Trials

STUDY PROTOCOL

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PROthrombin complex concentrate versus fresh frozen Plasma for bleeding in adults undergoing HEart SurgerY (PROPHESY-2 trial): a phase III, randomised control trial in England and Wales

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Abstract

Background Fresh frozen plasma (FFP) is the standard treatment for severe bleeding following cardiac surgery. Despite increasing use of prothrombin complex concentrate (PCC) for coagulopathic bleeding in preference to FFP in the UK, the evidence comparing FFP versus PCC in this setting is lacking.

Hypothesis In adults who develop severe bleeding, PCC is superior to FFP in reducing a composite of mortality, organ failure, or infection up to 90 days following cardiac surgery, and is more cost-effective.

Methods Phase III pragmatic, multicentre, parallel group, superiority, non-blinded, open-label, two-stage group sequential randomised controlled trial with internal pilot embedded. Participants will be recruited by the research team at up to 20 hospitals in England and Wales. Those who have provided informed consent and who develop bleeding within 24 h of cardiac surgery (elective and urgent procedures) will be randomised to PCC (1500 IU if ≤70 kg or 2000 IU if >70 kg; a maximum of 2 doses) or FFP (4 units if ≤70 kg and 5 units if >70 kg; no maximum dose). Randomisation will be stratified by site and will allocate participants using minimisation, with a 1:1 ratio to receive PCC or FFP. Age (≥70 and <70 years) and planned type of surgery (valve only, major aortic surgery, coronary artery bypass graft + valve, and complex/combined procedure) will be the minimisation factors. The primary outcome is a composite of mortality or new onset of respiratory failure, myocardial injury, renal failure, liver injury, intestinal injury, focal neurological deficit, or infection at 90 days. Secondary outcomes will compare safety (transfusion-related reactions, thrombosis), quality of life, healthcare costs, and cost-effectiveness. A sample size of 496 participants will have a 90% power (with a 5% significance level) to detect a relative risk of 0.7 between the two groups at 90 days. The date of the 1st patient enrolled was 11th February 2025.

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Discussion This trial will provide evidence on the clinical/cost-effectiveness of PCC versus FFP in cardiac surgery patients who bleed post-surgery. Its outcome will provide high-quality evidence to inform the management of bleeding following cardiac surgery.

Trial registration ISRCTN 92114384. Registered on 16/04/2024. ISRCTN—ISRCTN92114384: PROthrombin complex concentrate versus fresh frozen Plasma for bleeding in adults undergoing HEart SurgerY (PROPHESY-2 trial)

Keywords Prothrombin complex concentrate, Fresh frozen plasma, Cardiac, Surgery, Haemorrhage, Randomised control trial, Transfusion

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	PROthrombin complex concentrate versus fresh frozen Plasma for bleeding in adults undergoing HEart SurgerY (PROPHESY-2 trial): a phase III, randomised control trial in England and Wales
Trial registration {2a and 2b}	ISRCTN 92114384 Item 2b is met
Protocol version {3}	Version 3.0, date: 30/04/2025
Funding {4}	National Institute for Health and Care Research—Health Technology Assessment (NIHR-HTA) Excess treatment costs reimbursed by National Health Service (NHS) Specialist Commissioning
Author details {5a}	Chief investigator: Professor Laura Green—Queen Mary University of London and NHS Blood and Transplant Co-leads: Dr Andrew Klein—Royal Papworth Hospital (co-lead) Professor Gavin Murphy—University of Leicester (co-lead) Sub-investigators: Dr Seema Agarwal—Manchester Royal Infirmary Professor Enoch Akowuah—South Tees Hospital Dr Josephine McCullagh—NHS Blood and Transplant and Barts Health NHS Trust Professor Mahmoud Loubani—Castle Hill Hospital Mrs Sarah Murray—Patient and Public Representative Professor Julie Sanders—King's College London Laura Simpson—Queen Mary University of London Professor Simon Stanworth—NHS Blood and Transplant Dr Florian Tomini—Queen Mary University of London NHS Blood and Transplant Clinical Trials Unit: Charlie Brown, Claire Rourke, Emily Arbon, Jessica Workman, Laura Smith, Cara Hudson, Eleanor Hounslea, Naomi Vides, Maisie Gardner
Name and contact information for the trial sponsor {5b}	Dr Gerry Collins, Research Governance Operations Manager, Queen Mary University of London
Role of sponsor {5c}	The trial sponsor, Queen Mary University of London (QMUL), and funder (NIHR HTA) do not have any role in study design; data collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

Introduction

Background and rationale {6a}

The health problem being addressed

Clinically important bleeding, defined as large volume blood loss (14%), non-routine treatment of coagulopathy (25%), or emergency reoperation for bleeding (3%), occurs in 30%–35% of cases [1, 2] and is associated with increased risks of infection and a four-fold increase in organ injury to the heart, lungs, or kidneys, or death [3–6].

Bleeding following cardiac surgery is commonly attributed to coagulopathy caused by consumption of coagulation factors resulting from activation in the cardiopulmonary bypass circuit. The existing standard of care for treatment of bleeding due to coagulopathy in cardiac surgery in the United Kingdom (UK) is transfusion of fresh frozen plasma (FFP) [7] which provides a balanced source of pro- and anti-coagulation factors. However, FFP transfusion has potential harms (e.g. allergic/anaphylactic reactions, transfusion-transmitted infection) [8], and more importantly, the evidence base for its benefit in cardiac surgery is limited [9].

Prothrombin complex concentrate (PCC) is an alternative agent increasingly being used worldwide instead of FFP in cardiac surgery patients who are bleeding not relating to vitamin K antagonists [10]. PCC is manufactured from large volumes of human plasma and is a more concentrated form of pro-coagulants. Potential clinical advantages over FFP include reduced volume load and risk of transfusion-associated circulatory overload, higher concentrations of clotting factors, lower risk of transfusion transmitted infection, and fewer immune modulatory allergic/anaphylactic reactions [11, 12]. One

possible adverse effect of PCC is thromboembolic complications, due to the administration of concentrated (pro-coagulant) clotting factors, although this has not been proven from the recent studies [11].

Until recently, the literature comparing FFP vs. PCC was dominated by two pilot randomised control trials (RCTs) [2, 13]. More recently, a phase III, RCT (the FARES-II: 420 patients analysed) that compared FFP versus PCC in adult patients who require coagulation factor replacement for bleeding during cardiac surgery demonstrated that PCC is a safe treatment and has superior haemostatic effectiveness to FFP (77.9% vs. 60.4%; difference, 17.6%; 95% CI, 8.7%–26.4%; $p < 0.001$ for noninferiority and superiority) [14]. However, more evidence is still needed on the effect of PCC on outcomes beyond haemostasis, underscoring the need for further research in this area. This paper describes the protocol of a multicentre RCT in England and Wales that will compare FFP versus PCC (four factors) in adult patients undergoing cardiac surgery.

Objectives {7}

Primary objective

To determine if the treatment of bleeding with PCC in adult patients who are actively bleeding within 24 h of the start of cardiac surgery is superior to FFP with respect to a composite of mortality, organ failure, or infection, up to and including 90 days from randomisation.

Secondary objectives

To determine if PCC is superior to FFP in terms of (1) components of the primary outcome, (2) clinical evidence of haemostasis, (3) length of stay in hospital during index hospitalisation, (4) duration of mechanical ventilation (during index hospitalisation), (5) hospital re-admission, (6) safety including thrombotic risks, (7) quality of life, and (8) cost-effectiveness.

Trial design {8}

Phase III, randomised, controlled, pragmatic, superiority, multicentre, open-label two-stage group sequential trial, with internal pilot and embedded health economic analysis. The allocation ratio is 1:1.

Methods: participants, interventions, and outcomes

Study setting {9}

NHS cardiac surgery centres in England and Wales.

Eligibility criteria {10}

Inclusion criteria

Age ≥ 18 years, who are undergoing cardiac surgery (elective and urgent procedures) not described in the exclusion criteria, and who provide informed consent.

Exclusion criteria

- Emergency and salvage procedures (defined below by the National Institute for Cardiovascular Outcomes Research (https://www.nicor.org.uk/) as there is not time for patients to provide consent:

  Emergency procedures include unscheduled patients with ongoing refractory cardiac compromise, where there should be no delay in surgery/intervention irrespective of the time of day.
  Salvage procedures include patients requiring cardiopulmonary resuscitation (external cardiac massage) en route to the operating theatre or prior to the induction of anaesthesia.

- First-time isolated coronary artery bypass graft (CABG) surgery given the low risk of significant bleeding.
- First-time isolated aortic valve replacement (excluding active endocarditis).
- First-time isolated mitral valve replacement.
- Surgeries that do not involve cardiopulmonary bypass.
- Heart transplant.
- Use of warfarin within 3 days prior to surgery.
- Use of direct oral anticoagulants (i.e. dabigatran, rivaroxaban, apixaban, or edoxaban) within 48 h prior to surgery (or 72 h if the patient has renal impairment—i.e. estimated glomerular filtration rate of <30 ml/min).
- Any contraindication to PCC or FFP or LG-Octaplas, for example known or suspected allergy to heparin, sodium citrate dihydrate, sodium dihydrogen phosphate dihydrate, and glycine, history of heparin-induced thrombocytopenia, and history of blood transfusion reaction due to IgA deficiency with known antibodies against IgA.
- Patients refusing blood transfusion for any reason.
- Inherited bleeding disorder (i.e. any inherited clotting factor deficiencies or platelet disorders).
- Pregnancy as PCC is contraindicated.
- Documented thrombophilia defects (antiphospholipid syndrome, severe protein S deficiency, antithrombin deficiency).
- Documented venous thromboembolism in the last 3 months prior to surgery.
- Patients who are expected to require extracorporeal membrane oxygenation after cardiac surgery.
- Patient previously randomised into this trial and has not reached 90 days post-randomisation.

Who will take informed consent? {26a}

Informed consent will be obtained prior to surgery by a trained and qualified staff member, who has been delegated this task by the site's principal investigator.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

There is no collection of biological specimens or use of participant data in ancillary studies as part of this trial.

Interventions

Explanation for the choice of comparators {6b}

Fresh frozen plasma (FFP) is the current standard of care in the UK [8] and is therefore the comparator in this trial.

The dose of FFP will be determined by the participant's weight: i.e. 4 units if participants ≤70 kg or 5 units if participant >70 kg.

Intervention description {11a}

A four-factor prothrombin complex concentrate (PCC) is the intervention. The PCC product administered to a participant will depend on the product already in use in each hospital. The products currently approved for use in the trial are Beriplex (CSL Behring), Octaplex (Octapharma Ltd), and Prothromplex (Takeda UK Ltd).

The dose of PCC will be determined by the participant's weight: i.e. 1500 IU if participants ≤70 kg and 2000 IU if participant >70 kg.

The control or the intervention will be issued at the point when clinicians request FFP from the transfusion laboratory for the treatment of active bleeding or in anticipation of bleeding. At this point, the laboratory staff will perform a randomisation via the virtual web randomisation system Sealed Envelope.

Criteria for discontinuing or modifying allocated interventions {11b}

A maximum of two doses can be administered to a participant for the intervention (PCC). If the participant continues to bleed after two doses, patients will be treated with standard of care.

There is no limit to the number of doses of FFP a participant may receive.

Strategies to improve adherence to interventions {11c}

To improve adherence with the protocol, all staff involved with recruiting patients and delivering the intervention and control will be trained. Non-adherence will be considered to have occurred if: (a) the laboratory fails to randomise the patients, (b) the wrong FFP or PCC doses are given, (c) the clinician fails to administer the allocated treatment. All these are prohibited and will be closely monitored throughout the study, with monitoring key performance indicators being agreed prior to the study starting, where sites will be expected to comply with these indicators.

Relevant concomitant care permitted or prohibited during the trial {11d}

- Any contraindication to PCC or FFP or LG-Octaplas as highlighted under exclusion criteria
- A positive pregnancy test on hospital admission

Provisions for post-trial care {30}

There are no provisions for ancillary and post-trial care as the procedure that participants are undergoing is considered routine for patients with their diagnoses. Their care is followed up as part of the treatment they would routinely receive.

The sponsor has insurance in place that provides cover for the design and management of the trial as well as 'No fault compensation' for participants, which provides indemnity to participants for negligent and non-negligent harm.

Outcomes {12}

Primary endpoint(s)

A composite of any of the following new events up to 90 days from randomisation:

- All-cause mortality
- Acute respiratory failure
- Acute myocardial injury
- Acute renal failure requiring renal replacement therapy (excluding dialysis during cardiopulmonary bypass)
- Acute liver injury
- Acute intestinal injury
- Focal neurological deficit
- Infection

Definitions of organ failure and infections are provided in Table 1.

Secondary endpoint(s)

Secondary outcomes include:

1. Individual components of the primary outcome up to 90 days from randomisation or death, whichever occurs first, as defined under primary outcome and Table 1.
2. Clinical evidence of haemostasis defined as [17]:
    - Amount of blood loss (in ml) collected in chest drains at 6 h and 24 h post end of surgery
    - Amount of total allogeneic (in units) blood transfusion (red blood cells, fresh frozen plasma, cryopre-

Table 1 Definition of organ failure and infection

Acute respiratory failure	Acute lung injury defined as PaO2/FiO2 ratio < 300 mmHg and CPAP/PEEP of 5 cmH2O (490 kPa)
Acute myocardial injury	New low cardiac output syndrome; mechanical circulatory support (i.e. extracorporeal membrane oxygenation, left ventricular assist device, impella, and balloon pump) or a primary inotrope support (levosimendan, milrinone, enoximone) persisting after 24 h post-surgery during the index admission, or during any subsequent admission
Acute renal failure	Renal failure requiring renal replacement therapy (excluding dialysis during cardiopulmonary bypass) [16]
Acute liver injury	Acute derangement of liver enzymes (AST or ALT) three times the upper limit of normal, or a serum amylase concentration > 1000 ng/ml
Acute intestinal injury	Radiological, operative, or post-mortem evidence of gut ischaemia due to hypoperfusion
Focal neurological deficit (stroke)	Diagnosed by brain imaging (CT or MRI), in association with new onset focal or generalised neurological deficit (defined as deficit in motor, sensory, or co-ordination functions)
Infections	Suspected or documented infection that results in the commencement of intravenous antibiotics or hospitalisation (excluding routine antibiotic treatment post-surgery for atelectasis)

cipitate, platelets), total dose of haemostatic factor concentrates (PCC, fibrinogen concentrate, activated recombinant factor VIIa, or any other blood product concentrate) at 24 h and 7 days from randomisation
- Whether re-exploration for bleeding up to 7 days post end of surgery was required, and whether a surgical point of bleeding was identified

3. Length of stay in hospital during index hospitalisation, measured in days, up to and including 90 days from randomisation, or hospital discharge or death, whichever occurs first.
4. Duration of mechanical ventilation (in days) during index hospitalisation up to 90 days from randomisation, or hospital discharge or death, whichever occurs first.
5. Number of hospital re-admissions (in days) up to and including 90 days from randomisation.
6. Safety measured from the point of randomisation through:

    a *Transfusion adverse events* up to 7 days or hospital discharge or death, whichever is first. These will be defined as per UK Serious Hazard of Transfusion (www.shotuk.org/reporting) definitions and will include:

    - Acute transfusion reactions that could result in shock or cardiac arrest
    - Haemolytic transfusion reactions (acute or delayed)
    - Post transfusion purpura
    - Transfusion-associated graft versus host disease
    - Transfusion-associated circulatory overload
    - Transfusion-associated dyspnoea
    - Transfusion-related acute lung injury

    b *Thrombotic events (arterial and venous)* confirmed by radiological imaging, autopsy, or through surgical means, up to 90 days or death, whichever occurs first.

    c Other serious adverse events reported up to 90 days or death, whichever occurs first.

7. Quality of life (QoL) measured using the:

    a EQ-5D-5L at baseline, hospital discharge or 28 days (whichever occurs first), and 90 days after randomisation [18].

The EQ-5D-5L is a health questionnaire comprised the EQ-5D descriptive system and the EQ visual analogue scale (EQ-5D-5L—EuroQol). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

    b Disease-specific QoL questionnaire, either:

        i. Coronary Revascularisation Outcome (CROQ) at baseline (prior to randomisation) and 90 days after randomisation for CABG + valve and complex/combined procedures, or
        ii. Kansas City Cardiomyopathy (KCCQ) at baseline (prior to randomisation) and 90 days after randomisation for valve only and major aortic surgery

    – Both meet the minimum metric properties and have been previously validated in coronary bypass surgery [19–21].

The CROQ is a patient-reported outcome designed to evaluate patient health and quality of life prior to and post cardiopulmonary artery bypass grafting and percutaneous transluminal coronary angioplasty. It comprises 4 core content domains: symptoms, physical functioning, psychosocial functioning, and cognitive functioning. The post-surgery version contains two extra content domains: adverse effects and satisfaction [19]. The questions are organised into categories, each with 1–10 questions in each category and 5–6 options for the respondent to select from in each of those categories. The options range from being moderately affected by their diagnosis and subsequent surgery, to not being affected at all, or the frequency of taking medication to alleviate symptoms in the pre-surgery questionnaire. The post-surgery version contains additional questions on the patient's recovery.

The KCCQ is a tool to assess health status in patients with heart failure, covering symptoms, functional limitations, and quality of life. The questionnaire is suitable for all ages 18 years and older.

The questionnaire includes 23 items, grouped into 7 domains, which are further used to calculate overall and summary scores.

8. In-patient hospital costs, and separately follow-up health care costs at 90 days.

We will collect resource-use information and costs related to care delivered in both the intervention and control groups. Resources related to the inpatient stay and treatment cost will be informed by the participant's medical records while in the hospital. During the follow-up period after discharge, we will collect additional resource usage information. A previously validated self-report resource utilisation measure, ModRUM [31], will be used for the collection of resource usage after initial discharge from the hospital. Resource-use data for each participant will be collected using this form from discharge to 90 days after surgery.

Participant timeline {13}

Patients can be approached by delegated members of the research team up to 90 days prior to surgery. Eligible participants who provide consent are considered enrolled in the trial.

If the participant does not develop bleeding that requires treatment with FFP within 24 h of the start of surgery, that participant is no longer part of the trial and all data collection stops (Table 2).

If the participant develops bleeding that requires treatment with FFP or is anticipated to bleed and require FFP within 24 h of the start of surgery, the participant will be randomised into the trial and will be followed up for a period of 90 days after surgery. For this group, data will be collected at the following points:

1. Baseline
2. Surgery up to 24 h post-surgery or randomisation, whichever is later
3. Post-op until hospital discharge, death, or 28 days, whichever is first
4. D42 post-surgery or first routine outpatient appointment post-surgery
5. D90 post-surgery

Please refer to Fig. 1, the CONSORT diagram.

Sample size {14}

To detect a difference between a 50% primary outcome event rate in the FFP (control) arm and a 35% rate in the PCC arm (relative risk of 0.7) with 90% power and 5% type I error in a standard two-arm trial, 454 randomised participants would be required. A two-stage group sequential design was used to allow for one planned interim analysis for harm or benefit after 75% recruitment (using non-binding O'Brien-Fleming stopping rules [22]), and this increases the required sample size to 470.

Finally, the sample size is inflated to include a 5% allowance for withdrawal or loss to follow-up, which is twice that observed in the pilot trial [2], giving a final sample size of 496 participants randomised (248 per group). The rate of loss to follow-up will be assessed at the pilot stage, and if any increased allowance for drop-out is required, this will be considered and discussed with the Trial Steering Committee and funder.

The assumptions in the sample size are based on the following: 1. The observed primary endpoint event rate in the pilot trial where 50% in the control arm developed one or more of the primary end points (mortality 4% [1/26], organ injury 31% [8/26], infection 31% [8/26]). 2. A relative risk of 0.7 for the PCC arm versus the control for the primary outcome, as observed in the pilot trial. 3. This treatment effect is similar to the minimally important treatment effect specified in other effectiveness trials of organ protection interventions in cardiac surgery [23–25] and is likely to change practice.

Recruitment {15}

In this trial, we aim to open one site in month 1, then a further 2 sites every 2 months, so we will have 9 sites recruiting by month 9. We have estimated to randomise 2 participants per month per site, achieving 144 randomised participants in the first year (due to this staggered opening) and 352 in year two (496 randomised participants in total over 24 months) from 15 sites.

Table 2 PROPHESY-2 participant timeline for randomised participants

Trial procedure	Screening Pre-op	Hospital admission	Surgery up to 24 h post-surgery or randomisation, whichever is later	**Post-op until hospital discharge, death or 28 days (whichever is first)	Day 42 or first routine outpatients appt post-surgery)	Day 90
Visit windows	−90 to 0 days	Day −1 or day 0	Day 0 up to 24 h	±2 days	±7 days	±14 days
Screening—assess eligibility	X					
Urine pregnancy test[a]		X				
Informed consent	X	X				
Medical/cardiac history		*X				
Weight	X					
Medications			*X (pre- and peri-op)	X (discharge)		X
EuroSCORE II		*X				
Routine laboratory results[b]		*X (pre-op)	*X (post-op)			
Add and remove the flag from transfusion lab system			X			
Randomisation			X			
Time and dose of treatment			X			
Clinical assessment[c]			X	X	X	X
Thromboembolic AE/SAE[d]			X	X	X	X
Transfusion AE/SAE			X	X[e]		
Safety reporting			X	X	X	X
Hospital re-admission since discharge					X	X
Self-reported resource-use measure ModRUM (email, phone, or post)						X
EQ-5D-5L and CROQ or KCCQ questionnaires (email, phone or post)[f]		X (EQ-5D-5L and KCCQ/CROQ)		X (discharge or 28 days, whichever is first: EQ-5D-5L)		X (EQ-5D-5L, KCCQ/CROQ)
90-day survival status—end of trial form (phone or clinic visit)						X

Op operation, *AE* adverse events, *SAE* serious adverse events, *CROQ* Coronary Revascularization Outcome, *KCCQ* Kansas City Cardiomyopathy Questionnaire

* Includes pre-operative data to be added to the database post randomisation

** Post-operative data to be collected at 24 hours post surgery, day 5 and day 7 or until discharge, or death, whichever is first. For participants who stay in hospital more than 7 days, data will be collected every 7 days up to 28 days, or death or discharge, whichever is first

[a] Anyone of childbearing potential

[b] routine blood tests include: AST, ALT, creatinine, urea, haemoglobin, platelets, PT, APTT and fibrinogen

[c] Clinical assessment will include primary and secondary outcome measures captured from hospital clinical notes

[d] At 90 days, the following clinical outcomes will be collected based on a follow-up visit or via telephone call: All-cause mortality, new onset of renal, pulmonary and heart failure, stroke, infection, thromboembolic events or hospital re-admission since discharge

[e] Transfusion related AEs and SAEs are only collected until day 7

[f] Baseline questionnaires must be completed on paper prior to surgery, however data collection via the eCRFs is only required post randomisation

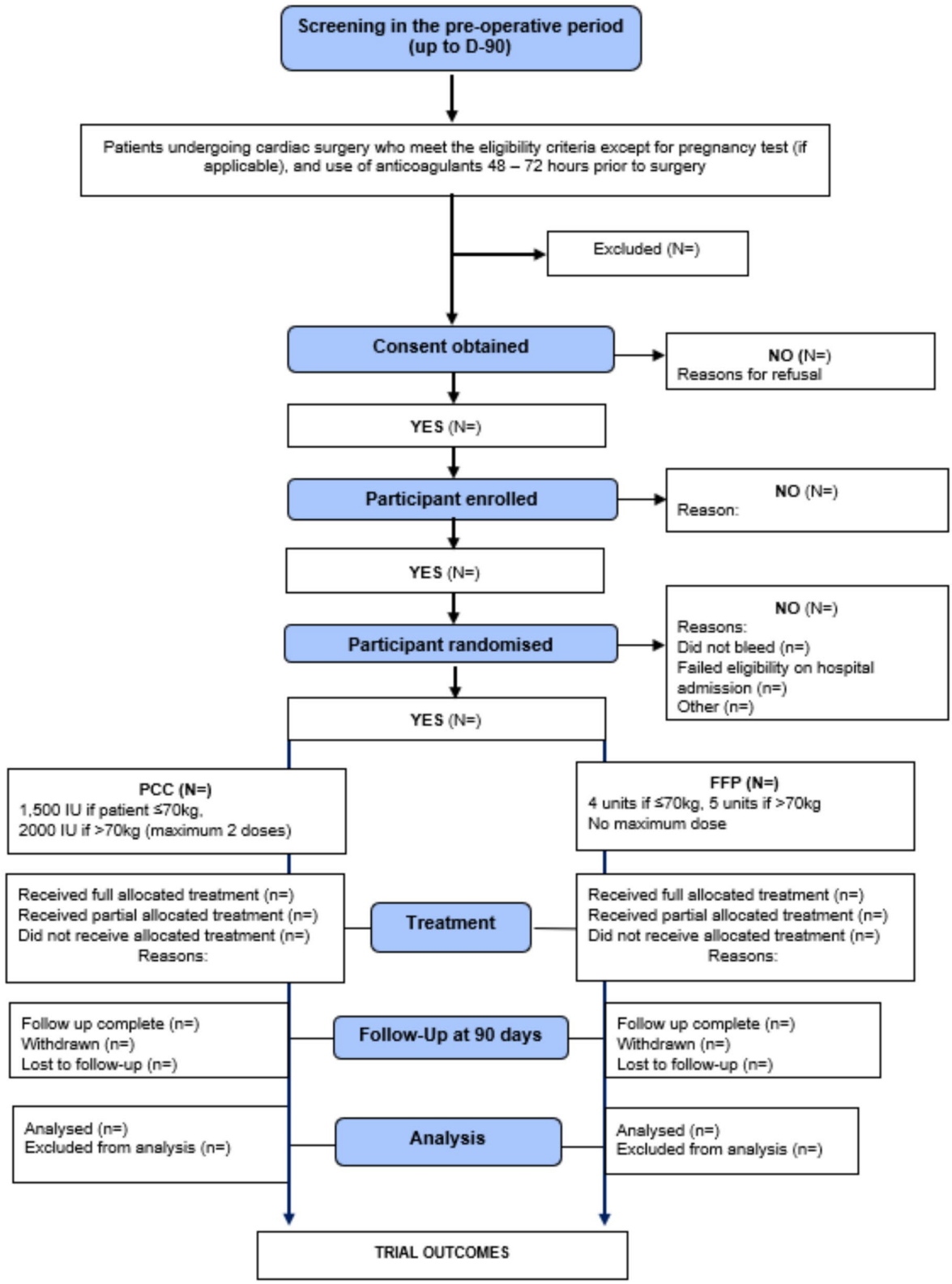

Fig. 1 PROPHESY-2 trial CONSORT flow diagram

Assignment of interventions: allocation

Sequence generation {16a}

Randomisation will be stratified by site and will allocate participants using minimisation, with a 1:1 ratio to receive PCC or FFP. The treatment group that would provide the most balance will be chosen with a probability approximately equal to 85%. Age (≥70 and <70 years) and planned type of surgery (valve only, major aortic surgery, CABG+valve, and complex/combined procedure) will be the minimisation factors. A centralised web-based randomisation service (Sealed Envelope Ltd, London, UK) will be used.

Concealment mechanism {16b}

The allocation is determined by the virtual web randomisation service Sealed Envelope. This ensures randomisation according to strata and requires no concealment.

Implementation {16c}

Treatment allocation will be generated by Sealed Envelope. Each result will be emailed to the site where the randomisation was performed. The allocated treatment will be issued by the transfusion lab, according to their established procedures.

Assignment of interventions: blinding

Who will be blinded {17a}

Due to physical differences between the two treatments, it is not possible to blind the care providers to the treatment allocation. To minimise bias: 1. The treating clinicians will be blinded to group assignments until immediately prior to infusion of interventions. 2. Choosing objective primary and secondary outcome measures means that the risk of detection bias is low. 3. Minor and major protocol deviations will be pre-specified, and these will be carefully monitored throughout the trial to assess performance bias. Trial participants will not specifically be told which arm they are randomised to, but because the trial is open-label, nothing will be done to prevent them from finding out which treatment they have received. The trial team and chief investigator will be blinded to the treatment allocations wherever possible. In Data Monitoring Committee (DMC) meetings, only members of the DMC and the trial statistician will be present for the closed section of the meeting which will contain trial data aggregated by treatment arm.

Procedure for unblinding if needed {17b}

Not applicable: there is no blinding in this trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data collection and data entry at all time points throughout the trial will be performed by the research team at each participating site according to the electronic case report forms (eCRFs) in the trial database. All data collection forms are contained within the trial electronic database and metadata documents.

Plans to promote participant retention and complete follow-up {18b}

As the intervention is only delivered by the clinical care team within the first 24 h from the start of surgery, there is no risk of participants deviating from intervention protocols. Participants are not required to attend any additional appointments for follow-up, and data collection can be completed over the phone to help lessen the burden on participants and reduce the risk of missing data.

For participants who do wish to withdraw from the trial, they will be asked:

a) Whether they are happy for the data collected so far to be retained
b) Whether they are happy for future data to be collected during the remainder of the 90-day follow-up period if it does not involve them being contacted

If participants request for their data to be deleted, they will be advised that it is a requirement for safety data to be retained.

Data management {19}

The principal investigator has overall responsibility for data collection at each site. Participant data will be entered onto the trial database, which was designed and will be administered by the NHSBT Clinical Trials Unit Data Management team using OpenClinica. The OpenClinica database will be used for electronic data capture (EDC) management and reporting on this trial. Training and instructions for completion of eCRFs will be given to each site during site activation.

All case report forms will be electronic. The eCRFs will be completed directly onto the EDC system (i.e. the database). The NHSBT CTU staff will be in regular contact with local site personnel to check on progress and to help with any queries that may arise. Incoming electronic forms will be checked for completeness, consistency, timelines, and compliance with the protocol.

Direct access to eCRF data will be granted to authorised representatives from the sponsor, NHSBT CTU, host institution, and the regulatory authorities to permit trial-related monitoring, audits, and inspections in line with participant consent.

Confidentiality {27}

No participants will be individually identifiable from any publications resulting from the trial.

Information regarding trial participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the UK Policy Framework for Health and Social Care, and Research Ethics Committee approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act and as defined in the sponsor's standard operating procedure.

De-identification of participants

A screening log will be maintained by each site throughout the trial. Participants will be assigned a screening number as they are entered on to the screening log. The participants' initials (the first letter of their first name and the first letter of their last name) will be used as a means of pseudo-anonymising parameters and to allow their identification by authorised research staff. This information will be kept on the screening log.

Patients who provide consent to participate in the trial will be entered into the clinical database and assigned a trial ID. If they are randomised into the trial, they will also be assigned a randomisation number. Participants who are not enrolled into the trial (i.e. patients undergoing an eligible procedure who decline to give consent) will be referred to by their screening number. Identifiable information (name, hospital number) will be recorded for the purposes of identification, consent, and data collection. In addition, contact information for the participant (address, telephone number, and email address) will be collected for follow-up purposes. General practitioner details will be collected to inform them of their participant's involvement in the trial.

Identifiable information will be stored in a secure location at the study site, accessible only to members of the local research team.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable: there is no biological specimen collection in this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The main analysis of the primary outcome will be performed on an intention-to-treat population and will include all randomised participants, including participants randomised in error, participants withdrawn, lost to follow-up, or any with a protocol deviation, where possible. A per-protocol population will be used for a sensitivity analysis. Full details of the statistical analysis will be specified in a separate Statistical Analysis Plan.

All tests and 95% confidence intervals for measures of treatment effect will be two-sided, and a significance level of 0.05 will be used (however, the primary outcome significance level will be adjusted to account for the sequential design using O'Brien-Fleming boundaries). For key baseline characteristics, mean and standard deviation will be used to summarise continuous data (significantly skewed data will be summarised as a median alongside an interquartile range), and categorical data will be presented as counts and proportions.

Primary endpoint analysis

The proportion of participants with a new event of any of the primary endpoints listed under outcomes will be calculated for each arm. The arms will be compared using mixed logistic regression, adjusted for site as a random effect to account for clustering, age (≥70 and <70 years), and type of surgery (valve only, major aortic surgery, CABG + valve, and complex/combined procedure) as fixed effects.

The primary outcome significance level will be adjusted to account for the sequential design using O'Brien-Fleming boundaries.

Secondary endpoint analysis

The proportion of participants in each arm will be calculated for each of the component parts of the primary outcome. The arms will be compared using mixed logistic regression, adjusting for site, age, and type of surgery. Other binary data will be analysed in the same way.

Time to event data will be analysed using mixed Cox proportional hazards regression. The Kaplan-Meier method will be used to estimate the proportion experiencing the event (and 95% confidence interval) in each arm. Competing risks methodology will be used where appropriate.

Continuous data will be summarised using mean and standard deviation for each arm (or median and interquartile range if the data are skewed) and will be analysed using mixed linear regression, adjusting for site, age, and type of surgery.

Safety analysis

The number of transfusion adverse events, thrombotic events, and other serious adverse events will be reported by arm.

Interim analyses {21b}

There will be a formal interim analysis after 75% recruitment ($n = 372$ participants randomised and reached the primary outcome) to check if it is possible to stop the trial early due to harm or benefit (the trial will not be stopped for futility). The primary outcome rates will be compared between the arms, as specified for the main

primary outcome analysis. Based on the O'Brien-Fleming stopping boundaries, significant evidence of harm or benefit will be identified with a p value < 0.02. The trial statistician will perform the analyses. The Data Monitoring Committee (DMC) will review the results of the interim analysis and will use these as a guideline alongside other safety data to provide a recommendation to the Trial Steering Committee (TSC). This will indicate if they believe that the trial should be stopped early.

The DMC will also review accumulating safety data periodically and will be the only group (along with the trial statisticians) who will see the endpoint data (from the interim analysis) while the trial is ongoing. Neither will be blinded to the trial groups. The TSC and the sponsor retain the right to stop the trial, should the need arise.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Subgroup analyses of the primary outcome will be conducted by including an interaction term in the mixed logistic regression model. These will include age, sex assigned at birth, type of surgery, median baseline EuroSCORE II, and presence of anaemia pre-surgery. All these factors have been associated with an increased risk of post-cardiopulmonary bypass blood product usage in adult cardiac surgical patients.

Sensitivity analysis: The primary outcome analysis will be repeated for a per-protocol population, where patients randomised in error, withdrawn, or with protocol deviations will be excluded. It will also be repeated (per protocol) after risk adjustment for relevant baseline risk factors (age, gender, type of surgery, and eGFR) by building a multivariable logistic regression model and, separately, presented for each site in a forest plot. The analysis of the individual components of the primary outcome, achievement of haemostasis, and overall transfusion and thrombosis rates will also be repeated using the per-protocol population.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

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

We anticipate that the primary outcome will be available in >95% of participants, and our sample size calculation allows for this. However, if the primary outcome is missing in more than 5% of participants and to explore if missing values have an undue impact on the primary outcome result, we will also undertake sensitivity analysis by using multiple imputations based on full conditional specification to impute missing primary outcome data. Multiple imputations will also be used to impute the values of any missing data for relevant baseline risk factors in the fully risk-adjusted sensitivity analysis.

Health economic evaluation {20dq}

A within-trial cost-utility analysis will be conducted from the perspective of the UK National Health Service and Personal Social Services, following the National Institute for Health and Care Excellence (NICE) reference case standards [18]. Costs will be derived from individual-level data on hospital resource use during the index admission (from medical records) and post-discharge care (from self-reported ModRUM questionnaires) [26]. Unit costs will be applied using national sources including NHS Reference Costs, PSSRU, and the BNF [28]. Outcomes will be measured in quality-adjusted life years (QALYs), calculated using EQ-5D-5L responses collected at baseline, 28 days after hospital discharge, and 90 days after hospital discharge. Utility values will be derived using the van Hout et al. mapping function to convert EQ-5D-5L responses to the EQ-5D-3L UK value set, in line with NICE's current reference case guidance and position statement [18, 29]. An incremental cost-effectiveness ratio (ICER) comparing PCC to FFP will be calculated. Uncertainty around the ICER will be explored through bootstrapping and presented using cost-effectiveness acceptability curves. Subgroup and scenario analyses will be conducted, and results will be presented in accordance with the CHEERS 2022 reporting standards [30]. Full details will be provided in a separate Health Economic Analysis Plan.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The full trial protocol is available on request. Access to the participant-level data and statistical codes will be available on request from the sponsor.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

NHS Blood and Transplant (NHSBT) Clinical Trials Unit (CTU) is the trial coordinating centre and data coordinating centre for the trial. The CI and the CTU will undertake trial management responsibilities for the trial.

The Trial Management Group (TMG) consists of the CI, co-investigators, trial manager, data manager, patient researcher, statistician, PPI lead, health economist, sponsor representative, and other key collaborators in the CTU. The TMG is responsible for the day-to-day

running and management of the trial. It will meet at least monthly, and more often during set-up and close-down phases of the trial.

The role of the Trial Steering Committee (TSC) is to provide overall supervision for the trial and provide advice on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the principles of Good Clinical Practice in Clinical Trials. The ultimate decision on the continuation of the trial lies with the TSC. The TSC will meet bi-annually and will be chaired by an independent member. The other members of the TSC include two independent clinical experts, patient representative, statistician, independent health economist, the TMG chair, and the sponsor.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Data Monitoring Committee (DMC) consists of independent clinicians with an interest in bleeding, in cardiac surgery and one independent statistician. The responsibilities of the DMC will be to (1) periodically review and evaluate the accumulated trial data for participant safety, trial conduct and progress, recruitment, and, when appropriate, efficacy, and (2) make recommendations to the TSC concerning the continuation, modification, or termination of the trial.

The DMC considers trial-specific data as well as relevant background knowledge about the disease, trial treatments, or patient population under trial. The DMC will meet every 6 months, or more frequently if required.

Adverse event reporting and harms {22}

All serious adverse events (SAEs) will be reported in the trial database, OpenClinica, for the following time periods from the first dose of IMP:

- Transfusion-related SAEs: 7 days
- Thromboembolic SAEs: 90 days
- All other SAEs: hospital discharge, 28 days, or death, whichever is soonest

All SAEs that occur after hospital discharge, 28 days from treatment, or death will be recorded in the source data and as adverse events (AEs) unless they relate to thromboembolic events, in which case they must be reported as an SAE. All deaths of randomised participants will be reported as an SAE regardless of when they occurred.

All events that are assessed to meet the definition of serious and have a reasonable causal relationship to the IMP up to 90 days will be reported to the NHSBT CTU within 24 h of awareness. These will be investigated as potential suspected unexpected serious adverse reactions (SUSARs).

Frequency and plans for auditing trial conduct {23}

The sponsor retains the right to audit any aspect of the trial, trial sites, or central facilities. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable. All sites and vendors are asked to inform the sponsor if notified of any audit or inspection affecting this trial. Inspections may be carried out by the competent authority at any time, and the investigator should notify the sponsor immediately if there are any such plans for an inspection.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any substantial protocol amendments to the approved protocol will be communicated to all relevant parties in an expedited manner by the CTU via email.

Dissemination plans {31a}

On completion of the trial, the data will be analysed and tabulated, and a final trial report prepared by NHSBT CTU. The manuscript will be prepared by the relevant members of the writing group and the trial investigators. Draft copies of all trial manuscripts will be circulated to all collaborators for review prior to their submission for publication. Responsibility for all trial publications will rest with the TMG. The main trial results will be presented at national and international conferences and published in a peer-reviewed journal, on behalf of all collaborators. Participants will be able to access the results through the trial website. No data may be made public before publication and without agreement from the CI and sponsor.

Discussion

PROPHESY-2 is a phase III, randomised controlled trial that will determine if PCC is superior to FFP (current standard of care) in reducing the composite of mortality, organ failure, or infection in adult patients who are undergoing cardiac surgery and who develop bleeding within 24 h of surgery. Moreover, the trial also has an integrated health economic evaluation to determine if PCC is a cost-effective treatment for the National Health Service (NHS).

The choice of the primary outcome follows our hypotheses that presuppose that PCC having more concentrated clotting factors and lower volume will promote effective haemostasis and reduce organ injury, infections, and death, whereas FFP will not. Indeed, in a post hoc analysis of two RCTs that compared PCC and FFP for warfarin reversal ($n = 181$ patients), FFP increased fluid overload and cardiac events versus PCC (12.7% vs. 4.7%) [31].

Recently, Karkouti and colleagues published the results of the FARES-II trial [14] and demonstrated a significant

reduction in the requirement for additional haemostatic interventions in people with bleeding after cardiac surgery who were allocated to receive four-factor PCC versus FPP. However, the use of 'additional haemostatic interventions' as the primary outcome in the FARES-II trial does not align with the COMET minimum core outcome set for cardiac surgery trials [32], which recommend that clinically important outcomes (mortality, organ injury, hospitalisation, and quality of life) should be used in cardiac surgery trials. Further, the analyses showing differences in severe adverse events and acute kidney injury in FARES-II did not provide sufficiently robust evidence to inform practice.

This is because treatment allocation was not blinded to clinicians, these outcomes were not pre-specified in the study protocol [33] or adjudicated, the analyses were post hoc, and the safety outcomes pre-specified in the protocol did not demonstrate differences. In previous trials of other haemostatic agents like recombinant factor VII, including in cardiac surgery, safety effects were only apparent after meta-analyses of multiple randomised controlled trials [15]. Together, these considerations argue for more evidence to compare PCC versus FFP in cardiac surgery.

The other important element of the trial is the pragmatic nature. We considered mandating the use of viscoelastic point of care testing or the conventional clotting test for deciding when to randomise patients; however, we decided not to mandate these for the following reasons: in clinical practice, the decision to administer FFP is based on multiple factors, only one of which may be the clotting test results; the diagnostic accuracy of TEG/ROTEM for coagulopathy is poor [34]; the largest RCT in cardiac surgery that evaluated a TEG/ROTEM-based algorithm to administer the intervention [35] demonstrated difficulties in implementing these in the trial, which resulted in a low proportion of patients being randomised, high rates of non-adherence to the study protocol, and unreliable results.

In conclusion, further evidence on the clinical and cost-effectiveness of PCC versus FFP in cardiac surgery patients who are bleeding is needed. It is essential for patients and healthcare professionals that these outcomes are evaluated in a large trial.

Trial status

Trial protocol V3.0, date: 30/04/2025. Date the first hospital opened to recruitment was 24th of January 2025. Recruitment will complete end of December 2026.

Abbreviations

A&E	Accident and emergency
AE/AR	Adverse event/adverse reaction
BMS	Biomedical scientist
CABG	Coronary artery bypass graft
CAG	Confidentiality Advisory Group
CI	Chief investigator
CROQ	Coronary Revascularisation Outcome Questionnaire
DMC	Data Monitoring Committee
(e)CRF	(Electronic) case report form
FFP	Fresh frozen plasma
IMP	Investigational medicinal product
JRMO	Joint Research Management Office
KCCQ	Kansas City Cardiomyopathy Questionnaire
ModRUM	Modular resource-use measure
MHRA	Medicines and Healthcare Products Regulatory Agency
NHSBT CTU	NHS Blood and Transplant Clinical Trials Unit
NIHR HTA	National Institute for Health and Care Research Health Technology Assessment
PCC	Prothrombin complex concentrate
PI	Principal investigator
PROPHESY-2	PROthrombin complex concentrate versus fresh frozen Plasma for bleeding in adults undergoing HEart SurgerY
RCT	Randomised control trial
REC	Research Ethics Committee
QMUL	Queen Mary University of London
QoL	Quality of life
SAE	Serious adverse event
SmPC	Summary of product characteristics
TMF	Trial master file
TMG	Trial Monitoring Group
TSC	Trial Steering Committee
VKA	Vitamin K antagonist

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09410-8.

Supplementary Material 1.

Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Authors' contributions {31b}

LG, AK, GM, SA, ML, SS, and EAk conceived the trial and lead the proposal and protocol development, following on from the pilot trial. JS, FT, SM, JM, LSi, and CR contributed to the trial design and development of the proposal. CH, LSm, and NV are the trial statisticians. CB and EH are the trial managers. EAr and JW contributed to the database development. In addition to the previously mentioned authors, MG also contributed to the study development and writing of the protocol. All authors have read and approved the final manuscript. CB is the corresponding author.

Funding {4}

The trial is funded by the National Institute for Health and Care Research Health Technology Assessment Programme (NIHR152151).

Data availability {29}

The chief investigator and the trial statistician will have access to the final trial dataset. Access to the final data set for additional analyses will be available upon request from the sponsor. Data will be shared with investigators whose use of the data has been assessed and approved by the trial review committee as a methodologically sound proposal.

Declarations

Ethics approval and consent to participate {24}

Research Ethics Committee approval was provided by the London-Fulham REC on 30th April 2024. Written, informed consent to participate will be obtained from all participants prior to being involved in any trial activities.

Consent for publication {32}

Patient information and consent form attached.

Competing interests {28}
Co-applicants Professor Laura Green, Professor Simon Stanworth, and Dr Josephine McCullagh are employees of NHS Blood and Transplant (manufacturer and provider of FFP); they each report no direct relevant financial disclosures. Dr Andrew Klein or his institution has received educational grant funding, honoraria, or travel expenses from Fisher & Paykel, Pharmacosmos, Massimo, and Nordic Pharma. Professor Gavin Murphy is a paid consultant for Pharmacosmos.

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