in the constituent-trial SAPs or the original IPDMA plans. Following its publication, the score was added to this SAP as an exploratory tertiary outcome and will not be regarded as a prospectively prespecified outcome.

8.4.1 Component scoring rules

For participants weighing more than 50 kg, the following CHIPS thresholds will be applied to the closest available CLIP variables. The first platelet transfusion, whether study or open-label, will be excluded. The final score will be the maximum of the component scores.

- Delayed sternal closure: no = 1; yes = 4.
- Chest-tube blood loss within 12 hours: <600 mL = 1; 600-800 mL = 2; 801-1000 mL = 3; 1001-2000 mL = 4; >2000 mL = 5.
- Red blood cells: 0 units = 1; 1 unit = 2; 2-4 units = 3; 5-10 units = 4; >10 units = 5. CHIPS counts only red blood cells administered for bleeding rather than dilutional anaemia.
- Plasma: 0 units = 1; 1 unit = 2; 2-4 units = 3; 5-10 units = 4; >10 units = 5.
- Platelets after the first platelet transfusion: none = 1; any = 3.
- Cryoprecipitate: no = 1; yes = 3.
- Factor concentrates: no prothrombin complex concentrate or fibrinogen concentrate = 1; any use = 3.
- Recombinant activated factor VII: no = 1; yes = 5.
- Re-exploration or tamponade: no = 1; yes = 4.
- Death during the intervention period: score 5, irrespective of the other components.

8.4.2 Modifications required for the CLIP datasets

The score cannot be reproduced exactly because the principal differences between CHIPS and the CLIP studies concern the timing and anchoring of the assessment windows. The following modifications will be applied consistently in both constituent studies:

- Twelve-hour chest-tube loss will be measured from ICU admission rather than chest closure and will include blood present in the drains on ICU arrival.
- Red-cell exposure will include all intraoperative transfusions and those administered during the first 24 hours in ICU. Plasma, additional platelets, cryoprecipitate, factor concentrates and recombinant activated factor VII will be assessed using the available CLIP collection periods, which are generally broader than the CHIPS intervention period. The first platelet transfusion will be excluded.
- Re-operation for bleeding after sternal closure will be included using the available follow-up period, which is broader than that used in CHIPS. Tamponade without re-operation was not recorded separately.
- Delayed sternal closure was not recorded systematically and will be assumed absent. Re-operation for bleeding will not be used as a proxy for delayed initial closure.
- For participants weighing 50 kg or less, the CHIPS weight-adjusted thresholds cannot be applied because red-cell and plasma volumes in mL/kg are unavailable. The score will therefore be missing for these participants, and for those with missing weight, unless the early-death criterion assigns a score of 5.
- Death occurring within one recorded day of the first study platelet transfusion will be assigned a score of 5. This approximates the CHIPS criterion of death within 24 hours because exact elapsed time is not available for all participants.

If an otherwise available component is missing, the overall score will be missing unless the early-death criterion assigns a score of 5. These modifications may result in either underclassification or overclassification. The outcome will therefore be described as the modified CHIPS-adapted haemostatic efficacy score and not as the original CHIPS score or the Universal Definition of Perioperative Bleeding.

9. Primary outcome analysis

The primary outcome is postsurgical chest-drain blood loss during the first 24 hours after ICU admission, excluding blood already present in the drains at ICU arrival.

9.1 Descriptive analysis

The primary outcome will be summarised by treatment group using geometric mean (95% CI) and median (IQR), with the number analysed reported. Summaries will be presented overall and separately by constituent study.

9.2 Principal pooled analysis

Blood loss will be natural-log transformed and analysed using a linear model including treatment and constituent study, without EuroSCORE II or hospital-site adjustment. This preserves the unadjusted comparison reported in CLIP-II while accounting for constituent study in the pooled analysis. The treatment coefficient will be exponentiated and reported as the ratio of geometric means for cryopreserved relative to liquid-stored platelets, with a two-sided 95% confidence interval.

The primary conclusion will be based on this model. Non-inferiority will be concluded if the upper bound of the 95% confidence interval is below 1.20, equivalent to a one-sided test at alpha=0.025. Study-specific unadjusted estimates will also be reported.

9.3 Adjusted model

A supporting adjusted analysis will use a linear mixed-effects model of natural-log-transformed blood loss, with treatment, constituent study and total EuroSCORE II as fixed effects and a random intercept for hospital site nested within study. The treatment effect will be reported as the cryopreserved-to-liquid ratio of geometric means with a 95% confidence interval. The adjusted estimate will be presented alongside the principal estimate to assess consistency after adjustment for hospital site and baseline surgical risk.

9.4 Sensitivity analyses

- Adherence sensitivity population.
- Post hoc sensitivity analysis of the primary outcome including chest-drain blood present at ICU arrival.
- Median regression reporting the adjusted difference in medians, including treatment, constituent study, EuroSCORE II and hospital site nested within study as a fixed categorical effect. With a limited, fixed set of recruiting hospitals, this directly adjusts for observed site differences without estimating a site-level variance distribution.
- Treatment-by-study interaction model.

10. Exploratory analysis of secondary, tertiary and additional outcomes

10.1 Continuous positively skewed outcomes

The primary outcome analyses are specified in Sections 9.2 and 9.3: the principal model includes treatment and constituent study, and the supporting adjusted model additionally includes EuroSCORE II and a random intercept for hospital site nested within study. Positively skewed secondary continuous outcomes will be analysed on the natural-log scale where appropriate, with treatment and constituent study in the principal pooled model and EuroSCORE II and a random site intercept added for the supporting adjusted analysis. Results will be reported as geometric means and ratios of geometric means with 95% confidence intervals. Additional and tertiary continuous outcomes will follow the outcome-specific CLIP-II analysis; site and severity adjustment will not be imposed routinely. Pooled comparative models will include study.

10.2 Other continuous or discrete outcomes

Approximately normally distributed continuous outcomes will be reported using means and standard deviations and mean differences with 95% confidence intervals. Where an adjusted analysis is specified for the corresponding CLIP-II outcome, a linear mixed-effects model will include treatment, constituent study and EuroSCORE II as fixed effects and hospital site nested within study as a random intercept.

Other continuous or discrete outcomes unsuitable for normal-scale or log-scale modelling will be reported using medians and interquartile ranges and differences in medians with 95% confidence intervals. Adjusted primary and secondary analyses will use median regression including treatment, study, EuroSCORE II and site nested within study as fixed effects. Additional and tertiary comparisons will include treatment and study without routinely adding site or EuroSCORE II.

10.3 Binary outcomes

Binary outcomes will be reported as counts and percentages and risk differences with 95% confidence intervals, defined as cryopreserved minus liquid-stored and expressed in percentage points. Consistent with CLIP-II, risk differences will be estimated using Poisson regression with an identity link and robust standard errors. Pooled comparisons will include treatment and constituent study. Adjusted analyses of prespecified secondary outcomes will additionally include total EuroSCORE II and account for hospital site nested within study using generalised estimating equations with an exchangeable working correlation and empirical robust standard errors, implemented in PROC GENMOD. Additional and tertiary binary outcomes, including cryoprecipitate and other haemostatic treatment exposure, will include treatment and study without routine EuroSCORE II adjustment or site clustering. Sparse outcomes will be handled as specified in Section 10.7.

10.4 Time-to-event outcomes with competing risk of death

Total duration of mechanical ventilation will be summarised descriptively as median (IQR), consistent with JAMA Table 3. The comparative analysis will be time to extubation using the Fine-Gray model below; a separate difference-in-medians analysis of ventilation duration is not planned. Total ventilation duration and time to extubation will retain their distinct source definitions.

Time to extubation, ICU discharge, hospital discharge, commencement of postoperative aspirin and commencement of prophylactic heparin will be analysed using Fine-Gray subdistribution hazard models, with death as a competing event, consistent with CLIP-II. Pooled models will be stratified by constituent study, with robust standard errors clustered by hospital site nested within study. Results will be reported as subdistribution hazard ratios with 95% confidence intervals and presented as cumulative incidence curves. For desirable events, a subdistribution hazard ratio above 1 indicates a higher cumulative incidence of the event over follow-up.[7]

Fine-Gray models are used because these analyses concern the cumulative incidence of clinically desirable events by a specified time in the presence of the competing risk of death, rather than the cause-specific instantaneous event rate among participants who remain alive and event free.

Time from first study platelet transfusion to hospital discharge will use first study platelet transfusion as time zero. Time to aspirin and heparin will use ICU admission as time zero and will be administratively censored at day 7 or hospital discharge, whichever occurs first.

10.5 Mortality

All-cause mortality through 90 days is a prespecified tertiary safety outcome. It will be analysed using Cox proportional hazards regression, and stratified by study with robust standard errors clustered by site. Time zero will be first study platelet transfusion, and participants alive at 90 days will be administratively censored at day 90. The treatment effect will be reported as a hazard ratio with 95% confidence interval, without a P value. Kaplan-Meier curves by treatment group and study will also be presented. Proportional hazards will be assessed using Schoenfeld residuals and graphical methods. Mortality at 90 days, ICU discharge and hospital discharge will also be reported as counts and percentages by study and treatment group.

10.6 Longitudinal outcomes

Repeated blood-loss and transfusion measurements will be summarised by study, treatment and recorded time. Trajectory models will follow the corresponding CLIP-II analysis, adding constituent study for pooling and retaining the relevant participant and site structure.

10.7 Rare adverse events

Rare adverse events will be reported as counts and percentages by treatment group and study. Treatment-effect estimates and confidence intervals will be reported where estimable. Adjusted analysis is reserved for prespecified secondary outcomes and explicitly specified outcome-specific models; event availability alone will not trigger additional adjustment of tertiary adverse events. Very sparse events will be described without formal hypothesis tests.

10.8 Modified CHIPS-adapted haemostatic efficacy score

The five score categories will be summarised by treatment group overall and within each constituent study using counts and percentages. The score will additionally be summarised using mean (SD), median (IQR), range and number analysed.

The principal exploratory estimand will be the study- and site-adjusted mean score difference, defined as mean score for cryopreserved platelets minus mean score for liquid-stored platelets. The score will be treated as approximately continuous and analysed using a linear mixed-effects model with treatment and constituent study as fixed effects and hospital site nested within study as a random intercept. Kenward-Roger degrees of freedom will be used. The adjusted mean difference and 95% confidence interval will be reported without a P value. Higher scores indicate worse bleeding; therefore, a negative mean difference favours cryopreserved platelets. EuroSCORE II will not be included in this outcome-specific principal model.

Treatment-effect heterogeneity will be explored by adding a treatment-by-study interaction to the principal model. The interaction contrast and its 95% confidence interval, together with study-specific mean score differences and 95% confidence intervals, will be reported without a P value. The magnitude and precision of the interaction will be interpreted cautiously; an interval containing the null will not be interpreted as evidence that the study-specific effects are identical.

A proportional-odds cumulative-logit mixed model will be fitted as a sensitivity analysis, retaining the ordered five-level outcome. The model will include treatment and constituent study as fixed effects and hospital site nested within study as a random intercept. The treatment effect will be reported as the common odds ratio for being in a lower, better bleeding category, with a 95% confidence interval; an odds ratio greater than 1 favours cryopreserved platelets. The proportional-odds assumption and model convergence will be assessed, and any material limitation will be reported.

The score analysis will use participants in the primary analysis population with a derivable score. Components and overall scores will not be multiply imputed. The number and proportion without a derivable score, together with the reason, will be reported by study and treatment group. No CHIPS Bayesian storage-duration model, posterior-probability decision rule or 1-point non-inferiority margin will be applied.

11. Heterogeneity of treatment effect

11.1 Treatment effect by study

Treatment heterogeneity between CLIP-II and CLIPNZ-II will be assessed using a treatment-by-study interaction. Because there are only two studies and study is confounded with country and platelet preparation method, the interaction will be interpreted cautiously as a comparison of the total bundle of between-study differences. Study-specific estimates and 95% confidence intervals will be shown in forest plots.[8]

11.2 Subgroups

Subgroup analyses will be restricted to the primary outcome. Four analyses will retain the definitions used in CLIP-II, and eight additional analyses will explore treatment-effect heterogeneity in the IPDMA. All subgroup analyses are exploratory.

Except for the restricted ABO-compatible comparison below, natural-log-transformed blood loss will be analysed using linear mixed-effects models including treatment, constituent study, subgroup and treatment-by-subgroup interaction, with a random intercept for hospital site nested within study.

Original four CLIP-II analyses

1. ABO-compatible comparison: group O recipients allocated to cryopreserved platelets versus ABO-type-matched recipients allocated to liquid-stored platelets. This is a restricted treatment comparison, analysed using treatment and constituent study with a random intercept for hospital site nested within study; no treatment-by-compatibility interaction will be fitted for this restricted comparison.
2. Complex surgery: more than one valve; valve plus coronary artery, aortic root or ventricular wall surgery; aortic arch or descending aorta surgery; infective endocarditis; or pulmonary circulation surgery.
3. Aspirin administered within 7 days before surgery: yes versus no.

4. Location of first study platelet transfusion: operating theatre versus ICU.

Eight additional exploratory IPDMA subgroups

1. Previous cardiac surgery: yes versus no.
2. Surgical urgency: elective versus non-elective.
3. Recipient blood group: group O versus non-O.
4. Severe renal impairment: baseline creatinine clearance 50 mL/min or less or dialysis versus greater than 50 mL/min.
5. Sex: female versus male.
6. Cardiopulmonary bypass duration: at or below versus above the pooled median.
7. EuroSCORE II: at or below versus above the pooled median.
8. Thoracic aortic surgery: yes versus no.

Subgroup treatment effects and, where applicable, interaction estimates will be reported with 95% confidence intervals, without P values. The ABO-compatible restricted comparison will be reported as a treatment effect with a 95% confidence interval. All subgroup analyses are exploratory; the eight additional subgroups were not specified in the constituent-trial protocols and will be interpreted cautiously given multiple comparisons and limited precision.

12. Missing data

The extent and patterns of missing baseline covariates and outcomes will be reported by study and treatment group. Analyses will be performed using participants with available outcome data, with denominators reported for each analysis. As only one participant in CLIP-II and no participants in CLIPNZ-II had missing primary outcome data, multiple imputation will not be performed.

13. Protocol deviations and treatment adherence

Protocol deviations will be summarised by treatment group and study. Particular attention will be given to participants receiving no study platelets, early open-label platelet transfusion, treatment withholding, crossover and unblinding. The primary analysis will retain participants after treatment deviations once at least one allocated study unit has been received.

14. Model diagnostics and contingency procedures

- Residual distributions and homoscedasticity will be assessed for linear mixed models.
- Random-effect variances, singular fits, convergence warnings, influential observations and instability associated with sparse site-by-outcome data will be reviewed.
- Model convergence and the adequacy of site representation will be reviewed. The original CLIP-II grouping of smaller sites will be retained where applicable and documented; any additional grouping will remain within constituent study. An estimated zero site variance alone will not require site regrouping. Material estimation problems will be addressed using a suitable simpler model, with the change and reason documented. Such changes will not introduce adjusted analyses for outcomes designated as descriptive or study-adjusted only.
- Proportional hazards assumptions will be assessed for Cox models. Fine-Gray model fit will be evaluated using time-varying treatment interactions and graphical checks where feasible.
- If a prespecified comparative model cannot be fitted, the outcome will be reported descriptively or using a suitable simpler comparison, with the reason documented. For an outcome absent in one study, that study will be described separately and an estimable comparison within the contributing study will be reported.

15. Multiplicity and interpretation

The primary non-inferiority hypothesis is the sole confirmatory hypothesis and will be assessed at a one-sided alpha of 0.025. No P values will be reported for secondary, tertiary, safety, subgroup, treatment-by-study interaction or other ancillary analyses. These exploratory analyses will be reported using treatment-effect estimates and 95% confidence intervals, which will be interpreted according to their magnitude, direction,

precision and clinical plausibility rather than as formal hypothesis tests. No multiplicity adjustment will be applied because no confirmatory claims will be made for these outcomes. The modified CHIPS-adapted haemostatic efficacy score remains an exploratory tertiary outcome, and no formal non-inferiority, superiority or Bayesian decision rule will be applied.

16. Statistical reporting

- Treatment effect estimates will be reported overall.
- Continuous outcomes: means (SD) and mean differences, geometric means and ratios, or medians (IQR) and differences in medians, with 95% confidence intervals for comparative estimates as specified for each outcome. Total ventilation duration will be descriptive; its time-to-extubation comparison follows Section 10.4.
- Modified CHIPS-adapted score: counts and percentages in each category; mean (SD) and median (IQR); adjusted mean difference and proportional-odds sensitivity estimate, each with 95% confidence intervals.
- Binary outcomes: counts and percentages, with risk differences and 95% confidence intervals expressed in percentage points. Differences are cryopreserved minus liquid-stored. The level of adjustment will follow Section 10.3 and will be stated for each estimate.
- Time-to-event outcomes: event counts, cumulative incidence or Kaplan-Meier estimates and hazard ratios with 95% confidence intervals.
- The one-sided P value for the primary non-inferiority analysis will be reported to three decimal places; $P<0.001$ will be reported as $P<0.001$. P values will not be reported for any secondary, tertiary, safety, subgroup, heterogeneity or ancillary analysis.
- No P values will be reported for baseline comparisons.
- Forest plots will display pooled treatment effects for the primary outcome and prespecified heterogeneity analyses.

17. Mock Tables, Listings and Figures

The planned mock tables, listings and figures form Appendix 2 of this SAP. They contain no pooled analysis results and may be promoted or demoted between the main manuscript and supplement according to journal requirements without changing the prespecified outcome hierarchy or inferential status.

1. Participant flow by study and treatment group.
2. Baseline characteristics overall and by study.
3. Study platelet exposure, adherence and protocol deviations.
4. Primary and secondary outcomes with unadjusted and adjusted estimates.
5. Additional effectiveness outcomes.
6. Modified CHIPS-adapted haemostatic efficacy score distribution and exploratory treatment-effect analyses.
7. Safety outcomes and adverse events.
8. Study-specific and pooled primary outcome forest plot.
9. Prespecified subgroup forest plot.
10. Cumulative incidence plots for extubation, ICU discharge, hospital discharge, aspirin and heparin.
11. Kaplan-Meier survival plot.
12. Sensitivity analyses for adherence and alternative primary-outcome specifications.

18. SAP Deviations

This IPDMA SAP follows the prospective protocol and the CLIP-II SAP update accompanying JAMA. Routine site adjustment is retained for the primary and prespecified secondary outcomes and is not extended automatically to additional or tertiary outcomes. Differences necessary for pooling and retained additional exploratory objectives are listed below. The primary outcome, analysis population and 20% non-inferiority margin remain unchanged. Source corrections identified after harmonisation and their implications for the pooled analyses are documented at the start of this SAP.

Inclusion of constituent study and hospital site. Pooled comparisons will account for constituent study. Site handling and patient-severity adjustment will follow the corresponding CLIP-II outcome-specific analysis. For adjusted primary and secondary models, site will be nested within study. Time-to-event study stratification and site-clustered robust standard errors are IPDMA adaptations specified in Sections 10.4 and 10.5.

- **Treatment-effect heterogeneity between studies.** Treatment-by-study interactions and study-specific estimates will be reported for the primary and selected major outcomes. These analyses are exploratory. Between-study differences cannot be attributed separately to country, randomisation timing or cryopreserved platelet preparation method.
- In addition to the four original CLIP-II subgroup analyses, eight additional clinically motivated subgroup analyses will explore whether treatment effects vary with patient characteristics and surgical context. These analyses were not specified in the original constituent-trial protocol and are exploratory. Findings will be interpreted cautiously given multiple comparisons and limited precision and will not support confirmatory subgroup claims. These subgroups include:
    1. Previous cardiac surgery: yes versus no.
    2. Surgical urgency: elective versus non-elective.
    3. Recipient blood group: group O versus non-O.
    4. Severe renal impairment: baseline creatinine clearance ≤50 mL/min or dialysis versus >50 mL/min.
    5. Sex: female versus male.
    6. Cardiopulmonary bypass duration: at or below versus above the pooled median.
    7. EuroSCORE II: at or below versus above the pooled median.
    8. Thoracic aortic surgery: yes versus no.
- **Missing data.** Analyses will use available outcome and covariate data without multiple imputation. This differs from the JAMA imputation sensitivity analysis but reflects the minimal primary-outcome missingness: one participant in CLIP-II and none in CLIPNZ-II.
- Additional exploratory outcome and mortality reporting. The modified CHIPS-adapted haemostatic efficacy score is retained as an additional exploratory tertiary outcome. Mortality will be reported through the specified Cox analysis, Kaplan-Meier curves and counts; an additional adjusted 90-day binary mortality model is not required.
- **Inferential reporting.** The pooled primary non-inferiority analysis will be the sole confirmatory analysis. All other analyses will be reported using effect estimates and 95% confidence intervals without P values or multiplicity adjustment. No formal superiority hypothesis will be tested.

19. References

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Appendix 1. Summary of primary model specifications

Outcome type	Model	Study handling	Site handling	Effect measure
Primary blood loss	Principal: linear model of log blood loss; supporting: adjusted linear mixed model	Fixed effect in both models	None in principal model; random intercept nested within study in supporting adjusted model	Ratio of geometric means
Other continuous	Outcome-specific mean, log-linear or median regression; adjustment follows CLIP-II	Fixed effect	As specified for the corresponding outcome; no routine addition for tertiary outcomes	Mean difference, difference in medians or ratio of geometric means
Binary	Poisson identity-link with robust SE; outcome-specific adjustment	Fixed effect	Site-clustered GEE for adjusted secondary models; none routinely for additional binary outcomes	Risk difference (percentage points)
Competing-risk time to event	Fine-Gray	Stratified baseline subdistribution hazard	Robust SE clustered by site	Subdistribution hazard ratio
Mortality	Cox model	Stratified baseline hazard	Robust SE clustered by site	Hazard ratio
Longitudinal	Corresponding CLIP-II trajectory model, adding study	Fixed effect	Site nested within study; participant repeated/random effect	Time-specific ratio/difference
Modified CHIPS-adapted score	Linear mixed model; proportional-odds mixed model as sensitivity	Fixed effect	Random intercept nested within study	Mean difference; common odds ratio for a lower score

Appendix 2. Mock Tables, Listings and Figures

Individual participant data meta-analysis of CLIP-II and CLIPNZ-II

Cryopreserved versus liquid-stored platelets for the treatment of surgical bleeding

Document version	Version 2
Date	15 October 2026
Constituent trials	CLIP-II and CLIPNZ-II
Purpose	Integrated mock shells for the definitive one-stage IPDMA reporting package

A2.1 Shell conventions

XX denotes a value to be populated after database lock. NE denotes not estimable and NA denotes not applicable. All effect directions and analysis populations must be checked against the signed SAP before table production.

These shells deliberately contain no pooled analysis results.

A2.2 Recommended IPDMA output structure

The JAMA CLIP-II tables are retained where they map directly to a pooled randomized comparison, split where one published table mixed distinct reporting purposes, and omitted where the analysis was sparse, post hoc, site-specific or not consistently harmonizable. New outputs address cross-trial comparability, outcome completeness, treatment-by-study heterogeneity and the modified CHIPS-adapted score.

Published item	IPDMA action	Planned IPDMA output	Rationale
JAMA Figure 1	Adapt	Combined participant flow figure	Show consent, randomisation, study platelet receipt and analysis inclusion separately for both trials.
JAMA Table 1	Retain and expand	Main Table 1; eTables 2 and 3	Pooled baseline table plus new overall study comparison and detailed treatment-by-study table.
JAMA Table 2	Split	Main Tables 2 and 3; eTable 5	Separate intervention delivery from primary/key outcomes and additional haemostatic outcomes.
JAMA Figure 2	Adapt	Primary outcome forest plot	Show pooled unadjusted and adjusted estimates with the 1.20 noninferiority margin.
JAMA Table 3	Retain and expand	Main Table 4; eTable 8	Retain key safety outcomes and move additional safety details to the supplement.
JAMA eTable 1	Retain and expand	eTables 2 and 3	Use harmonized EuroSCORE II and surgery variables; add cross-trial standardized differences.
JAMA eTable 2	Adapt	eTable 4	List recruitment by hospital within study and randomized treatment.
JAMA eTable 3	Split	eTables 5 to 7	Separate haemostatic/transfusion outcomes, laboratory outcomes, and organ support/resource use.

Published item	IPDMA action	Planned IPDMA output	Rationale
JAMA eTable 4	Omit from core package	None	Viscoelastic measurements were sparse, instrument-specific and unsuitable for a definitive pooled comparison unless harmonization and sample size prove adequate.
JAMA eTable 5	Retain	eTable 8	Additional safety outcomes remain descriptive/exploratory.
JAMA eTables 6 and 7	Omit	None	Repeated baseline tables for the adherence subset and included-versus-excluded comparison add little to the IPDMA reporting package.
JAMA eTable 8	Retain and adapt	eTable 9	Report adherence sensitivity effects for the primary and prespecified secondary bleeding outcomes.
JAMA eTable 9	Omit	None	Post hoc platelet-nadir/open-label interaction is not a prespecified IPDMA objective.
JAMA eFigures 1 to 9	Retain and adapt	eFigures 1 to 9	Use pooled data and the IPDMA study/site structure.
JAMA eFigure 10	Omit	None	Sparse site-specific early open-label analysis is not appropriate for the pooled report.
Not in JAMA CLIP-II	Add	eTables 1, 2, 10 and 11; outcome-specific denominators	Describe constituent trials, compare study cohorts, assess heterogeneity and present the modified CHIPS score. Report missingness through outcome-specific denominators and Section 12.

The final manuscript may promote or demote a table between the main paper and supplement according to journal limits, but the outcome hierarchy and inferential status will remain unchanged.

Table 1. Baseline characteristics by randomized treatment group in the pooled IPDMA

Primary analysis population. No P values will be reported for baseline comparisons.

Characteristic	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Overall (N=XX)
Demographics			
Age, mean (SD), y	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Sex, No. (%)			
Male	XX (XX.X)	XX (XX.X)	XX (XX.X)
Female	XX (XX.X)	XX (XX.X)	XX (XX.X)
Body mass index, mean (SD), kg/m2	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
EuroSCORE II, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX (XX-XX)
Surgery			
Urgency of operation, No. (%)			
Elective	XX (XX.X)	XX (XX.X)	XX (XX.X)
Urgent	XX (XX.X)	XX (XX.X)	XX (XX.X)
Emergency or salvage	XX (XX.X)	XX (XX.X)	XX (XX.X)
Complex surgery, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Previous cardiac surgery, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Surgery on thoracic aorta, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Deep hypothermic circulatory arrest, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Minimally invasive operation, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Cardiopulmonary bypass time, mean (SD), min	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Preoperative laboratory values			
Creatinine, median (IQR), micromol/L	XX (XX-XX)	XX (XX-XX)	XX (XX-XX)
Haemoglobin, mean (SD), g/L	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Platelet count, mean (SD), x10^9/L	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
aPTT, mean (SD), s	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Fibrinogen, mean (SD), g/L	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
INR, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Preoperative treatment			
Any anticoagulant therapy in preceding 7 d, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Aspirin in preceding 7 d, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Tranexamic acid in preceding 24 h, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Data are mean (SD), median (IQR), or No. (%). Denominators will be shown when they differ from the column total. Complex surgery will use the harmonized CLIP-II definition. aPTT indicates activated partial thromboplastin time; INR, international normalized ratio.

Table 2. Study platelet delivery, open-label platelet use and treatment adherence

Descriptive pooled comparison; no multiplicity adjustment or formal treatment-effect claim.

Treatment delivery measure	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Absolute or median difference (95% CI)
First study platelet transfusion in operating theatre, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Time from platelet order to commencement of first study platelet, median (IQR), min	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)
Study platelet units received, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)
Received open-label platelets before first study platelet, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Received open-label platelets after first but before completion of intended study units, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Received open-label platelets after completion of intended study units, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Received open-label platelets at any time, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Open-label platelet units received, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)
Total study plus open-label platelet units, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)
Met adherence sensitivity population definition, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

Differences are cryopreserved minus liquid-stored. Treatment-delivery comparisons are descriptive because these are post-randomization process measures. Timing definitions will follow the harmonized data dictionary.

Table 3. Primary and prespecified secondary outcomes

Primary analysis population; pooled one-stage IPDMA estimates.

Outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Unadjusted effect (95% CI)	Adjusted effect (95% CI)
Primary outcome				
Postsurgical chest-drain blood loss in first 24 h after ICU admission, geometric mean (95% CI), mL	XX (XX to XX)	XX (XX to XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
Median (IQR), mL	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Prespecified secondary outcomes (exploratory)				
Total postsurgical chest-drain blood loss, geometric mean (95% CI), mL	XX (XX to XX)	XX (XX to XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
BARC4 bleeding, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
RBC units in the first 24 h after ICU admission, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Receipt of any RBC transfusion in the first 24 h after ICU admission, No. (%) (derived summary)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Total RBC units from operation commencement to ICU discharge, death or day 7, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)

All pooled models account for constituent study. Adjusted models additionally include EuroSCORE II, with hospital site nested within study handled as a random intercept for log-linear blood-loss models, a GEE cluster for binary outcomes, and a fixed categorical effect for median regression. Ratios compare cryopreserved with liquid-stored platelets; differences are cryopreserved minus liquid-stored. The primary conclusion is based on the principal ratio of geometric means, without site or EuroSCORE II adjustment, and its 95% confidence interval relative to the 1.20 non-inferiority margin. Secondary outcomes are exploratory and will be reported with effect estimates and 95% confidence intervals without P values.

Table 4. Prespecified safety and major clinical outcomes

Mortality and all other safety and major clinical outcomes are prespecified exploratory analyses.

Outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Effect estimate (95% CI); adjustment as specified
Mortality				
All-cause mortality through 90 d, No. (%)	XX (XX.X)	XX (XX.X)	Hazard ratio	XX.X (XX.X to XX.X)
Died in ICU, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Died in hospital, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Prespecified composite and components				
Venous thromboembolism, arterial occlusion, acute coronary syndrome or ARDS, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Deep vein thrombosis, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Pulmonary embolism, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)

Outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Effect estimate (95% CI); adjustment as specified
Peripheral arterial occlusion, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Acute coronary syndrome, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Acute respiratory distress syndrome, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Other major clinical outcomes				
Re-operation after closure of sternotomy for bleeding, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Total duration of mechanical ventilation, median (IQR), h	XX (XX-XX)	XX (XX-XX)	Descriptive; time-to-extubation comparison in eTable 7	Not applicable
ICU length of stay, median (IQR), d	XX (XX-XX)	XX (XX-XX)	Subdistribution hazard ratio	X.XX (X.XX to X.XX)
Hospital length of stay, median (IQR), d	XX (XX-XX)	XX (XX-XX)	Subdistribution hazard ratio	X.XX (X.XX to X.XX)

Mortality through 90 days will use the Cox model specified in Section 10.5. The prespecified secondary safety composite will retain adjusted analysis. Individual component events and other tertiary clinical outcomes will follow the corresponding CLIP-II level of adjustment, with study accounted for when pooling. Sparse events will be descriptive. Effect estimates and 95% confidence intervals will be reported without P values. Total ventilation duration is descriptive, consistent with JAMA Table 3. The separate time-to-extubation comparison is reported as a Fine-Gray subdistribution hazard ratio in eTable 7 and as a cumulative incidence curve in eFigure 5.

eTable 1. Constituent trial design, intervention and analysis-population characteristics

New IPDMA table describing study-level differences that are inseparable from country and cryopreserved platelet preparation.

Characteristic	CLIP-II	CLIPNZ-II
Country	Australia	New Zealand
Trial registration	NCT03991481	ACTRN12621000271808
Randomization timing	Preoperative	At first platelet request
Cryopreserved platelet preparation	Platelet concentrate reconstituted in separately thawed compatible plasma	Platelets and plasma frozen in one bag and separated before freezing
Maximum allocated study platelet units	3	3
Hospital sites contributing to analysis, No.	XX	XX
Randomized participants, No.	XX	XX
Received at least one allocated study platelet unit, No. (%)	202 (XX.X)	229 (XX.X)
Primary analysis population, No.	202	229
Cryopreserved platelets, No. (%)	XX (XX.X)	XX (XX.X)
Liquid-stored platelets, No. (%)	XX (XX.X)	XX (XX.X)
Primary-outcome ascertainment window	First 24 h after ICU admission	First 24 h after ICU admission
Follow-up for mortality	90 d	90 d

This table is descriptive. Study is completely confounded with country, randomization timing and cryopreserved platelet preparation; no attempt will be made to attribute between-study differences to one of these factors.

eTable 2. Baseline characteristics of the primary analysis population by constituent study

New direct comparison of CLIP-II and CLIPNZ-II participants, irrespective of randomized treatment.

Characteristic	CLIP-II (n=202)	CLIPNZ-II (n=229)	Standardized difference
Demographics and risk			
Age, mean (SD), y	XX.X (XX.X)	XX.X (XX.X)	X.XX
Male, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Body mass index, mean (SD), kg/m2	XX.X (XX.X)	XX.X (XX.X)	X.XX
EuroSCORE II, median (IQR)	XX (XX-XX)	XX (XX-XX)	X.XX
Creatinine clearance category, No. (%)			
>85 mL/min	XX (XX.X)	XX (XX.X)	X.XX
51-85 mL/min	XX (XX.X)	XX (XX.X)	X.XX
<=50 mL/min or dialysis	XX (XX.X)	XX (XX.X)	X.XX
Surgery			
Elective operation, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Complex surgery, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Previous cardiac surgery, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Surgery on thoracic aorta, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Deep hypothermic circulatory arrest, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Cardiopulmonary bypass time, mean (SD), min	XX.X (XX.X)	XX.X (XX.X)	X.XX
Preoperative laboratory values and treatment			
Haemoglobin, mean (SD), g/L	XX.X (XX.X)	XX.X (XX.X)	X.XX
Platelet count, mean (SD), x10^9/L	XX.X (XX.X)	XX.X (XX.X)	X.XX
Aspirin in preceding 7 d, No. (%)	XX (XX.X)	XX (XX.X)	X.XX
Any anticoagulant in preceding 7 d, No. (%)	XX (XX.X)	XX (XX.X)	X.XX

No significance tests will compare baseline characteristics between studies. Standardized differences describe the magnitude of between-study imbalance and are not used to decide covariate inclusion.

eTable 3. Detailed baseline characteristics by randomized treatment group within each constituent study

Expanded version of the published baseline table; intended for supplementary reporting.

Characteristic	CLIP-II cryopreserved (n=XX)	CLIP-II liquid-stored (n=XX)	CLIPNZ-II cryopreserved (n=XX)	CLIPNZ-II liquid-stored (n=XX)
Age, mean (SD), y	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Male, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Body mass index, mean (SD), kg/m2	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
EuroSCORE II, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX (XX-XX)	XX (XX-XX)
Chronic lung disease, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Extracardiac arteriopathy, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Previous cardiac surgery, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Active endocarditis, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Critical preoperative state, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Diabetes treated with insulin, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Left ventricular function, No. (%)				
Good	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Moderate	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Poor or very poor	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Pulmonary hypertension, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Operation urgency, No. (%)				
Elective	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Urgent	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Emergency or salvage	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Complex surgery, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Surgery on thoracic aorta, No. (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Data are mean (SD), median (IQR), or No. (%). Denominators will be shown where they differ from the column total. No P values will be reported.

eTable 4. Participants in the primary analysis population by hospital and treatment group

Expanded from the JAMA hospital table to retain the nesting of hospital within constituent study.

Constituent study and hospital	Cryopreserved platelets, No. (%)	Liquid-stored platelets, No. (%)	Total, No. (%)
CLIP-II hospitals			
Austin Hospital	XX (XX.X)	XX (XX.X)	XX (XX.X)
Townsville University Hospital	XX (XX.X)	XX (XX.X)	XX (XX.X)
Alfred Hospital	XX (XX.X)	XX (XX.X)	XX (XX.X)
Royal Prince Alfred Hospital	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other CLIP-II hospitals	XX (XX.X)	XX (XX.X)	XX (XX.X)
CLIPNZ-II hospitals			
Auckland	XX (XX.X)	XX (XX.X)	XX (XX.X)
Christchurch	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dunedin	XX (XX.X)	XX (XX.X)	XX (XX.X)
Wellington	XX (XX.X)	XX (XX.X)	XX (XX.X)
Waikato	XX (XX.X)	XX (XX.X)	XX (XX.X)

Percentages will be calculated within treatment group and constituent study. Individual hospitals will be retained for descriptive reporting; any grouped site categories used in modelling will be documented and will follow the original CLIP-II grouping where applicable.

eTable 5. Additional bleeding, transfusion and haemostatic treatment outcomes

Adapted from JAMA Table 2 and eTable 3; pooled one-stage IPDMA estimates where harmonization permits.

Outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Effect estimate (95% CI); adjustment as specified
Bleeding and transfusion				
Postoperative 24-hour blood loss including ICU-arrival blood, geometric mean (95% CI), mL	XX (XX to XX)	XX (XX to XX)	Ratio of geometric means	X.XX (X.XX to X.XX)
Blood in drains at ICU admission, geometric mean (95% CI), mL	XX (XX to XX)	XX (XX to XX)	Ratio of geometric means	X.XX (X.XX to X.XX)
Received RBC in first 24 h in ICU, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
RBC units in first 24 h in ICU, median (IQR)	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Receipt of any RBC transfusion from operation commencement to ICU discharge, death or day 7, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Total RBC units from operation commencement to ICU discharge, death or day 7, median (IQR)	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Received plasma at any time, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Plasma units to ICU discharge, death or day 7, median (IQR)	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Received cryoprecipitate at any time, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Cryoprecipitate units to ICU discharge, death or day 7, median (IQR)	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Other haemostatic treatment				
Prothrombin complex concentrate, No. (%); NZ zero exposure reported separately	XX (XX.X)	XX (XX.X)	CLIP-II risk difference	XX.X (XX.X to XX.X)
Fibrinogen concentrate, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Recombinant activated factor VII, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Desmopressin, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Tranexamic acid on day of surgery, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)

Outcome-specific analyses follow Sections 10.1 to 10.3. Adjustment for EuroSCORE II and site will be retained for the primary and prespecified secondary outcomes and any explicitly specified corresponding CLIP-II adjusted analysis. Cryoprecipitate and other additional haemostatic exposures will use study-adjusted comparisons without routine site or EuroSCORE II adjustment. PCC will be compared within CLIP-II only, with NZ zero exposure reported descriptively. The sensitivity analysis of 24-hour blood loss including ICU-arrival blood will use the principal and supporting adjusted models specified in Sections 9.2 and 9.3.

eTable 6. Postoperative laboratory outcomes

Descriptive summaries and outcome-specific comparisons will follow the corresponding CLIP-II analysis, adding study for pooled comparisons without routinely imposing additional site or EuroSCORE II adjustment.

Laboratory outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Effect estimate (95% CI); adjustment as specified
First 24 hours in ICU				
Lowest platelet count, median (IQR), x10^9/L	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Lowest haemoglobin, median (IQR), g/L	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Lowest fibrinogen, mean (SD), g/L	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Highest INR, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Highest aPTT, median (IQR), s	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
At ICU discharge				
Platelet count, median (IQR), x10^9/L	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Haemoglobin, median (IQR), g/L	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Fibrinogen, mean (SD), g/L	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
INR, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
aPTT, mean (SD), s	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Change from baseline to ICU discharge				
Platelet count change, mean (SD), x10^9/L	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Haemoglobin change, mean (SD), g/L	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Fibrinogen change, median (IQR), g/L	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)

The number analysed will be shown for each outcome when incomplete. Viscoelastic testing is not included in the core IPDMA tables because of sparse, instrument-specific measurements; it may be added descriptively only if harmonization and sample size are adequate.

eTable 7. Organ support, fluid exposure and resource-use outcomes

Supportive and exploratory outcomes adapted from JAMA eTable 3 and the prespecified time-to-event analyses.

Outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Effect estimate (95% CI); adjustment as specified
Cardiovascular support				
Norepinephrine on day 1, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Norepinephrine on day 2, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Epinephrine on day 1, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Dobutamine on day 1, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Vasopressin on day 1, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Fluid and cell-saver exposure				
Intraoperative crystalloid, median (IQR), mL	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Crystalloid from ICU admission to 6 h, median (IQR), mL	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Crystalloid from 6 to 24 h, median (IQR), mL	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Crystalloid from 24 to 48 h, median (IQR), mL	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Cell saver used intraoperatively, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Cell-saver blood returned, median (IQR), mL	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Time-to-event and resource use				
Time to extubation	Cumulative incidence at t	Cumulative incidence at t	Subdistribution hazard ratio	X.XX (X.XX to X.XX)
Time to ICU discharge	Cumulative incidence at t	Cumulative incidence at t	Subdistribution hazard ratio	X.XX (X.XX to X.XX)
Time to hospital discharge	Cumulative incidence at t	Cumulative incidence at t	Subdistribution hazard ratio	X.XX (X.XX to X.XX)
Time to postoperative aspirin	Cumulative incidence at t	Cumulative incidence at t	Subdistribution hazard ratio	X.XX (X.XX to X.XX)
Time to prophylactic heparin	Cumulative incidence at t	Cumulative incidence at t	Subdistribution hazard ratio	X.XX (X.XX to X.XX)

eTable 8. Additional safety outcomes and adverse events

Expanded safety detail; sparse outcomes will be reported descriptively.

Safety outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Effect estimate (95% CI)
APACHE II at ICU admission, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Lowest PaO2/FiO2 ratio in first 24 h in ICU, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference	XX.X (XX.X to XX.X)
Tracheostomy, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Maximum creatinine change from baseline, median (IQR), micromol/L	XX (XX-XX)	XX (XX-XX)	Difference in medians	XX.X (XX.X to XX.X)
Renal replacement therapy, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Intracranial haemorrhage, No. (%)	XX (XX.X)	XX (XX.X)	Descriptive	NE/XX
Systemic infection, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Local sternal wound infection, No. (%)	XX (XX.X)	XX (XX.X)	Descriptive; risk difference if estimable	NE/XX
Temperature >39 C during ICU stay, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Any prespecified DMSO-related complication, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)
Serious adverse event, No. (%)	XX (XX.X)	XX (XX.X)	Risk difference (percentage points)	XX.X (XX.X to XX.X)

Rare adverse events will be reported as counts and percentages. Comparisons will follow the corresponding CLIP-II approach and Section 10.7; adjusted modelling will not be introduced solely because event counts permit it. NE will be used where a treatment effect cannot be estimated. No P values will be reported.

eTable 9. Adherence sensitivity analysis for the primary and prespecified

secondary bleeding outcomes

Participants receiving early open-label platelets without meeting protocol-defined withholding criteria are excluded.

Outcome	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Unadjusted effect (95% CI)	Adjusted effect (95% CI)
Postsurgical chest-drain blood loss in first 24 h, geometric mean (95% CI), mL	XX (XX to XX)	XX (XX to XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
Total postsurgical chest-drain blood loss, geometric mean (95% CI), mL	XX (XX to XX)	XX (XX to XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
BARC4 bleeding, No. (%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
RBC units in the first 24 h after ICU admission, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Receipt of any RBC transfusion in the first 24 h after ICU admission, No. (%) (derived summary)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Receipt of any RBC transfusion from operation commencement to ICU discharge, death or day 7, No. (%) (derived summary)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Total RBC units from operation commencement to ICU discharge, death or day 7, median (IQR)	XX (XX-XX)	XX (XX-XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)

Effect measures and adjustment match the corresponding primary analysis. A separate baseline table for this subset is not planned because the sensitivity analysis addresses adherence rather than defining a new target population.

eTable 10. Treatment effects by constituent study and pooled IPDMA estimates

New table corresponding to the study-specific and pooled treatment-effect forest plot.

Outcome	Effect measure	CLIP-II effect (95% CI)	CLIPNZ-II effect (95% CI)	Pooled effect (95% CI)	Treatment-by-study interaction estimate (95% CI)
Primary 24-h chest-drain blood loss	Ratio of geometric means	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
Total postsurgical chest-drain blood loss	Ratio of geometric means	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
BARC4 bleeding	Risk difference (percentage points)	X.XX (X.XX to X.XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
Receipt of any RBC transfusion in the first 24 hours following ICU admission	Risk difference (percentage points)	X.XX (X.XX to X.XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)
All-cause mortality through 90 d	Hazard ratio	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)	X.XX (X.XX to X.XX)
Thrombotic/ARDS composite	Risk difference (percentage points)	X.XX (X.XX to X.XX)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)	XX.X (XX.X to XX.X)

Ratios compare cryopreserved with liquid-stored; risk differences are cryopreserved minus liquid-stored in percentage points. Treatment-by-study interactions are exploratory and compare the total bundle of between-study differences, including country, randomisation timing and platelet preparation. Interaction contrasts and 95% confidence intervals will be reported without P values.

eTable 11. Modified CHIPS-adapted haemostatic efficacy score

Exploratory tertiary outcome; no formal noninferiority or CHIPS Bayesian decision rule.

Score category or analysis	Cryopreserved platelets (n=XX)	Liquid-stored platelets (n=XX)	Effect measure	Estimate (95% CI)
Score distribution				
1 - Insignificant bleeding, No. (%)	XX (XX.X)	XX (XX.X)		
2 - Mild bleeding, No. (%)	XX (XX.X)	XX (XX.X)		
3 - Moderate bleeding, No. (%)	XX (XX.X)	XX (XX.X)		
4 - Severe bleeding, No. (%)	XX (XX.X)	XX (XX.X)		
5 - Massive bleeding, No. (%)	XX (XX.X)	XX (XX.X)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)		
Median (IQR)	XX (XX-XX)	XX (XX-XX)		
Exploratory treatment-effect analyses				
Principal linear mixed model			CPP minus LSP adjusted mean difference	XX.X (XX.X to XX.X)
Treatment-by-study interaction			Treatment-by-study interaction contrast	XX.X (XX.X to XX.X)
CLIP-II trial-specific estimate			CPP minus LSP mean difference	XX.X (XX.X to XX.X)
CLIPNZ-II trial-specific estimate			CPP minus LSP mean difference	XX.X (XX.X to XX.X)
Proportional-odds sensitivity model			Common OR for a lower, better category	X.XX (X.XX to X.XX)

Higher scores indicate worse bleeding. The principal estimand is cryopreserved minus liquid-stored mean score, so a negative mean difference favours cryopreserved platelets. For the cumulative-logit sensitivity model, an odds ratio greater than 1 favours cryopreserved platelets. Derivation limitations and complete-case rules are specified in SAP Sections 8.4 and 10.8.

A2.3 Planned figures and listings

Output	Title	Planned content
Figure 1	Combined participant flow	New combined flow showing both trials from randomization to study platelet receipt and analysis inclusion.
Figure 2	Primary outcome forest plot	Unadjusted and adjusted pooled ratios of geometric means with the 1.20 noninferiority margin.
Figure 3	Study-specific and pooled treatment effects	CLIP-II, CLIPNZ-II and pooled effects for primary and selected major outcomes, with interaction estimates.
eFigure 1	Cumulative chest-drain blood loss through 48 h	Treatment group trajectories, with study-specific summaries if useful.
eFigure 2	Cumulative blood components transfused through 48 h	RBC, plasma, platelets and cryoprecipitate trajectories.
eFigure 3	Time to postoperative aspirin	Cumulative incidence with death as a competing event.
eFigure 4	Time to prophylactic heparin	Cumulative incidence with death as a competing event.
eFigure 5	Time to extubation	Cumulative incidence with death as a competing event.
eFigure 6	Time to ICU discharge	Cumulative incidence with death as a competing event.
eFigure 7	Time to hospital discharge	Cumulative incidence with death as a competing event.
eFigure 8	Survival through 90 days	Kaplan-Meier curves by treatment group, with study indicated or stratified.
eFigure 9	Prespecified subgroups for the primary outcome	Pooled subgroup-specific estimates and treatment-by-subgroup interactions.

The site-specific early open-label cumulative-incidence figure from the JAMA supplement is not planned. No formal patient listings are proposed for publication; analysis-quality-control listings will be generated separately and retained with the statistical programming archive.