JRMO Research Protocol for MHRA Regulated Studies

Full Title: **PRO**thrombin complex concentrate versus fresh frozen **P**lasma for bleeding in adults undergoing **HE**art **S**urger**Y** (PROPHESY-2 trial): a phase III, randomised control trial

Short Title	PROPHESY-2 Trial
Sponsor	Queen Mary, University of London Contact person: Dr Mays Jawad Research Governance Operations Manager Joint Research Management Office Dept. W 69-89 Mile End Road London E1 4UJ **Phone:** +44 (0) 20 7882 7275/6574 **Email:** research.governance@qmul.ac.uk
IRAS Number	1009308
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Chief Investigator	Prof Laura Green Professor of Haemostasis and Transfusion Medicine, Queen Mary, University of London Consultant Haematologist, NHSBT and Barts Health NHS Trust Blizard Institute, 4 Newark Street London E1 2AS **Phone**: 07720275360 **Email**: laura.green@qmul.ac.uk
Trial Contacts **Trial Manager**	Charlie Brown NHS Blood & Transplant Long Road Cambridge CB2 0PT **Phone:** 07823351963 **Email:** prophesy2trial@nhsbt.nhs.uk

Funder(s)	National Institute for Health and Care Research Health Technology Assessment Programme **Address**: Alpha House Enterprise Road Southampton SO16 7NS
Clinical Trials Unit	NHS Blood and Transplant CTU Long Road Cambridge CB2 0PT **Email:** CTU@nhsbt.nhs.uk
Statistician	Naomi Vides NHS Blood and Transplant Filton 500, North Bristol Park Filton BS34 7QH **Email:** naomi.vides@nhsbt.nhs.uk
Trial pharmacist	Stuart Chandler Royal London Hospital Floor 5, Pathology and Pharmacy Building 80 Newark St E1 2ES **Phone:** 02032460604 **Email:** stuart.chandler@nhs.net
Committees **(DMC, TSC, TMG)**	Data Monitoring Committee DMC Chair: Professor Nawwar Al-Attar **Email**: Nawwar.Al-Attar@gjnh.scot.nhs.uk Trial Steering Committee TSC Chair: Professor Michael Gilles **Email**: Michael.Gillies@ed.ac.uk Trial Management Group Chair: Professor Laura Green Role: Chief Investigator

Key protocol contributors

Name	Department	Organization
Sub- Investigators		
Dr Andrew Klein (Lead Anaesthetist)	Anaesthesia	Royal Papworth Hospital Papworth Rd, Trumpington, Cambridge CB2 0AY
Professor Gavin Murphy (Lead Surgeon)	Cardiothoracic Surgery	University of Leicester, Leicester, LE3 9QP
Dr Seema Agarwal	Anaesthesia	Manchester Royal Infirmary Manchester, M13 9WL
Professor Mahmoud Loubani	Cardiothoracic Surgery	Castle Hill Hospital, Cottingham, HU16 5JQ.
Dr Florian Tomini	Health Economics Research Unit	Queen Mary, University of London, E1 2AT
Professor Simon Stanworth	Haematology	NHS Blood and Transplant Oxford, OX3 9BQ
Mrs Sarah Murray	Patient and Public	Eastwards, Birchy Hill Sway SO41 6BJ
Professor Julie Sanders	Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care	King's College London, SE1 8WA
Professor Enoch Akowuah	Cardiothoracic Surgery	South Tees Hospital, Middlesbrough, TS4 3BW
Dr Josephine McCullagh	Consultant Clinical Scientist in Blood Transfusion	NHS Blood and Transplant, Colindale, & Barts Health London
Professor Aylin Baysan	Equality, Diversity and Inclusion Patient Researcher	Queen Mary, University of London, E1 2AT
Clinical Trials Unit		
Claire Rourke	Clinical Operations Manager	NHS Blood and Transplant Cambridge, CB2 0PT
Emily Arbon	Clinical Data Manager	NHS Blood and Transplant Cambridge, CB2 0PT
Jessica Workman	Clinical Data Services Manager	NHS Blood and Transplant Cambridge, CB2 0PT
Maisie Gardner	Senior Clinical Trial Administrator	NHS Blood and Transplant Cambridge, CB2 0PT
Naomi Vides	Trial Statistician	NHS Blood & Transplant Stoke Gifford, BS34 8RR
Laura Smith	Trial Statistician	NHS Blood & Transplant 500, North Bristol Park, Filton, Bristol BS34 7QH
Cara Hudson	Lead Statistician	NHS Blood & Transplant 500, North Bristol Park, Filton, Bristol BS34 7QH
Charlie Brown	Clinical Trial Manager	NHS Blood and Transplant Cambridge, CB2 0PT
Eleanor Hounslea	Clinical Trial Manager	NHS Blood and Transplant Cambridge, CB2 0PT

I. Contents

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II. Glossary of terms and abbreviations

AE	Adverse Event
ACT	Activated clotting time
AR	Adverse Reaction
APR	Annual Progress Report
APTT	Activated Partial Thromboplastin Time
BSQR	Blood Safety and Quality Regulations 2005
CABG	Coronary Artery Bypass Graft
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
CROQ	Coronary Revascularization Outcome
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
HDU	High Dependency Unit
HRQoL	Health Resource Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
Index Hospitalisation	The hospitalisation during which the procedure of interest was performed
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITU	Intensive Therapy Unit
KCCQ	Kansas City Cardiomyopathy Questionnaire
MHRA	Medicines and Healthcare Products Regulatory Agency
ModRUM	Modular Resource-Use Measure
NHSBT	National Health Service Blood and Transplant
NIMP	Non-Investigational Medicinal Product
PCC	Prothrombin Complex Concentrates
PI	Principal Investigator

PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PT	Prothrombin time
PROPHESY	PROthrombin complex concentrate versus fresh frozen Plasma for bleeding in adults undergoing HEart SurgerY
QoL	Quality of Life
RCT	Randomised Control Trial
RBC	Red Blood Cells
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
VKA	Vitamin K antagonist
TEG	Thromboelastography
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

III. Signature page

Chief Investigator Agreement

The clinical trial as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Professor Laura Green**

Signature:

Date: Prof Laura Green Digitally signed by Prof Laura Green Date: 2026.01.09 08:50:12 Z

Statistician's Agreement

The clinical trial as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 – Statistical principles for Clinical Trials and ICH E10 – Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this trial.

Statistician's name: **Naomi Vides**

Signature:

Date: Naomi Vides Digitally signed by Naomi Vides Date: 2026.01.13 15:24:29 Z

Principal Investigator Agreement Page

The clinical trial as detailed within this research protocol **(Version 4.0, dated 28 OCT 2025)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name: _____

Principal Investigator Site: _____

Signature and Date: _____

IV. Synopsis

Full title	**PRO**thrombin complex concentrate versus fresh frozen **P**lasma for bleeding in adults undergoing **H**Eart **S**urgerY (PROPHESY-2 trial): a phase III, randomised control trial.
Short title and / or acronym	PROPHESY-2 trial
Sponsor	Queen Mary, University of London
MHRA Risk level	Type A = No higher than the risk of current standard care
Phase of the trial	III
Medical condition or disease under investigation	Cardiac surgery
Trial design and methodology	Randomised controlled, pragmatic, non-blinded, multi-site (up to 20) trial in NHS hospitals in England and Wales.
Planned number of participants	496
Objectives	<u>Primary objective</u> To determine if treatment of bleeding with prothrombin complex concentrate (PCC) in adult patients who are actively bleeding within 24 hrs of cardiac surgery is superior to fresh frozen plasma (FFP) with respect to a composite of mortality, organ failure or infection, up to and including 90 days from randomisation. <u>Secondary objectives</u> 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 7. Quality of Life 8. Cost-effectiveness
Inclusion and exclusion criteria	<u>Inclusion criteria</u> Age ≥18 years, who are undergoing cardiac surgery (Elective and Urgent procedures) not described in the exclusion criteria. Is able to provide informed consent.

	<u>Exclusion criteria</u> • Emergency and Salvage procedures (as per definitions in section 6.0). • 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, rivaroxban, apixaban or edoxaban etc.) within 48 hrs prior to surgery (or 72 hours if patient has renal impairment – i.e. estimated glomerular filtration rate of <30ml/min). • Any contraindication to PCC or FFP or LG-Octaplas, for example: known or suspected allergy to heparin, Sodium citrate dihydrate, sodium dihydrogenphosphate dihydrate and Glycine, History of Heparin-induced thrombocytopenia, 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.
Investigational Medicinal Product(s)	Prothrombin complex concentrate, intravenously: • 1,500 IU if participants are ≤70kg • 2,000 IU if participants are >70kg Maximum of two doses. Fresh Frozen Plasma or LG-Octaplas, intravenously: • 4 units if participants are ≤70kg • 5 units if participants are >70kg No maximum dose
Treatment duration	Up to 24 hours from the start of surgery
Follow up duration	90 days, or death, whichever occurs first
End of Trial definition	The date of the last follow up visit (i.e. 90 days) of the last participant recruited into the trial.

1.0 Introduction

1.1 Background

1.1.1 The health problem being addressed:

Major bleeding is a feared complication after surgery. Over 33,000 open-heart operations are performed each year in the UK. 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] or potentially over 10,000 people per year.[3] Severe bleeding can result in shock, or large volume blood transfusion, and is associated with increased risks of infection, as well as a four-fold increase in organ injury to the heart, lungs, or kidneys, or death.[4-7] The treatment of post-cardiac surgery bleeding and its complications is estimated to cost the NHS a mean of £3,143 per person, or > £33M per year.[3]

Bleeding following cardiac surgery is commonly attributed to coagulopathy caused by consumption of coagulation factors resulting from activation in the cardiopulmonary bypass circuit. Hence, the existing standard of care for treatment of bleeding in cardiac surgery is transfusion of fresh frozen plasma (FFP)[8] which contains balanced pro- and anti-coagulation factors. However, FFP transfusion has potential harms including allergic/anaphylactic reactions, increased risk of transfusion-associated fluid overload, transfusion related acute lung injury, and transfusion transmitted infection.[9] The administration of FFP following cardiac surgery is common. Over 25% of cardiac surgery patients receive FFP, utilising >30,000 units per year or 1 in every 12 units of FFP nationally, despite uncertainty as to its safety or clinical effectiveness.

Prothrombin Complex Concentrate (PCC) is increasingly used in the UK instead of FFP in cardiac surgery patients who are bleeding not relating to vitamin K antagonists (VKA). The European Society of Anaesthesiology currently recommends the use of PCC in patients not on oral anticoagulant therapy and who are actively bleeding.[10]

PCC is manufactured from large volumes of human plasma. Potential clinical advantages over FFP include reduced volume load (20-40mL PCC vs. ~1000mL FFP for one adult dose) and risk of transfusion-associated circulatory overload, higher concentrations of clotting factors II, VII, IX and X leading to faster correction of depleted clotting factors and cessation of bleeding, pathogen inactivation treatment to reduce the risk of transfusion transmitted infection, lower risk of bacterial contamination, 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 (by comparison FFP contains a more balanced mixture of pro- and anti-coagulants, which might reduce any associated thrombotic risk). In a systematic review of observational studies, the reported thromboembolic events following PCC treatment was very unclear and ranged between 0% and 41%.[11]

1.1.2 Current practice

In 2022, we surveyed bleeding management in 25 UK cardiac centres. Of 21 responses, 33% stated that they use PCC as part of local major haemorrhage protocol to treat bleeding following cardiac surgery not relating to VKA, and 71% had used at some points PCC instead of FFP in their practice. Another study in England hospitals reported that 86% of PCC use was for treatment of bleeding in cardiac surgery not relating to VKA, and that the use of PCC in

cardiac surgery was increasing[13] despite the absence of evidence of effectiveness. This variation in care reflects clinical uncertainty as to the relative risks and benefits of FFP versus PCC for the treatment of coagulopathic bleeding in cardiac surgery.[14] This means that clinical teams are treating potentially life-threatening bleeding following cardiac surgery in the absence of high-quality evidence.

An important barrier to the widespread use of PCC is cost. PCC is much more expensive (500IU vial £250: average adult dose £750) than FFP, and it is unclear whether the increased transfusion related costs from routine PCC use would be offset by clinical benefits or reductions in FFP usage. In contrast a standard adult dose of FFP (4 units, unit cost £36) costs £144, however, the overall FFP use in cardiac surgery is high (>30,000 units used in cardiac surgery per year, or >12% of all FFP use). PROPHESY-2 will determine which treatment is more cost-effective. More effective treatment of bleeding and reductions in complications should reduce NHS costs.

1.1.3 Existing evidence

A Cochrane review and an updated literature search of FFP trials demonstrated the very low certainty of benefit from FFP use in cardiac surgery.[14] At present, it would be unethical to randomise patients with severe bleeding to either FFP or no FFP, but it is appropriate to compare FFP to an alternative coagulopathy treatment, like PCC.

Two systematic reviews evaluated PCC use in cardiac surgery patients who were bleeding and not taking VKA treatment before surgery. Neither identified a randomised control trial (RCT) and most studies compared PCC in combination with FFP versus FFP alone.[11,12] The PCC dose varied greatly across studies ranging between 10 IU/kg -50 IU/kg.[11,12] One review showed that PCC may reduce blood loss (mean difference −293 mL; 95% CI: −546; 41), without effects on death (odds ratio [OR] 1.04; 95% CI: 0.72; 1.51), stroke (OR, 0.80; 95% CI: 0.41; 1.56), or thromboembolic rates.[11] The other, showed that FFP was associated with reduced renal replacement therapy compared with PCC (OR, 0.41; 95% CI: 0.16; 1.02).[12] In a post-hoc analysis of two RCTs comparing PCC and FFP for warfarin reversal (n =181 patients), FFP increased fluid overload and cardiac events versus PCC (12.7% vs. 4.7%).[15]

1.1.4 Ongoing trials

There have been two pilot RCTs comparing FFP versus PCC in adults.[2,16] One of these was from our group (PROPHESY-1).[2] These trials have demonstrated it is feasible to randomise patients and that PCC is a safe treatment.[2,16]

Currently, two trials are registered in the ClinicalTrials.gov that will compare PCC versus FFP in adult patients undergoing cardiac surgery. Both trials use non-inferiority designs: **1.** The FARES-2 trial (NCT05523297) followed on from the pilot trial FARES-1.[16] The trial has started and has a target sample size of 500 patients in Canada. The primary outcome of FARES-2 trial is the number of patients requiring additional haemostatic intervention including transfusion (funded by Octapharma, a manufacturer of PCC). **2.** The second trial (NCT04244981) will recruit 560 subjects in China and its primary outcome is the volume of blood loss within the 24 hours of surgery.

Neither trial will evaluate clinically important outcomes that matter to patients, and neither trial will compare the cost-effectiveness of two treatments, which is vital for NHS and blood

services. Our survey and the patient and public input (PPI) work showed that patients are much less interested in the number of blood units transfused versus getting back to their own home in a timely manner and without any disability or organ failure.

1.2 Rationale for trial design

Bleeding during cardiovascular surgery that requires blood transfusion is associated with significant morbidity/mortality, and substantial costs to NHS. FFP is the accepted standard treatment for clotting factor replacement in bleeding patients (cardiac surgery included) in the UK, even though the evidence for its efficacy is scarce. PCC is being used commonly in the UK[13], instead of FFP, for management of bleeding during cardiac surgery, because of its advantages of: having more concentrated clotting factor levels and potentially stopping bleeding quicker than FFP; and being administered rapidly and in small volume resulting thus in less volume overload and haemodilution effect during cardiac surgery. However, there has been no large RCT to compare the clinical effectiveness and safety of PCC versus FFP in bleeding patients undergoing cardiac surgery not relating to VKA.

1.3 Assessment and management of risk

PCC is a blood product and contains concentrated levels of coagulation factors II, VII, IX and X (final concentration being ~25 times higher than normal plasma). PCC is produced from fractionation of large pools of human plasma, which undergo treatment to reduce the risk of enveloped viruses (HIV, Hepatitis B and C).[17] Further, PCC has several other advantages over FFP as described above. However, due to the concentrated level of clotting factors, one of the most important side effects of PCC is thromboembolic complications. The incidence of this has been reported to be 1.8% in one meta-analysis of 1,032 patients.[18] The two pilot RCTs (one of them from our group) and several observational studies in cardiac surgery setting that have compared PCC and FFP have demonstrated that the risk of thromboembolic complications is not different between the two products.[2,16,19-21]

This trial is categorised as: ***Type A = No higher than the risk of standard medical care***

Reasons for categorizing as Type A are:
The Summary of Product Characteristics (SmPC) for PCC (Octaplex, Beriplex and Prothromplex) states that these products are indicated for 'treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required'.

Bleeding during cardio-thoracic surgeries falls under acquired bleeding disorders, and results in the deficiency of vitamin K dependent coagulation factors.[22] The European Society of Anaesthesiology currently recommends the use of PCC in patients not on oral anticoagulant therapy and who are actively bleeding during cardiac surgery.[10] Hence the use of PCC in this setting is considered to be within licensed indication, and as such, the trial is classified as Type A category.

2.0 Trial objectives

Our hypotheses 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. The intervention (PCC) will act in the same direction on all elements of the composite outcome, and all are significant clinical issues that determine mortality, morbidity and resource use, and were also considered important to patients, clinicians and service providers as part of the PPI work. In this trial we will measure all of these, together with cost-effectiveness of the two treatments.

2.1 Primary objective(s)

To determine if treatment of bleeding with PCC in adult patients who are actively bleeding within 24 hrs 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.

Start of surgery is defined as 'knife to skin'.

2.2 Secondary objective(s)

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, 7) Quality of Life, and 8) Cost-effectiveness.

2.3 Endpoints

2.3.1 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** below.

Table 1. Definition of organ failure and infection*

Acute respiratory failure	Acute lung injury defined as PaO2/FiO2 ratio <300mmHg and CPAP/PEEP of 5 cmH2O (490kPa).[23]
Acute myocardial injury	New low cardiac output syndrome; mechanical circulatory support (i.e. Extracorporela membrane oxygenation, Left Ventricular Assist Device, impellar and balloon pump) or a primary inotrope support (levosimendan, milrinone, enoximone) persisting after 24 hrs 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)
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 generalized 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).

**During hospitalisation, clinical assessment for organ failure will be at 24 hours, day 5 and day 7, or discharge, or death, whichever is first. For participants who stay in hospital more than 7 days, clinical assessment will be made every 7 days up to hospital discharge, 28 days or death, whichever is first.*
For participants who are re-admitted to hospitals, organ failure will be taken from discharge summaries, or hospital notes if the participant is still in hospital.

2.3.2 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 **Table 1.**
- 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

2. Clinical evidence of haemostasis defined as:[3]
    - amount of blood loss (in mls) collected in chest drains at 6 hours and 24 hours post end of surgery

- amount of total allogeneic (in units) blood transfusion (red blood cells, fresh frozen plasma, cryoprecipitate, platelets), total dose of haemostatic factor concentrates (PCC, fibrinogen concentrate, activated recombinant factor VIIa, or any other blood product concentrate) at 24 hours 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 – i.e. time to discharge from acute care after index hospitalisation; this includes time to discharge from satellite acute care units.
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 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. The EQ-5D-5L includes five dimensions (mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression, each scored on five levels) and the visual analogue scale.[26]
    b. Disease-specific QoL questionnaire, either:
        i. Coronary Revascularization Outcome (CROQ) at baseline and 90 days after randomisation for CABG+valve and complex/combined procedures, or
        ii. Kansas City Cardiomyopathy (KCCQ) at baseline 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.[27-29]

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. This will include the following categories: surgery performed, units of RBC transfused, length of hospital stay – broken down by General Ward, Intensive Care Unit (ICU), and High Dependency Unit (HDU) - laboratory tests, medications, examinations, and other procedures performed during inpatient stay. Treatment costs will include the number of units of FFP or PCC administered.

During the follow-up period after discharge, we will collect additional resource usage information. These resources will include A&E visits and hospital re-admissions, outpatient care, primary care, medications, allied health care, home health care, social care received, medical devices, laboratory and diagnostic tests, prescribed medication (including any out-of-pocket paid), travel costs for receiving health care and information on any informal care. A previously validated self-report resource utilisation measure, ModRUM [43], 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.

2.5 Objectives and end points summary

Primary Objective	Primary Endpoint
In adult patients who are actively bleeding within 24 hrs of cardiac surgery, is PCC superior to FFP with respect to a composite of mortality, organ failure or infection, up to 90 days from randomisation.	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
Secondary Objectives	Secondary Endpoints
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 4. Duration of mechanical ventilation (during index hospitalisation) 5. Hospital re-admission 6. Safety 7. Quality of Life 8. Cost-effectiveness	1. Components of the primary outcome 2. Clinical evidence of haemostasis a. Amount of blood loss collected in chest drains at 6 hours and 24 hours post end of surgery b. Amount of total allogeneic blood transfusion (red blood cells, fresh frozen plasma, cryoprecipitate, platelets), total dose of haemostatic factor concentrates (PCC, fibrinogen concentrate, activated recombinant factor VIIa, or any other blood product concentrate) at 24 hours and 7 days from randomisation c. 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, up to 90 days from randomisation, or hospital discharge or death, whichever is first 4. Duration of mechanical ventilation (in days) during index hospitalisation up to 90 days from randomisation, or hospital discharge or death, whichever is first.

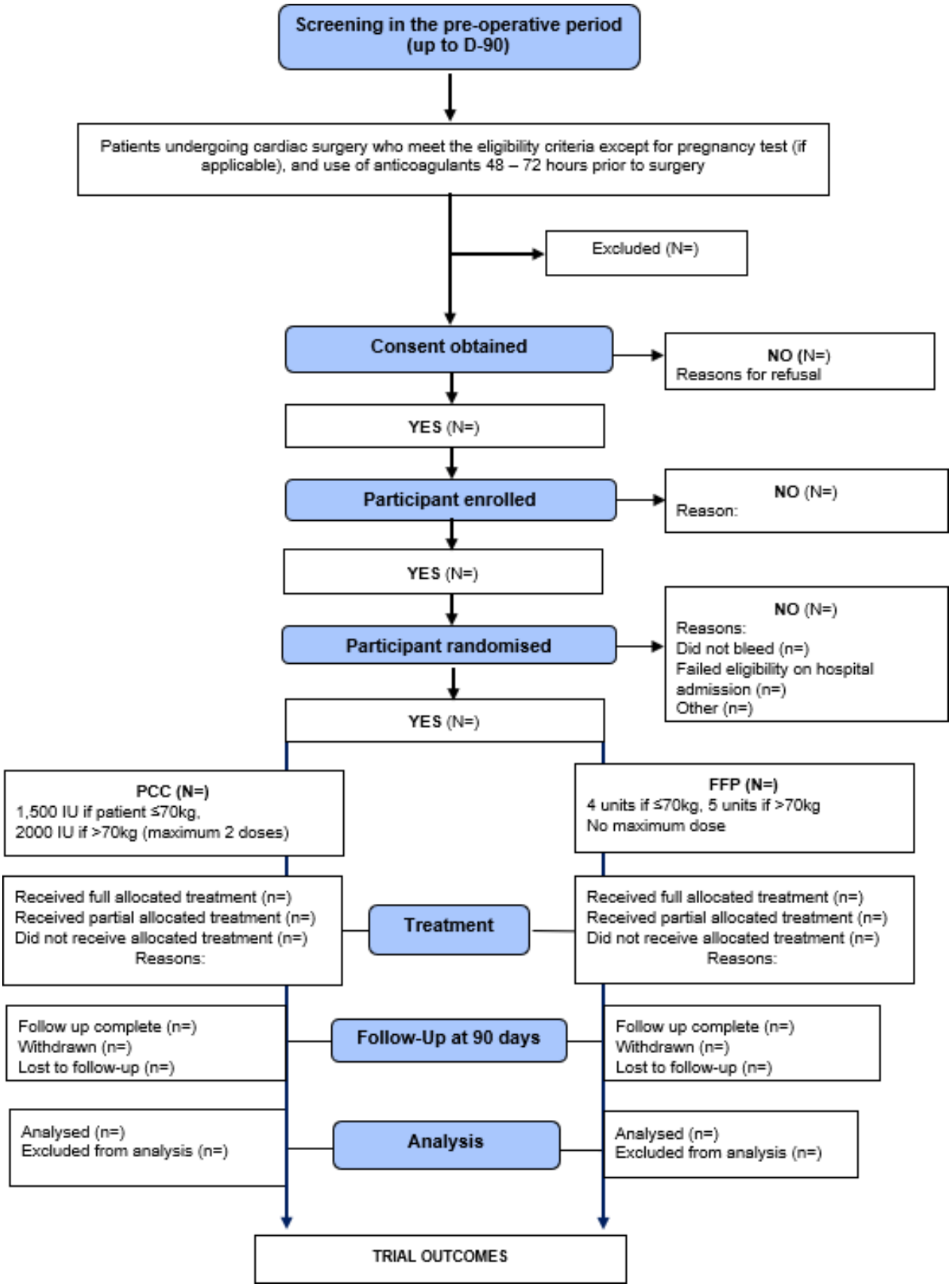
	5. Number of hospital re-admissions up to and including 90 days from randomisation. 6. Safety measured through: *a. Transfusion adverse events* up to 7 days from randomisation, or hospital discharge or death, whichever is first, as defined by UK Serious Hazard of transfusion (www.shotuk.org/reporting) which will include: 7. Acute Transfusion Reactions, that could result in shock or cardiac arrest 8. Haemolytic Transfusion Reactions (acute or delayed) 9. Post Transfusion Purpura 10. Transfusion-associated Graft versus Host Disease 11. Transfusion-Associated Circulatory Overload 12. Transfusion-Associated Dyspnoea 13. Transfusion-Related Acute Lung Injury **i.** *Thrombotic events (arterial and venous)* confirmed by radiological imaging, autopsy, or through surgical means, up to 90 days from randomisation or death whichever occurs first. **ii.** Other serious adverse events reported up to 90 days from randomisation or death whichever occurs first. 14. 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. b. Disease-specific QoL questionnaire, either Coronary Revascularization Outcome (CROQ) for CABG+valve and complex/combined procedures, or Kansas City Cardiomyopathy (KCCQ) for valve only and major aortic surgery patients, at baseline and 90 days after randomisation. 15. Hospital costs at hospital discharge and follow up health care costs at 90 days.

2.6 Trial design

Design: Phase III, randomised, controlled, pragmatic, superiority, group-sequential, multicentre, open label trial, with internal pilot and embedded health economic analysis.

The consort diagram is described in **Figure 1.**

Figure 1. PROPHESY-2 trial CONSORT Flow Diagram



2.7 Trial setting

Up to 20 tertiary NHS cardiac centres in England and Wales.

3.0 Patient Evaluability and Replacement

3.1 Target Accrual

A total of 496 participants will be randomised (248 per group).

3.2 Participant identification and recruitment

All eligible patients will be identified in the preoperative anaesthesia or cardiac surgery clinics or ward at each hospital up to 90 days before the index surgical event. In the case of patients undergoing urgent surgery, it is essential that they are approached as early as possible to allow sufficient time to consider participation in the trial. This can be up to the day of surgery as long as the patient feels that they have had enough time to consider their participation in the trial prior to being asked to provide consent. If a patient does not feel they have had enough time to contemplate participation, they can decline without this affecting their care.

Patients undergoing procedures out of hours during which there is no research team available to approach and obtain consent from patients cannot be enrolled in the trial.

In some Trusts, the research team is considered part of the clinical care team. In Trusts where this is not the case, the research team will have authorisation to screen patient notes for eligibility without prior consent under CAG section 251 approval. In both cases, the research team are authorised to approach eligible patients directly.

Once eligible patients have been identified, the clinical/research teams will provide patients with the Participant Information Sheet (PIS). All eligible patients will be seen by the research team to discuss in person the PIS and what the trial will involve.

Eligible patients who have received PIS about the trial, will be approached to answer any questions or concerns they may have, and after satisfactory discussion, informed consent will be sought. Other eligible cases (for example inter-hospital transfers), who have not received PIS in advance, will be approached at the earliest opportunity after their admission to hospital and be given verbal and written information. After satisfactory discussion and sufficient time to discuss their participation with friends and/or family members if desired, informed consent will be sought. Written informed consent will be requested from potential participants by a member of the clinical team or a medically qualified member of the research team.

4.0 Informed consent procedures

Patients will be identified by local research teams and approached at the earliest opportunity, ideally in the pre-admission clinic. In cases of urgent surgery, patients may be approached

after their admission to hospital. In both cases, patients will be given verbal and written information, and provided with the opportunity to ask questions. Once the patient is satisfied with the information they have been provided, written informed consent will be requested from them by a member of the clinical team or a medically qualified member of the research team who is appropriately trained and delegated this activity by the PI as documented on the trial delegation log.

Prophesy-2 participants will be randomised during surgery or within 24 hours of the start of surgery. Therefore, if consent is obtained at a pre-admission clinic, there may be an extended period of time (up to 90 days prior to surgery) between initial consent and randomisation. In these circumstances, consent will be re-confirmed when the participant is admitted to hospital prior to surgery. Consent can be re-confirmed verbally or in writing as per local practice – participants should not sign another consent form. Reconfirmation of consent will be captured in the participant's medical notes. Consent is an ongoing process throughout their participation in the trial.

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs as part of the trial team member's roles and responsibilities, details will be provided in the site delegation log, which will have been reviewed and authorised by the local PI.

The right of a patient to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the trial. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the trial, or following an amendment that affects the participant, or new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner and prior to the next dose of IMP (where applicable).

4.1 Remote consent

Consent may be obtained remotely by a delegated member of the clinical team or a medically qualified member of the research team contacting the patient by telephone or video call and the patient completing the paper consent form sent with the remote consent cover letter and PIS. On the call, the delegated member of the clinical team or medically qualified member of the research team must confirm the patient's identity by asking the patient their date of birth and home post code. If these match the patient's details:

1. Read through each statement on the consent form, ensuring the patient understands the statement
2. Ask the patient to write their initial next to each item on the paper consent form as you read them
3. Ask the patient to sign the form to consent to the study.

Optional consent items require the patient to tick "Yes" or "No" and write their initials.

The patient should return the signed consent form to the local research team by post. Alternatively, the patient may bring the consent form with them when they are admitted to hospital for their cardiac procedure.

On receipt of the patient signed consent form, the member of the local research team who obtained consent will review the form and sign to confirm they obtained consent and date with the date consent was obtained. The member of the local research team will either give the patient a copy of the consent form signed by both parties to for their records in person, or send it in the post. The original consent form with signatures of both the patient and the person obtaining consent should be filed in the ISF.

4.2 Writing, reading, and translation considerations

For patients who cannot read or write or who require translators, methods for supporting the informed consent process will be employed. These include having a witness to sign on a patient's behalf (in the case of problems with reading or writing) or having an independent interpreter via a hospital interpreter in line with participating sites' local hospital policy. Telephone translation services are acceptable in line with local hospital policy.

4.3 Patients lacking capacity

Patients who lack capacity to provide informed consent are excluded from the trial.

4.4 Minors

Individuals <18 years old will be considered minors for the purpose of this trial and therefore will be excluded.

4.5 Consent for Ancillary Studies

Not applicable.

4.6 Co-enrolment

Co-enrolment in other clinical research will be considered on a case by case basis. Whether the patient has been co-enrolled will be collected on the trial database, including the names of the co-enrolled research studies.

5.0 Participant allocation

Screening Procedures

Patients aged 18 years or older who are undergoing a cardiac procedure not listed in the exclusion criteria will be identified by research staff. These patients will be approached at their pre-surgery assessment, and given the participant information sheet (PIS) and informed consent form (ICF) to read. If patients wish to discuss participation in the trial with trial staff on

the day, they may. Equally, patients may take home the information to read and consider in their own time, and contact the person stated in the PIS to discuss the trial further.

Research staff may make contact with potential participants by phone after screening medical records and prior to the patient's pre-surgical appointment to request permission for a member of the research team to approach the patient at their appointment to discuss participating in the trial.

Patients who are undergoing urgent procedures may be screened at the time of hospital admission, and will be asked, if clinically/ethically appropriate, to consider participation in the trial if they are able to provide consent at any point up until surgery. Written informed consent will be requested from potential participants by a member of the clinical team or a medically qualified member of the research team.

Anyone who is pregnant is excluded from the trial because PCC is not indicated in this group of patients. A routine urine pregnancy test will be performed in people of childbearing potential (<50 years old, as per World Health Organisation definition) for eligibility purposes at hospital admission as part of standard procedure for this type of surgery. This means that for anyone requiring a pregnancy test, eligibility cannot be confirmed until hospital admission for the cardiac procedure. There are no other trial-specific screening procedures that the patient will undergo prior to entry into the trial.

Screening logs: A screening log will be maintained by each research team, to record the number of patients screened, approached, number not consented, and the reason for not being consented. This will be maintained in a secure location at each trial site, only accessible to the local research team. It will record data for patients who did not pass screening or provide consent and will be entered into OpenClinica with no patient identifiable information. The initials of any patient who was screened and did not provide consent to enrol in the trial must be redacted within 90 days.

If a patient agrees to participate and provides consent, the patient is enrolled in the trial. If enrolled participants do not develop bleeding or are not anticipated to bleed within 24 hours of surgery, they will not be randomised to the trial. In these circumstances, clinical data for enrolled participants who have not been randomised will only be collected for up to 24 hours post-surgery as per the schedule of events (see Table 3).

For enrolled participants who are randomised, clinical data will be collected for up to 90 days post-randomisation or death, whichever is first.

6.0 Participant eligibility criteria

The National Institute for Cardiovascular Outcomes Research definition, categorises cardiac surgeries as Elective and Non-elective: the latter is further subdivided into:

- *Urgent procedures*, include patients who have not been scheduled for routine admission from the waiting list but who require intervention or surgery on the current admission for medical reasons. On average they present to hospital 1 – 3 days before surgery, and they cannot be sent home without a procedure.

- *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. On average they present to hospital one day prior to surgery.
- *Salvage procedures*, include patients requiring cardiopulmonary resuscitation (external cardiac massage) en-route to the operating theatre or prior to the induction of anaesthesia.

6.1 Inclusion criteria

Age ≥18 years, who are undergoing cardiac surgery (Elective and Urgent procedures) not described in the exclusion criteria, and where the patient is able to give informed consent.

6.2 Exclusion criteria

- Emergency and Salvage procedures as per definitions above (section 6.0). We have excluded them for the following reasons: **A.** They have a different pathogenesis for bleeding compared to other surgeries. **B.** There is not enough time to allow patients to give informed consent. **C.** Overall, these surgeries make up 3% of all cases (UK Cardiac Activity and Outcomes Report, 2002-2016).
- First-time isolated coronary artery bypass graft 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, rivaroxban, apixaban or edoxaban etc.) within 48 hrs prior to surgery (or 72 hours if patient has renal impairment – i.e. estimated glomerular filtration rate of <30ml/min).
- Any contraindication to PCC or FFP or LG-Octaplas, for example: known or suspected allergy to heparin, Sodium citrate dihydrate, sodium dihydrogenphosphate dihydrate and Glycine, History of Heparin-induced thrombocytopenia, 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.

7.0 Trial Schedule

7.1 Schedule of treatment for each visit

For participants who are randomised to the trial, the timing and doses of randomised treatments will be recorded. Further anticoagulant doses (e.g. unfractionated heparin), and

results of point of care and laboratory assessments that are performed as part of standard care prior to surgery and within 24 hours of surgery will be collected. These tests include AST, ALT, creatinine, urea, haemoglobin, platelets and standard clotting tests (Prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen, activated clotting time [ACT])., Clinical assessment of randomised participants will include documentation of organ failure, infections and clinical signs of thrombosis (arterial or venous). If a participant is on ITU, further standard assessments will be required which include: time of mechanical ventilatory support in hours; length of stay on ITU or HDU, and these assessments will be performed at 24 hours, at day 5 and day 7 or discharge or death, whichever is first. For participants who stay more than 7 days in hospital, this assessment will be done every 7 days. The research nurse will be responsible for collecting trial data and samples outside the ITU.

At 90-days follow-up, contact will be conducted in the outpatient clinic or via telephone by the local research team to assess hospital re-admission and perform clinical assessment for development of organ failure, infection, or thromboembolic complications since hospital discharge. The quality of life and health questionnaires, EQ-5D-5L and CROQ/KCCQ, as well as the self-reported resource use measure, ModRUM, will be collected via email, post or phone call (whichever is easier for participants) at the same time.

For enrolled participants who are not randomised to the trial because they do not develop bleeding or are not anticipated to bleed within 24 hours of surgery, clinical data will be collected for up to 24 hours as described in **Table 3.**

7.2 Schedule of events (in diagrammatic format)

The schedule of events for randomised participants is provided in **Table 2** below.

Table 2. Schedule of events for Randomised subjects

Trial Procedure	Screening Pre-op	Hospital Admission	Surgery up to 24hrs 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 24hrs	+/- 2 days	+/-7 days	+/- 14 days
Screening - Assess eligibility	X					
Urine pregnancy test[1]		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[2]		*X (pre-op)	*X (post op)			
Add & remove the Flag from transfusion lab system.			X			
Randomisation			X			
Time and dose of treatment			X			

Clinical assessment[3]			X	X	X	X
Thromboembolic AE/SAE[4]			X	X	X	X
Transfusion AE/SAE			X	X[5]		
Safety reporting			X	X	X	X
Hospital readmission since discharge					X	X
Self-reported resource use measure ModRUM (email, phone or post)						X
EQ-5D-5L & CROQ or KCCQ Questionnaires (email, phone or post) [6]		X (EQ-5D-5L & 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*
[1]Anyone of childbearing potential.
[2]routine blood tests include: AST, ALT, creatinine, urea, haemoglobin, platelets, PT, APTT and fibrinogen [3]Clinical assessment will include primary and secondary outcome measures captured from hospital clinical notes.
[4]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.
[5]Transfusion related AEs and SAEs are only collected until day 7
[6]Baseline questionnaires must be completed on paper prior to surgery, however data collection via the eCRFs is only required post randomisation.This can be up to 4 days prior to surgery, or on hospital admission, whichever is sooner.

Schedule of Assessments for enrolled participants who are not randomised because they do not develop bleeding or are not anticipated to bleed within 24 hours of surgery, will not be followed up, and their data will not be collected longitudinally or included in the analysis of the main outcomes of the trial (**Table 3**).

Table 3. Schedule of events for participants who are enrolled but not randomised

Trial Procedure	**Screening Pre-op**	**Hospital admission**	**Surgery up to 24hrs post-knife to skin**
Visit Windows	-90 to 0 days	D-1 or D0	Day 0 up to 24hrs
Screening - Assess eligibility	X		
Urine pregnancy test[1]		X	
Informed consent	X	X	
Weight	X		
Quality of Life – EQ5D & CROQ or KCCQ	X	X	

Questionnaires[2]			
Assess need for FFP during or post surgery			X
Add & remove the Flag from transfusion lab system.			X

[1]*Anyone of childbearing potential.*
[2] *Baseline questionnaires must be completed on paper prior to surgery, however data collection via the eCRF of the questionnaires is only required for randomised participants. This can be up to 4 days prior to surgery, or on hospital admission, whichever is sooner*

7.3 Randomisation method

Randomisation will be stratified by site and will allocate participants using minimisation, with 1:1 ratio to receive PCC or FFP. The treatment group that would provide the most balance will be chosen with probability approx. equal to 85% (simple randomisation used with 30% probability and minimisation will be used with 70% probability, hence (0.3 x 0.5) + 0.7 = 0.85). Age (≥70 and <70 years) and type of surgery (valve only, major aortic, 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.

Full details of the randomisation methods will be specified in a Randomisation Specification Form.

7.4 Randomisation procedure

Once consent is obtained the patient will be enrolled in the trial.

Theatre

Prior to surgery, the research team will inform the surgical team that the participant has been enrolled to the trial, and if the participant bleeds or is anticipated to bleed and the clinical team requests FFP, they may receive PCC as part of the trial.

The research team will give a copy of the consent form to the surgical team, so that it is attached with the theatre notes.

Prior to going to theatre, a coloured wristband indicating that the participant has been enrolled to PROPHESY-2 trial, will be put on the participant's wrist. Where possible, this is to remain on the participant's wrist until 24 hours have elapsed since the start of surgery.

Most participants are likely to go to ITU in the first 24 hours after surgery. Hence, the handover of a participant's enrolment to the trial will also be made to the ITU staff by the research or clinical team in theatre.

On the day of the surgery, the research team should document the date and time when surgery started (which is defined in this trial as knife to skin), participant's age, type of surgery (valve only, major aortic, CABG + valve and complex/combined procedure) and participant's weight as this is essential to informing the transfusion laboratory.

Transfusion laboratory

PCC will be stored in the transfusion laboratory, where FFP/LG-Octaplas are also kept.

Randomisation will be performed by the transfusion laboratory using the web-based randomisation system Sealed Envelope at the point when clinician requests FFP for treatment of bleeding.

On the day of the surgery, once the patient has given consent for the trial, the research team will telephone and email the transfusion laboratory asking them to put a flag in the participant's transfusion electronic record stating:

- that participant has enrolled to the PROPHESY-2 trial from the start of surgery (which is defined as knife to skin) to 24 hours post knife to skin.
- participant's weight (required to determine the dose)
- participant's age (required to perform randomisation)
- type of surgery: valve only, major aortic, CABG + valve and complex/combined procedure (required to perform randomisation)

If the participant bleeds or is anticipated to bleed in the 24 hours from start of surgery and the clinical team requests FFP, the transfusion laboratory team will randomise the participant to either FFP or PCC, using the centralised web-based randomisation service Sealed Envelope. The randomisation system will confirm to the transfusion laboratory team the treatment allocated.

The research team must telephone and email the information stated above to the transfusion laboratory team, to allow for randomisation of subjects outside of normal working hours.

The flag will be removed from the participant's transfusion electronic record:

- 24 hours has elapsed from the time of knife to skin and the participant has not developed severe bleeding
- The participant has been randomised to receive FFP
- The participant has been randomised to receive PCC and two doses have been issued, OR one dose has been issued, and 24 hours has elapsed from the time of knife to skin.

Local research staff will update the randomisation allocation in the trial database using OpenClinica.

The transfusion laboratory team will have trial-specific training, documented in the staff training log and randomisation responsibility, as authorised by the PI on the delegation log. Instructions on how to calculate the dose of trial treatment(s) will be given to the transfusion team.

The transfusion laboratory manager (and a deputy) at each site will complete the GCP course, and a proportionate approach to GCP requirements will be made for other biomedical scientists in the laboratory who meet the standard of proficiency for issuing, dispensing and keeping accountability of all blood components (FFP) and products (PCC) as part of their roles: these standards are regulated by their professional body (Health and Care Council) and align with the GCP standards. The proportionate approach will be delivered in the form of documented bespoke GCP training specific to the role the biomedical scientists will be fulfilling in the trial.

Transfusion Laboratory Sites will be responsible for storing and issuing FFP (or LG-Octaplas) and PCC in accordance with the randomisation procedure.

The surgical/clinical team will only know which arm the patient has been randomised to, after they have requested FFP from the laboratory.

7.5 Blinding

Due to physical differences of the two treatments, it is not possible to blind them. To minimize bias: **1.** The treating clinicians will be blinded to group assignments until immediately prior to infusion of treatment. **2.** Choosing objective primary and secondary outcomes measures, means that the risk of detection bias is low. **3.** Minor and major protocol deviations will be carefully monitored throughout the trial to assess performance bias.

7.6 Trial assessments

7.6.1 Intra-operative period

Pre-operative, anaesthetic and transfusion management of participants will be in accordance with local protocols. Prior to surgery, anticoagulants and anti-platelet therapy (apart from aspirin in some cases) will be stopped few days before as per standard of care. Participants will also be asked to stop all other medications on the day of the surgery.

During surgery, all participants will be administered intravenous heparin as per hospital protocol, and the monitoring of heparin will be performed as per standard of care. After discontinuation of cardiopulmonary bypass, heparin will be reversed with intravenous protamine according to hospital protocol. All participants will receive an anti-fibrinolytic agent (e.g. tranexamic acid), according to hospital local protocol.

Before sternal closure, chest drains will be inserted by the surgeon as per standard protocol, and as soon as the chest is closed, the drains will be placed on suction of -2.5 kPa.

7.6.2 Management of bleeding

If bleeding is judged excessive by the anaesthetists or surgeon (based on their clinical judgement), a decision to transfuse blood will be made. Standard laboratory blood testing or point of care testing will be carried out as per local protocol to establish changes in coagulopathy or altered platelet function.

As this is a pragmatic trial, we will collect details about bleeding management but allow sites and clinicians to continue to use their agreed local protocols, if they are aligned with the national guidelines,[8] which recommend that:

- FFP is given if PT or APTT are >1.5 x mean normal, or R time on the Thromboelastography (TEG) or equivalent test (e.g. ROTEM) are abnormal;
- Cryoprecipitate if fibrinogen levels are <1.5 g/L or if fibrinogen on the TEG or equivalent test (e.g. ROTEM) demonstrates an abnormal maximal amplitude; and
- Platelet transfusion if platelet count are $<100x10^9$/L or if the maximum amplitude on the TEG or equivalent test is abnormal or in the presence of documented abnormalities of platelet function.

If laboratory results are not available, FFP, Platelet and Cryoprecipitate should be given in line with the national recommendation (i.e. British Society for Major Haemorrhage guideline).[8]

7.6.3 Administration of trial treatment

Once a decision has been made that the participant requires treatment with FFP, the clinical team will phone transfusion laboratory to request FFP. At this time the transfusion team will undertake randomisation and issue the trial treatment. The randomised treatment will be given to the subject, and the timing and doses will be recorded. Laboratory results will be documented if they have been taken as part of standard of care.

If the participant continues to bleed after the first dose of PCC, a second PCC dose can be administered. If bleeding continues despite the second dose of PCC, standard transfusion care will be followed. Currently, these do not advocate administration of PCC, and therefore, a trial participant will not receive a third dose of PCC, but they may receive further doses of FFP.

There is no dose restriction for FFP or LG-Octaplas.

7.6.4 Data Collection for participants who have given consent

Baseline (post-consent, prior to randomisation)

- Baseline data will include age, sex assigned at birth, ethnicity, weight, height and BMI
- Type of admission (i.e. urgent or elective) and type of cardiac surgery
- Previously randomised in this trial (Y/N) and if yes, their previous randomisation number
- Co-enrolment in other clinical research
- QOL questionnaire (EQ5D) and KCCQ or CROQ
- Urine pregnancy test for anyone of child-bearing potential under the age of 50
- Presence of anaemia
  The following baseline data collection forms refer to baseline data that is not required to be collected in the trial database unless the participant is randomised:
- Previous medical history
- EuroSCORE II
- Standard laboratory tests as part of routine care. These include AST, ALT, creatinine, urea, haemoglobin, platelets, PT, APTT and fibrinogen
- Medication pre-op

Randomisation (covering from the start of surgery until treatment is administered)

- Whether the participant developed bleeding and required blood transfusion
- Whether the participant was randomised or not.
- Date and time of randomisation, and randomisation arm
- Time and date of knife to skin
- Amount of blood component given pre-randomisation
- Amount of intravenous fluid administered pre-randomisation
- Date and time when trial treatment were requested, started and completed, and dose administered
- Total heparin dose administered
- Total dose of heparin reversal administered.

Randomisation up to 24 hours post-surgery or 24 hours post randomisation (whichever is later)

- Amount of total allogeneic (in units) blood transfusion (RBC, FFP, Platelets and cryoprecipitate) up to 24 hours after randomisation.
- Total dose of haemostatic factor concentrates (PCC, recombinant Factor VIIa, fibrinogen concentrate, any other blood product concentrate, cell salvage) up to 24 hours after randomisation.
- Amount of blood lost through the chest drains at 6 hours and 24 hours post end of surgery – this will be recorded as part of routine care by nursing staff after surgery. If drains are removed before 24 hours have elapsed, the total drainage when removing the drains will be recorded.
- Standard laboratory tests as part of routine care. These include AST, ALT, creatinine, urea, haemoglobin, platelets, PT, APTT and fibrinogen.
- Admission to ITU (level 3); High Dependency units (Level 2)
- Organ failure – i.e. acute respiratory failure; acute myocardial injury; acute renal failure; acute liver injury; acute intestinal injury; focal neurological deficit.
- Thrombosis (arterial and venous thrombosis)
- Safety reporting: All SAEs and acute transfusion reactions
- Suspected or documented infection that results in the commencement of intravenous antibiotics or hospitalisation (excluding routine antibiotic treatment post surgery for atelectasis).
- Medications
- Mortality

5 days and 7 days post end of surgery, or discharge, or death – whichever is first

- Mortality
- Amount of total allogeneic (in units) blood transfusion (RBC, FFP, platelets, cryoprecipitate,) up to 7 days from randomisation
- Total dose of haemostatic factor concentrates (PCC, fibrinogen concentrate, activated recombinant factor VIIa, any other blood product concentrate,) at 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
- Duration of organ support (i.e. ventilatory support, cardiovascular support, other respiratory support and renal replacement therapy)
- Organ failure – i.e. acute respiratory failure; acute myocardial injury; acute renal failure; acute liver injury; acute intestinal injury; focal neurological deficit.
- Thrombosis (arterial and venous thrombosis)
- Safety reporting: Acute transfusion reactions and all SAEs
- Suspected or documented infection that results in the commencement of intravenous antibiotics or hospitalisation (excluding routine antibiotic treatment post surgery for atelectasis).
- Transfusion adverse events. 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

Until day 28, or discharge, or death – whichever is first

The following complications will also be recorded prospectively using the participant's clinical notes from the period of randomisation:

- Organ failure – i.e. acute respiratory failure; acute myocardial injury; acute renal failure; acute liver injury; acute intestinal injury; focal neurological deficit.
- Suspected or documented infection that results in the commencement of intravenous antibiotics or hospitalisation (excluding routine antibiotic treatment post surgery for atelectasis).
- Duration of organ support (i.e. ventilatory support, cardiovascular support, and renal replacement therapy)
- Safety reporting: all SAEs
- Medications
- EQ-5D-5L at hospital discharge or at 28 days, whichever is first
- Mortality

At 42 days post randomisation

- Mortality
- Re-hospitalisation
- Thromboembolic event (arterial and venous)
- Organ failure – i.e. acute respiratory failure; acute myocardial injury; acute renal failure; acute liver injury; acute intestinal injury; focal neurological deficit.
- Suspected or documented infection that results in the commencement of intravenous antibiotics or hospitalisation (excluding routine antibiotic treatment post-surgery for atelectasis).

At 90 days post randomisation

- Mortality
- Re-hospitalisation
- Duration of hospital stay, total days in ITU and HDU (separately).
- Safety reporting: Thromboembolic events (arterial and venous)
- Organ failure – i.e. acute respiratory failure; acute myocardial injury; acute renal failure; acute liver injury; acute intestinal injury; focal neurological deficit.
- Suspected or documented infection that results in the commencement of intravenous antibiotics or hospitalisation (excluding routine antibiotic treatment post-surgery for atelectasis).
- Duration of mechanical ventilation
- Medications
- EQ-5D-5L and CROQ or KCCQ questionnaires
- The self-reported resource use measure (ModRUM)

7.6.5 Data Collection for enrolled participants who were not randomised (i.e. do not bleed or were not anticipated to bleed).

Baseline (post-consent)

- Baseline data will include age, sex assigned at birth, ethnicity, weight, height, BMI
- Type of admission (i.e. urgent or elective) and type of cardiac surgery
- Previously randomised in this trial (Y/N) and if yes their previous randomisation number
- Co-enrolment in other clinical research
- Previous medical history

- EuroSCORE II
- Standard laboratory tests as part of routine care. These include AST, ALT, creatinine, urea, haemoglobin, platelets, PT, APTT and fibrinogen
- QOL questionnaire (EQ5D) and KCCQ or CROQ
- Medications pre-op
- Urine pregnancy test for anyone of child-bearing potential under the age of 50

24 hours from the start of surgery

- Whether the participant developed bleeding and required blood transfusion
- Whether the participant was randomised or not

7.7 Follow up procedures

The duration of follow up for participants who are enrolled in the main trial but not randomised (i.e. do not bleed or were not anticipated to bleed) is 24 hours from knife to skin.

The duration of follow up for randomised participants will be up to 90 days from randomisation, or death – whichever occurs first.

The outcome data will be ascertained through hospital records for randomised participants who die in hospital. For those participants who have died following hospital discharge and within 90 days of surgery, the NHS Spine will be used first to obtain data on participant's survival before contacting the GP.

If randomised participants have been discharged prior to 28 days, data will be collected from outpatient appointments at 42 days and 90 days. The 42 days is a routine outpatient appointment for all patients after cardiac surgery, while the 90 days is an extra follow up time point for the trial. Data collection for both appointments can be conducted face to face or by phone consultation, depending on the availability of the participant and research staff. Research teams may offer participants an in-person D90 appointment if they have the capacity. Questionnaires can be returned by post or email, or completed during the day 90 consultation.

If a randomised participant reports in the EQ-5D-5L trial questionnaire that they are experiencing a new moderate or severe depression, and/or that their level of depression has worsened during the trial follow-up period, then the research team have a duty of care to inform the participant's GP. This information will be included in a letter to the patient's GP notifying them of the participant's end of participation in the trial.

8.0 Participant, Trial, and Site discontinuation

A participant can withdraw from the trial for any reason if they wish. Any participant who chooses to withdraw during the treatment or follow up period will not be contacted further. In line with the Health Research Authority guidance on data retention in participants who withdraw from clinical trials, we will retain all data collected up to the point of withdrawal. Unless advised otherwise by the withdrawing participant, we will continue to collect data to be assessed as part of the primary and secondary end points from NHS hospital records for the remainder of the participant's 90 day follow up period.

In all cases of withdrawal, the reason will be recorded in detail in the eCRF and in the subject's medical records and trial file where possible. A screen failure subject will not be considered a

withdrawal subject. A withdrawn participant cannot be re-entered in the trial and will not be replaced.

There will be no pre-defined early withdrawal criteria for participants following trial entry. The local PI may choose to withdraw a participant, for example due to non-compliance with trial procedures or safety concerns.

9.0 Laboratories and samples

No research blood samples will be collected as part of the trial. We will only collect results of laboratory tests that have been performed as part of routine standard of care.

10.0 Trial medication

10.1 Name and description of Investigational Medicinal Product(s) (IMP)

The trial will compare two treatments – prothrombin complex concentrate (PCC) and standard care, which is fresh frozen plasma (FFP) or solvent-detergent treated and /ligant gel removed plasma (or LG-Octaplas). Of these, PCC and LG-Octaplas are deemed investigational medicinal products by the MHRA, while FFP is not.

10.1.1 Prothrombin Complex Concentrate (PCC)

There are currently several PCC products used in the UK for treatment/prevention of bleeding associated with vitamin K antagonist agent. These are:

- **Octaplex** (Octapharma Limited)
- **Beriplex** (CSL Behring Limited)
- **Prothromplex** (Takeda UK Limited)

All products are similar from the efficacy and safety point of view. For this trial, all products may be used, depending on site's availability.

Octaplex, Beriplex and Prothromplex are blood products produced through pooling of thousands of human plasmas. Both products are treated to inactivate enveloped viruses, such as HIV, hepatitis B virus and hepatitis C virus. From the pooled plasma, vitamin K dependent clotting factors (factors II, VII, IX and X, and protein C and protein S), are selected to produce the concentrated form called PCC.

10.1.2 LG-Octaplas

In the UK, some hospitals use solvent-detergent treated plasma (or **LG-Octaplas**) instead of FFP for treating these individuals. LG-Octaplas is manufactured by Octapharma Limited after pooling thousands of blood donor plasmas from the same blood group. Pooled plasma is pathogen inactivated with solvent detergent to reduce the risk of transmission of enveloped viruses, such as HIV, hepatitis B and hepatitis C.

11.0 Legal status of IMP

11.1 Name and description of each Non-Investigational Medicinal Product (NIMP)

Fresh frozen plasma (FFP) or LG-Octaplas are the recommended products for treatment of bleeding in patients who are undergoing cardiac surgery, and who are not receiving vitamin K antagonist agents.[30] Either can be used in the trial as the comparator against PCC.

FFP is manufactured by NHS Blood and Transplant (NHSBT) and it is regulated through the Blood Safety and Quality Regulation (BSQR), which is transposed into the UK law.[31] FFP is not deemed a medicinal product by MHRA.

In the UK, FFP is produced from whole blood donations (male donors only), which undergo leucocyte-depletion and centrifugation processes. Once centrifuged, FFP is rapidly frozen to ≤-25°C for up to 36 months to maintain the activity of labile coagulation factors. Factor VIII (FVIII) is used for quality monitoring because it is one of the most labile coagulation factors and is therefore a sensitive marker of changes to FFP induced by inappropriate processing/handling.[30]

FFP will be supplied as a frozen solution, and labelled, by NHSBT. Labelling of FFP is done in accordance with the current versions of ISO 3826-1 and EU Medical Devices Directive. The following information is included on the label:

- Fresh Frozen Plasma, Leucocyte Depleted and volume
- the blood component producer's name
- the donation number and, if divided, sub-batch number
- the ABO group
- the RhD group stated as positive or negative
- the date of collection
- the expiry date of the frozen component
- the temperature of storage
- the blood pack lot number
- the name, composition and volume of the anticoagulant.

11.2 Legal Status of IMP

11.2.1 PCC (Octaplex / Beriplex / Prothromplex)

Prothrombin Complex Concentrate (PCC) is currently licensed in Europe for the treatment of congenital or acquired deficiency of prothrombin complex coagulation factors deficiency, and for the emergency reversal of vitamin K antagonists (VKA), such as warfarin, for patients who are bleeding or when urgent surgery is planned.

Bleeding during cardiac surgery falls under acquired bleeding disorders, and results in the deficiency of prothrombin complex coagulation factors. Hence the use of PCC in this setting is considered to be within licensed indication, and as such, the trial is classified as Type A.

11.2.2 LG-Octaplas

LG-Octaplas is currently licensed in Europe for the treatment of acquired bleeding disorders (cardiac surgery included) and is the current standard of care in the UK. FFP and LG-Octaplas are equivalent and are used interchangeably in the UK.

11.3 IMP Manufacturer(s) and supply arrangements

11.3.1 Octaplex

Octaplex is manufactured by Octapharma Limited. Marketing authorisation number(s)are: Octaplex 500 IU - PL 10673/0027 and Octaplex 1000 IU - PL 10673/0041. Octaplex will be supplied from the hospital stock and be ring-fenced for the trial.

11.3.2 Beriplex

Beriplex is manufactured by CSL Behring UK Limited. Marketing authorisation number(s) are PL 15036/0029, PL 15036/0028, PL 15036/0034. Beriplex will be supplied from the hospital stock and be ring-fenced for the trial.

11.3.3 Prothromplex

Prothromplex is Manufactured by Takeda UK Limited. Marketing authorisation number is PL 34078/0037. Prothromplex will be supplied from hospital stock and be ring-fenced for the trial.

11.3.4 LG-Octaplas

LG-Octaplas is manufactured by Octapharma Limited. LG-Octaplas will be supplied as a frozen solution and labelled by Octapharma Limited.

11.3.5 FFP

FFP is manufactured by NHS Blood and Transplant (NHSBT) and it is supplied as a frozen component and labelled by NHSBT.

11.4 Packaging and labelling of IMP(s), placebo(s), and NIMP(s)

11.4.1 Octaplex

Octaplex will be labelled as ‘for clinical trial use only’ by the pharmacy or hospital transfusion laboratories (depending on local arrangement).

Octaplex is presented as a powder and comes in two different package sizes: 500 IU and 1000 IU.

Octaplex 500 IU contains:

- Powder in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 20 mL of Water for Injections in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 1 Mix2Vial™ transfer device.

Octaplex 1000 IU contains:

- Powder in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 40 mL of Water for Injections in a vial (type I glass) with a stopper (halobutyl rubber) and a flip off cap (aluminium)
- 1 Mix2Vial™ transfer device

11.4.2 Beriplex

Beriplex will be labelled as 'for clinical trial use only', by the pharmacy or hospital transfusion laboratories (depending on local arrangement).

Beriplex is presented as a powder and solvent for solution for injection containing human prothrombin complex. Beriplex comes in three different package sizes: 250 IU, 500 IU and 1000 IU.

One pack with 250 IU containing:
- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20

One pack with 500 IU containing:
- 1 vial with powder
- 1 vial with 20 ml water for injections
- 1 filter transfer device 20/20

One pack with 1000 IU containing:
- 1 vial with powder
- 1 vial with 40 ml water for injections
- 1 filter transfer device 20/20

11.4.3 Prothromplex

Prothromplex will be labelled as 'for clinical trial use only', by the pharmacy or hospital transfusion laboratories (depending on local arrangement).

Prothromplex is presented as a powder and solvent for solution for injection containing human prothrombin complex. Prothromplex comes in one package size that will be used for this trial: 500 IU.

One pack with 500 IU containing:
- 1 vial with Prothromplex TOTAL 500 IU powder for solution for injection
- 1 vial with 17 ml sterilised water for injections
- 1 Mix2vial for reconstitution

11.4.4 LG-Octaplas

LG-Octaplas will be supplied as a frozen solution and labelled by Octapharma Limited. LG-Octaplas comes in 200mL volumes for intravenous infusion. It contains 45 – 70 mg human plasma proteins/mL and possesses the same clinical activity as the average single-donor FFP unit but is more standardised. The finished product is tested for coagulation factors V, VIII, and XI, and the inhibitors protein C, protein S, and plasmin inhibitor.

A minimum of 0.5 IU/mL is obtained for each of the three coagulation factors, whereas the inhibitor levels are guaranteed equal or higher than 0.7, 0.3, and 0.2 IU/mL. The fibrinogen content is between 1.5 and 4.0 mg/mL. In routine production, all clinically important parameters are within the 2.5-97.5 percentiles reference range for single-donor FFP, except plasmin inhibitor (also known as α2-antiplasmin) that is just below.

11.4.5 FFP

FFP will be supplied as frozen solution and labelled by NHSBT.

11.5 Accountability

Octaplex, Beriplex, Prothromplex, LG-Octaplas and FFP are all blood components/product that will be stored and issued by the transfusion laboratory to clinical areas. As such their handling and accountability will comply with the Blood Safety and Quality Regulation (BSQR 2005), which transposes two EU Directives, 2002/98/EC and 2004/33/EC, into UK law. The BSQR regulations are enforced by the MHRA.

The BSQR imposes significant requirements on whole transfusion practice from laboratory to clinical areas, and vice versa. As a result, transfusion laboratories have standard operating procedures for:

- Storage, distribution and transport of blood and blood components and blood products within the hospital.
- temperature controlled storage, monitoring and management of the "cold chain" of blood components.
- validation and calibration of processes and equipment.
- document the issuing and fate of all blood components and blood products
- notification of serious adverse events and reactions through Serious Adverse Blood Reactions and Events scheme (SABRE) and SHOT (Serious Hazard of Transfusion national hemovigilance scheme).

There is an ongoing programme of self-inspections (audit) which includes periodic audit of compliance with the requirements of the BSQR.

11.6 Drug storage

Octaplex will be stored in the transfusion laboratory, at < 25°C in its original package in order to protect from light. The shelf life of Octaplex is 3 years.

Beriplex will be stored in the transfusion laboratory, at < 25°C in its original package in order to protect from light. The shelf life of Beriplex is 3 years.

Prothromplex should be stored in a refrigerator at 2 ° C to 8 ° C in its original package in order to protect from light. The shelf life of Prothromplex is 3 years. Within the stated shelf life, the product can be stored at room temperature (max. 25 ° C) for one period of up to six months. The beginning and end of storage at room temperature should be recorded on the package. After storage at room temperature, Prothromplex TOTAL must not be returned to the refrigerator (2 ° C to 8 ° C) but must be used within six months or be disposed of.

LG-Octaplas will be stored in the transfusion laboratory at ≤ -18 °C for 4 years, protected from light. LG-Octaplas is supplied in a separate preparation according to the following blood groups - group A, group B, group AB or group O)

FFP will be stored frozen to below -25°C for up to 36 months to maintain the integrity of labile coagulation factors.

11.7 Prescription and Dispensing of IMP(s), placebo(s), and NIMP(s)

There is no requirement in PROPHESY-2 for a trial-specific prescription, due to the low risk and pragmatic nature of the trial. Prescribing will follow the established local procedure at each participating Trust.

If the participant bleeds or is anticipated to bleed and FFP is requested, the transfusion lab will perform the randomisation and provide the allocated treatment. Administration of the allocated treatment (Octaplex, Beriplex or Prothromplex or FFP) will be performed by a qualified member of the clinical care team and will be recorded on the prescription chart.

Any bleeding after 24-hours of surgery will be treated in accordance with standard care.

A site delegation log will be completed by the Transfusion laboratory team to ensure that all staff working on the trial are trained in the trial protocol and procedures. . This is also to confirm that they will only dispense trial treatment for the trial participants as requested by the clinical team.

Transfusion Laboratory Sites will be responsible for supplying blood components and blood products (PCC) in accordance with the randomisation procedure and for updating/maintaining documentation for trial procedures.

11.8 Administration of IMP(s), placebo(s), and NIMP(s)

Administration of PCC and plasma (FFP or LG-Octaplas) will be done by the clinical team looking after the participants as per the standard of care.

11.8.1 PCC (Octaplex/Beriplex/Prothromplex)

Aseptic technique will be maintained when preparing Octaplex/Beriplex/Prothromplex. The products reconstitute quickly at room temperature. The solution should be clear or slightly opalescent. Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration. After reconstitution the solution must be used immediately.

11.8.2 LG-Octaplas

Prior to use, LG-Octaplas requires thawing in a water bath at +30 to 37°C for no more than 30 minutes. Once thawed, LG-Octaplas must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ±2°C or up to a maximum of 120 hours if stored at 4 ±2°C.

Administration of LG-Octaplas must be ABO-blood group compatibility. In emergency cases, group AB LG-Octaplas can be given to all participants regardless of blood group. Prior to transfusion, LG-Octaplas pack must be inspected for signs of deterioration or damage.

LG-Octaplas must be administered by intravenous infusion after thawing, using an infusion set with a filter over 5 to 20 minutes per unit. An aseptic technique must be used throughout the infusion.

11.8.3 Fresh Frozen Plasma

Prior to use, FFP requires thawing at 37ºC (between 33°C and 37°C are acceptable) for 15 to 20 minutes in a waterbath or other equipment designed for the purpose, within a vacuum-sealed overwrap bag according to a validated procedure.

Once thawed, FFP must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ±2°C or up to a maximum of 120 hours if stored at 4 ±2°C.

Administration of FFP should be ABO-blood group compatibility. If ABO group compatible component is not available, group AB, or group A of low anti-B titre can be transfused.[30] Prior to transfusion, FFP pack must be inspected for signs of deterioration or damage.

FFP must be administered by intravenous infusion after thawing, using an infusion set, over 5 – 20 min per unit. An aseptic technique must be used throughout the infusion.

11.9 Destruction, return, and recall of IMP(s) and placebo(s)

Any unused product or waste material will be disposed of in accordance with local requirements.

For used products, unambiguous traceability will be collected as part of Blood Safety and Quality Regulation (BSQR) 2015. The traceability process allows for electronic tracking of each individual unit of blood or blood component from the donor to its final destination (whether this is a recipient, a manufacturer of medicinal products or disposal) and from its final destination back to the donor.

All hospital transfusion laboratories are required to keep the evidence of traceability for every unit used (or wasted) for 30 years. The following data items will be electronically recorded:

- Donation number
- Component type
- Blood establishment which provided the blood component
- Date provided
- Identity of participant who received the blood component or final fate if not transfused

11.10 Dosage schedules

11.10.1 PCC (Octaplex, Beriplex or Prothromplex)

Based on recent systematic reviews, the PCC dose varied greatly across studies ranging between 10 IU/kg - 50 IU/kg.[11,12] The European Society of Anaesthesiology guidelines recommend a dose of 20 – 30 IU/kg.[10]

Based on the above studies, the results of our pilot trial,[2,22] and the current recommended dose for FFP, the following dose schedule will be used in this trial:

- 1,500 IU if participants ≤70kg
- 2,000 IU if participant >70kg

A maximum of two PCC doses will be administered to treat bleeding. If a participant continues to bleed after 2 doses, they will be given FFP as per standard of care.

11.10.2 FFP / LG-Octaplas

The recommended dose for FFP/LG-Octaplas for treatment of major bleeding is 15 - 20 mL/kg.[8] For this trial the following doses will be administered:

- 4 units of FFP if participants ≤70kg
- 5 units of FFP if participant >70kg

If bleeding continues, after administration of the first dose of FFP, participants will continue to receive standard care, and this will be with further FFP transfusion. There is no maximum allowed dose for FFP.

11.11 Dosage modifications and delays

There will be no dose modification.

11.12 Management of IMP-specific adverse events

All transfusion laboratories have standard operating procedures in place that accurately, efficiently and verifiably report blood and blood components involved in serious adverse events or reactions or that are judged to have the potential to cause harm to patients, through SABRE and SHOT haemovigilance schemes. All these steps will be used to report adverse events relating to FFP/LG-Octaplas and PCC and recall these if necessary.

One of the undesirable effects of PCC is the risk of thrombosis, which is dependent on the dose (i.e. the higher the dose the higher the risk). The risk of thrombosis associated with 4-factor PCC from the several studies [19-21] has been reported to be <2%, and this was similar between PCC and FFP. Rates of thrombosis will also be monitored throughout the trial up to 90 days after randomisation.

11.13 Known drug reactions and interventions with other therapies

According to the SmPC, there are no known interaction with other medicinal products and PCC (Octaplex/Beriplex/Prothromplex) or FFP/LG-Octaplas.

11.14 Recommended concurrent treatment

There are no treatments that the subjects cannot take whilst on treatment on the trial, besides those mentioned in the exclusion criteria. The CRF will capture data on any prior or concomitant therapies at admission, and within 24 hours of intervention.

11.15 Prohibited medication

11.15.1 PCC (Octaplex, Beriplex or Prothromplex)

Octaplex is contraindicated in:

- Hypersensitivity to the active substance or to any of the excipients listed in section

6.1 of the SmPC.
- Known allergy to heparin or history of heparin induced thrombocytopenia.
- Individuals who have IgA deficiency with known antibodies against IgA.

11.15.2 LG-Octaplas

LG-Octaplas is contraindicated in:
- IgA deficiency with documented antibodies against IgA.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC or residues from the manufacturing process, as stated in section - 5.3.
- Severe deficiencies of protein S.

All above conditions for PCC and LG-Octaplas are included in the exclusion criteria.

11.16 Trial restrictions

No trial restrictions required.

11.17 Management of overdose

Not applicable. Interventions will be issued and administered by the clinical teams looking after participants while in hospitals, using the dosage scheme above, so there is no risk of overdose.

11.18 Precautions regarding contraception

Not applicable.

11.19 Arrangements for post-trial access to IMP and care

Not applicable. Interventions will be provided within the first 24 hours of surgery, when participants are admitted to hospitals as part of standard surgical care.

12.0 Equipment and Devices

No clinical or non-clinical equipment and/or devices will be used outside of standard practice.

13.0 Safety Reporting

In addition to the trial safety reporting procedures, hospital staff will be responsible for reporting all transfusion-related adverse events/reactions via Serious Hazards Of Transfusion and Serious Adverse Blood reactions and events (SHOT/SABRE) according to standard procedures (as required by BSQR UK 2005). Each individual transfusion laboratory issuing blood has their own their local policies and procedures for the response to a possible transfusion event and should ensure full compliance with their own standard procedures and MHRA.

13.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "*response to an investigational medicinal product*" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation (i.e. A&E admission) or prolongation of existing hospitalisation (*Day cases is not considered hospitalisation)*. • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator or medical assessor, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

13.2 Site investigator assessment

The Principal Investigator is responsible for the care of the participant, or in their absence an authorised medical practitioner (Sub-Investigator) within the research team is responsible for assessment of any event for:

- **Seriousness**
  Assessing whether the event is serious according to the definitions given in section 0.

- **Causality**

Assessing the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

- **Expectedness**
  The PI will not make an expectedness assessment as this responsibility lies with the CI as medical assessor
- **Severity**
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event endpoint criteria.
    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

13.3 Reference Safety Information (RSI)

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected. **Expectedness will be evaluated against the trial Reference Safety Information (RSI) in use at the time of the reaction occurred.**

A Summary of Product Characteristics (SmPC) for **Octaplex** will be used for this trial (dated 06 Aug 2024) https://www.medicines.org.uk/emc/product/6566/smpc#gref **as amended.** RSI is Section 4.8 of the SmPC.

A Summary of Product Characteristics (SmPC) for **Beriplex** will be used for this trial (dated 21 Jan 2021) https://www.medicines.org.uk/emc/product/6236/smpc#gref **as amended.** RSI is Section 4.8 of the SmPC.

A Summary of Product Characteristics (SmPC) for **Prothromplex** will be used for this trial (dated 16 Aug 2023) https://www.medicines.org.uk/emc/product/15237/smpc **as amended.** RSI is Section 4.8 of the SmPC.

A Summary of Product Characteristics (SmPC) for **LG-Octaplas** will be used for this trial (dated Nov 2024) https://www.medicines.org.uk/emc/product/4171/smpc **as amended**. RSI is Section 4.8 of the SmPC.

There is no SmPC for FFP. The section titled 'Safety and adverse effects of plasmas' in the UK guidelines issued by the British Society for Haematology[30] will be used as an RSI for FFP https://pubmed.ncbi.nlm.nih.gov/29527654/ **as amended**.

13.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AE and ARs are to be documented in the participants' medical notes or other source data documents and the participant is followed up by the clinical care team. Unless they are related to blood transfusion, thromboembolic events, or primary and secondary outcomes, AEs and ARs do not need to be reported.

13.5 Notification of AEs of Special Interest (AESIs)

Not applicable.

13.6 Serious adverse event reporting

All SAEs must be reported for the following time periods from the first dose of trial treatment:

- 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 must be recorded in the source data as AEs unless they relate to thromboembolic events, in which case they must be reported as an SAE. All deaths must 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 must be reported to the NHSBT CTU within 24 hours of awareness as outlined under section 13.7 below. These will be investigated as potential SUSARs.

13.7 Notification and reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

NHSBT CTU has been delegated the responsibility of safety reporting by the Sponsor. All Serious Adverse Event (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded in the participants' notes, the CRF, and reported to the NHSBT CTU via the trial database within 24 hours of the site's trial research team (i.e. PI, investigators, research nurse) becoming aware of the event (except those specified in this protocol as not requiring reporting).

In the event that the clinical database is unavailable, SAE reports can be completed on an SAE report form and emailed to prophesy2trial@nhsbt.nhs.uk within 24 hours of awareness. As soon as the database is available, reports need to be entered as an SAE report in the participant's eCRF.

Delegated sub-investigators (as recorded in the site delegation log) may be authorised to assess and sign SAE reports in the absence of the PI at the participating sites.

When an SAE report is received at the NHSBT CTU, the report is reviewed by delegated staff. for completeness. Any additional information required to complete the report before sending it review will be requested from the site. NHSBT CTU delegated staff will send all SAE reports to the CI for review. The CI is the Sponsor's delegated medical assessor (see Section 13.8). NHSBT CTU delegated staff will review the SAE database on a regular basis to assess the status of all the SAEs and to ensure that those that have not yet resolved are followed up until they are.

SUSARs that occur during the trial will be reported to the NHSBT CTU within 24 hours of the site's trial research team becoming aware of the event. NHSBT CTU has been delegated the responsibility of safety reporting oversight by the Sponsor. NHSBT CTU delegated staff will notify the Sponsor (research.safety@qmul.ac.uk) in real time of any SUSAR, and the Sponsor will be kept updated on SUSAR reporting to REC and MHRA and Investigators in accordance with regulatory requirements. All fatal or life threatening SUSARs will be reported to the relevant REC and the MHRA by NHSBT CTU staff as soon as possible but no later than 7 days from the NHSBT CTU becoming aware. All other SUSARs will be reported within 15 days. NHSBT CTU delegated staff must also inform all the PIs participating in the trial of any SUSARs that may occur in a timely fashion.

NHSBT CTU team will also send the Sponsor (research.safety@qmul.ac.uk) line listings of new SAEs/SUSARs reported by the trial every quarter,

13.8 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of AEs, ARs, SAEs, SARs and SUSARs to the CI as medical assessor. The CI must review all SAEs within 72 hours of receipt. This review should encompass seriousness, causality, and expectedness. **Responsibility for expectedness lies with the CI as medical assessor.** Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the RSI), then it is a SUSAR. Day 0 for all SUSARs is when the SAE / SUSAR is received by the CI and / or NHSBT CTU coordinating team.

It is noted that the CI cannot downgrade the PI assessment of an event's causality. If there is disagreement between CI and PI assessment, no pressure should be placed on the PI to alter their assessment, but the CI can liaise with the site PI before the CI's final decision. The CI and PI assessment can differ.

13.9 Procedures for reporting blinded SUSARs

Not applicable.

13.10 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required.

The CI has an obligation to inform both the MHRA and Research Ethics Committee in writing **within 3 days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes with 14 days of implementing the urgent safety measure. The JRMO as Sponsor (research.safety@qmul.ac.uk) must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

13.11 Pregnancy

Pregnant participants will be excluded from the trial. If a participant falls pregnant after consent is obtained and prior to surgery, the participant will be withdrawn from the trial.

If a participant is randomised to receive PCC and falls pregnant after the surgery (i.e. after the intervention has been administered) up to the point of hospital discharge or 28 days, whichever is sooner, the participant will remain in the trial and all data will be collected until a birth outcome can be recorded with the participant's consent. Safety monitoring of these participants will be achieved as per standard practice.

Any pregnancies following randomisation will be self-reported. The PI will follow up the pregnancy until delivery as well as monitoring the development of the fetus for the appropriate time and where clinically appropriate after birth. Any events to the mother or child that occur during this time that could be considered to be an SAE will be reported to the Sponsor in line with section 0, using the trial SAE reporting form. If a participant falls pregnant after hospital discharge, safety reporting for the pregnancy will not be collected, as there will be very little PCC residing in any of the discharged participants randomized to PCC, due to the short half-life/wash out period of PCC (see section 13.6 above). This also aligns with the current routine practice, where PCC is used instead of FFP to treat the bleeding for any clinical settings.

There are no pregnancy reporting requirements for participants who were treated with FFP or LG-Octaplas, as these are both standard of care and pregnancy reporting is not required routinely.

14.0 Annual reporting

14.1 Development Safety Update Report (DSUR)

NHSBT CTU has been delegated the responsibility of safety reporting by the Sponsor. The DSUR will be written by the CI (following NHSBT CTU procedures) and submitted to the Sponsor (research.safety@qmul.ac.uk) for review prior to submission to the MHRA. NHSBT CTU is responsible for submitting the DSUR to the MHRA, and copying in the Sponsor (research.safety@qmul.ac.uk) in any relevant conversation. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "*Notice of acceptance letter*" from the MHRA. The Sponsor's delegated Medical Assessor, usually the CI, will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. NHSBT CTU will send a copy of the DSUR to the REC cc' ing the Sponsor (research.safety@qmul.ac.uk)

14.2 Annual Progress Report (APR)

Not applicable as Study received a favourable ethics opinion from a REC in England.

15.0 Statistical and data analysis

15.1 Sample size calculation

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,[32] implemented using proc seqdesign in SAS v9.4) 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, 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: **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 trial of organ protection interventions in cardiac surgery in cardiac surgery [33-35] and is likely to change practice.

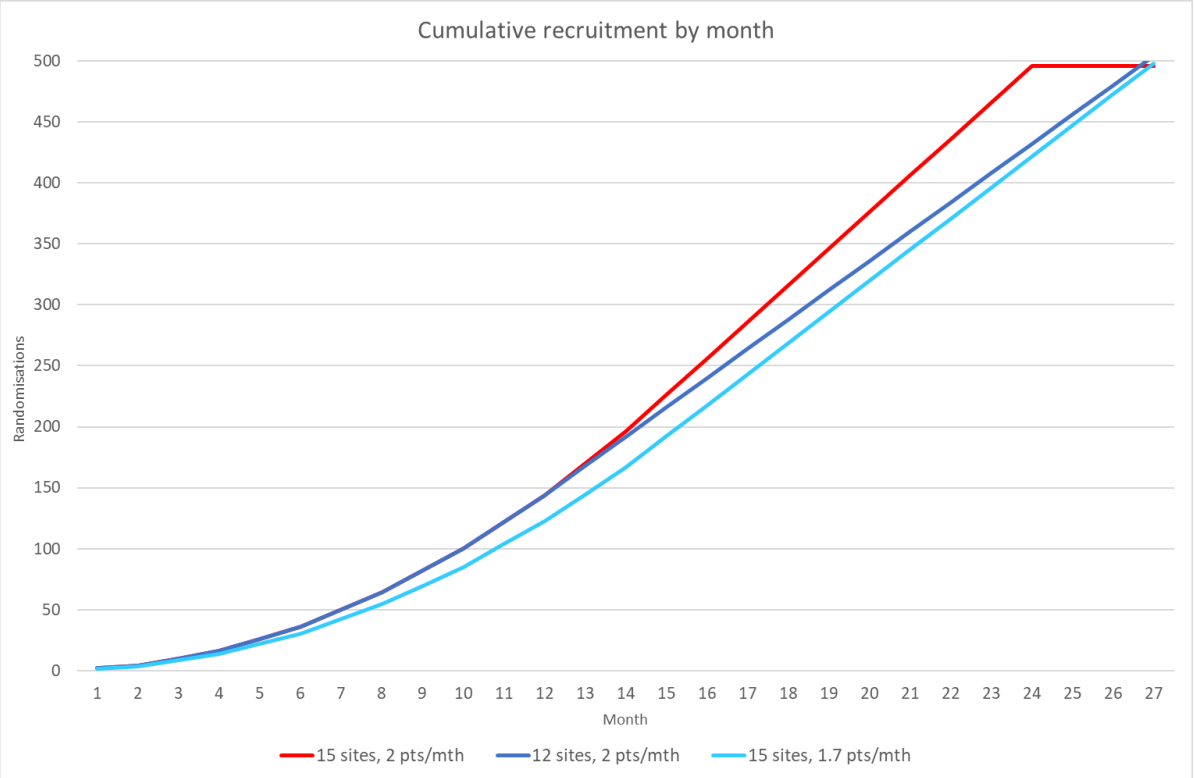
Pilot trial: In 2019 we completed a single-centre pilot RCT trial at Saint Bartholomew hospital (funded by the British Heart Foundation). Of the 180 patients screened, 74% (95%CI 67–81%) consented and of the latter 35% (95%CI 27–44%) developed bleeding and were randomised. We demonstrated high recruitment (7 randomised participants per month), adherence (90%), and low attrition rates (data completeness 100% at 30 days and 92% at 90-days).[2] No participant withdrew from the trial and 4 were lost to follow-up.

15.2 Planned recruitment rate

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 recruit 2 randomised 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.

Of the 15 sites that have said yes to our initial request to participate in the trial, we have estimated they would have a total of over 700 eligible patients between them, and randomise over 80 participants per month. This is more than double our target recruitment of 2 randomised participants per month per site. Even if we have a lower recruitment rate (i.e., 1.7 randomised participants per month/site from 15 sites or 2 randomised participants per month/site from 12 sites) then we would still be able to recruit 496 within our planned recruitment period of 27 months (see anticipated recruitment **Figure 2**).

Figure 2. Anticipated recruitment



All these have been taken into consideration to inform the internal trial stop/go criteria described below.

Internal pilot: An internal pilot phase will be completed at 9 months after randomisation of the first participant. The stop-go criteria for expanding to compete the full trial will be determined on recruitment rates and number of new sites set up (see table below). The traffic light criteria (**Red** [discuss with funder], **Amber** [investigate & implement improvements], **Green** [proceed]) will be assessed and action taken based on which metric is performing the lowest. Data quality will be monitored and any possible improvements to improve these will also be considered at this time point, together with assessing the rate of drop-out. The Trial Steering Committee in consultation with the funder will determine progression.

Progression criteria	**Red**	**Amber**	**Green**
Trial recruitment	<75%	75-99%	100%
Recruitment rate/site/month	<1.5/site/month	1.5-2/site/month	≥2/site/month
Number of sites opened	<5	5-8	≥9
Total number of participants recruited	<62	62-81	≥82

15.3. End of trial (EOT) definition

The EOT definition for PROPHESY-2 will be the last subject finishes the last visit and data collection point, or when the last alive subject recruited into the trial has completed the 90 day follow up visit - whichever is later.

The CI is delegated the responsibility of submitting the EOT notification to the REC and MHRA once reviewed by Sponsor. The EOT notification must be received by REC and MHRA within

90 days of the end of the trial. If the trial is ended prematurely, the CI will notify the Sponsor, REC & MHRA including the reasons for the premature termination (within 15 days).

15.4 Statistical 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).

15.5 Summary of baseline data and flow of participants

Full detail of the baseline characteristics which will be presented will be included in the Statistical Analysis Plan. No statistical comparisons of the two arms will be made for baseline data. Continuous data will be summarised as a mean with an accompanying standard deviation (significantly skewed data will be summarised as a median alongside an inter-quartile range). Categorical data will be presented as counts and proportions.

The key baseline characteristics for this trial include:

- Age, sex assigned at birth, ethnicity
- Weight, height and BMI
- Type of admission (i.e. urgent or elective)
- Type of cardiac surgery
- Previous medical history
- Medication pre op
- EuroSCORE II[36]
- Standard laboratory results (haemoglobin, platelet count, renal and liver function tests, PT and APTT)
- EQ-5D-5L quality of life score and & KCCQ/CROQ

15.6 Analysis of participant populations

The primary analysis 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.

15.7 Primary endpoint analysis

The proportion of participants with a new event (up to 90 days after randomisation) of any of the following: all-cause mortality, acute respiratory failure, myocardial injury, acute renal failure requiring renal replacement (excluding dialysis during cardiopulmonary bypass), acute liver injury, acute intestinal injury, focal neurological deficit, infection will be calculated for each arm and 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, 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 ($p<0.0439$ will be considered as statistically significant).

15.8 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.

Full details of all secondary outcome analyses will be presented in the Statistical Analysis Plan.

15.9 Safety analysis

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

15.10 Subgroup analyses

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.[37]

15.11 Adjusted analysis

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.

15.12 Interim analysis and criteria for the premature termination of the trial

There will be an internal pilot after 9 months to check the progression criteria, as specified in Section 15.2.

There will be a formal interim analysis after 75% recruitment (n= 372 participants randomised and reached the primary outcome) to check if it's 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 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 TSC. This will indicate if they believe that the trial should be stopped early.

The DMC will also review accumulating safety data periodically, as specified in Section 24.4 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.

15.13 Procedure(s) to account for missing or spurious data

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 imputation based on full conditional specification to impute missing primary outcome data. Multiple imputation will also be used to impute the values of any missing data for relevant baseline risk factors in the fully risk-adjusted sensitivity analysis.

15.14 Economic evaluation

Full details of the health economic analysis will be specified in a separate Health Economic Analysis Plan. The economic analyses we propose will inform policy decision-makers on the use of PCC relative to FFP in cardiac surgery patients developing bleeding in view of the main findings of the PROPHESY-2 trial. This will consist of:

1. within-trial economic analysis which will evaluate the effects of PCC compared to FFP on generic health-related quality of life and survival, and estimate the within-trial (over 90 days) cost-utility of PCC in cardiac surgery patients developing bleeding (additional cost per extra quality-adjusted life year), and
2. a longer-term analysis which will use an analytical model for projecting longer-term net effects of PCC treatment on patient's health-related quality of life and health and social care costs, and the cost-effectiveness of PCC relative to FFP in cardiac surgery patients developing bleeding.

The economic analysis will take the perspective of the UK NHS and personal social services. The health utility will be measured in QALYs using the EuroQoL EQ-5D-5L. Costs will be evaluated from the perspectives of UK NHS health and social care. Health states measured through HRQoL questionnaires will be assigned valuations derived from published UK population tariffs. Resource use data for each participants will be collected using case report forms for the hospitalisation and a self-reported resource use measure for capturing any health and social care resource use from administration of the trial treatment up to 90 days.

15.14.1 The within-trial (90 days of follow-up) economic analysis

During the trial's 90-day follow-up, the QoL profile will be analysed to calculate QALYs for each participant. The mean QALYs of participants assigned to PCC will be compared to those of participants assigned to FFP. The individual level patient data will be analysed further to assess the impact of all primary outcome components on HRQoL. This analysis will be more sensitive in identifying the effects of primary outcome changes on EQ-5D utility. The resulting associations will be utilised to predict participants' QoL and calculate the QALYs and differences between the two arms in the long-term model.

As part of the PROPHESY-2 trial, participants will be required to complete a self-reported resource use measure. This information includes details about primary, specialist, emergency, hospital care, any medications as well as social care used, over the past 90 days. Resource use will be costed using nationally published sources.[38-40] The costs for each participant during the follow-up period will be estimated, acknowledging that data was collected for 3-monthly periods. Information on participant lost time and work productivity will also be collected via a self-reported resource use measure but analysed separately from a societal perspective.

The effect of allocation to PCC on health and social care use will be evaluated using the intention-to-treat principle. In a further analysis, the annual costs will be related to organ failure or infection of participants to provide a more sensitive estimate as to the likely effect of PCC on resource use as well as inform costs in the cardiac surgery patients developing bleeding model. The cost of intervention, including drug cost, administration and monitoring costs will also be evaluated using trial data on the quantity and frequency of administered drugs and monitoring and national reference costs.

Missing data will be handled using multiple imputation in STATA. In case one arm has both higher costs and better QALY outcomes, an incremental cost-effectiveness ratio (ICER) will be estimated as additional cost per additional QALY gained. Uncertainty around the ICER point estimate will be assessed using probabilistic methods.[41] We will estimate the likelihood of the intervention being cost-effective in comparison to usual care using the NICE threshold of £20,000-30,000 per QALY gained. One-way sensitivity analyses will be conducted to address the uncertainty associated with costs of the intervention and healthcare services use. We will conduct subgroup analyses to determine if there are any variations in surgery types or heart conditions.

15.14.2 Longer-term effectiveness and cost-effectiveness

We will develop a model of follow-up in cardiac surgery patients developing bleeding to project patients' QoL and health and social care costs over time, and the effects of PCC compared to FFP on these outcomes. The model will use follow-up of patients with organ failure or infection. The PROPHESY-2 trial will provide most data with respect to HRQoL and costs related to organ failure or infection within 90 days.

We will compare our findings with external data for cardiac surgery patients developing bleeding.[42] However, the 90 days follow-up data in PROPHESY-2 will be insufficient to reliably evaluate the long-term progression of patients with organ failure or infection and, therefore, external data will likely inform the subsequent quality of life and resource use.[42] We will take into account data sources specific to the UK for the long-term analysis. Similarly, to the within-trial analysis. the long-term analysis will report the mean incremental cost per quality-adjusted life year (QALY) gained taking the perspective of UK NHS and personal social services. Utility will be expressed as QALYs, measured using the EuroQoL EQ- 5D-5L and costs evaluated from the perspectives of UK NHS health and social care. One-way and probabilistic sensitivity

analyses will be conducted to address the uncertainty associated with costs of the intervention and healthcare services use.

15.15 Other statistical considerations

Not applicable.

16.0 Data handling and record keeping

16.1 Source data and source documents

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to:

- Informed consent forms
- Participant's medical records
- Completed participant questionnaires (paper and electronic (entered directly onto the eCRF)

Electronic CRF entries will be considered source data where the eCRF is the site of original recording (e.g. there is no other written or electronic record of the data). This is the preferred data collection method. Where it is not possible to capture data directly into the eCRF, a paper source data form will be provided. Full details will be provided in the Data Management Plan and in the Trial Manual. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant Trial ID, not by name.

Only people who have a 'legitimate relationship' with the participant (i.e. are members of the team providing the participant's health care) are entitled to have access to their medical records.

Direct access will be granted to authorised representatives from the Sponsor, host institution, and the regulatory authorities to permit trial-related monitoring, audits, and inspections.

Source data forms, questionnaires, clinical notes and administrative documentation will be kept in a secure location at each site (for example, locked filing cabinets in a room with restricted access to NHS staff and direct care team only). Once the trial has ended and sites are given the instruction to archive records, this should be done in accordance with local policy and for 25 years or as required by subsequent clinical trial regulations. During this period, all data should be accessible to the competent authorities and the Sponsor with suitable notice.

16.2 Case Report Forms (CRFs)

Trial data will be captured electronically via an electronic case report form (eCRF). The eCRF will be designed according to NHSBT CTU's data policies, MPDs and SOPs, with input from the CI, trial team and NHSBT CTU team. eCRFs will capture data from each of the trial visits.

Only authorised users approved by the PI will have access to the central electronic database, and each user will be assigned specific user roles and rights. Sponsor representatives and CTU team members will have read-only access to the data. The research team are responsible for data entry and eCRF completion. The PI will have overall responsibility for data captured in the eCRF and be able to review, lock and electronically sign the completed eCRFs.

In the eCRF, repetitive data such as subject ID will be generated by the system automatically from the first page to all others, thus ensuring no duplication of CRF pages and data accuracy. The eCRF will also have built-in validation checks tagged to each data field as well as to the CRF as a whole. Therefore, the majority of data cleaning activities will take place during the completion of the eCRFs, and the dataflow query process will enable queries and data clarifications in real time on the data.

16.3 Data capture

Data capture will be done by appropriately delegated research site staff using the current version of OpenClinica, using single data entry methods. To access OpenClinica, the user must be using a device that can connect to the internet and any of the major internet browsers. Users of the database must be trained according to CTU MPD1572. The training is tailored to each user role as allocated in the database. Some users may not need data entry training if they only view and sign-off records, but for users who will be entering data, test data must be entered correctly into a test database before access will be given to the database in production (i.e. the database that will be used in the trial).

Where appropriate and possible, data validation will be built into each question to ensure accurate data entry in real time.

To facilitate data entry directly into the eCRFs, the forms will allow unanswered questions to be saved. This is preferable to having the entire form remain blank where one question is unknown at the time of data entry. Therefore, we expect to have missing values in the database which must be followed up with the research team to maximise data completeness. This is done by the CTU-based data manager raising a data query in OpenClinica which can be resolved directly by the site staff and enables an easy tracking of all queries.

The only information that can be captured on the eCRFs pertains to agreed variables in the database and all other information pertaining to a participant's research experience must be documented elsewhere (e.g. the clinical notes).

Any hard-copy source documents must be stored and secured according to local Trust policies. Data entered into the trial database is stored on servers owned and managed by OpenClinica. These are GDPR compliant and only servers located in the United Kingdom will be used for data storage.

As advances in technology and computing functionality advance, we will endeavour to use validated systems to enhance data quality, and the experience of the participants and research teams. Exact details of any interaction between the database and any other electronic system will be documented in the CTU Data Management Plan.

16.4 Transferring and transporting data

All data must be handled in accordance with the Data Protection Act (2018), and the General Data Protection Regulation (GDPR). Data will not be transferred outside of the UK. Identifiable information will not be stored or transported on any device unless it is encrypted. Data will only be sent electronically using end-to-end encryption.

16.5 Data Management

This trial has a dedicated Data Management Plan and many of the details and specifications relating to the data management activities for this trial are documented therein.

Data quality activities will include:

- Source-data verification at on-site monitoring visits, as specified in the Trial Monitoring Plan
- Remote monitoring activities, as specified in the Trial Monitoring Plan
- Automatic query generation in the eCRF
- Data validation rules applied at the question level to ensure real-time data quality
- Final sign-off by the PI for participants' data as they exit the trial

Data lock will be authorised by CTU statisticians after final data cleaning activities have been completed. The database will initially be frozen to allow the statistician to pull the first clean extract. Thereafter data cleaning may continue, or database lock could be performed. This is described in detail in the data management plan and the CTU MPD997.

The CTU statisticians have read-only access to the database and will pull their analytical dataset directly from OpenClinica. This will be stored and processed according to CTU MPD1177.

17.0 Confidentiality

The Chief Investigator will be the data custodian for all data generated during the trial.

The Chief Investigator and the trial team will ensure that all participants' identities are protected at every stage of the trial. To ensure this, at time of consent each participant will be allocated a unique screening number before undergoing any screening procedures.

The Principal Investigator is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique trial identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, Sponsor, or anyone associated with the trial.

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. Trial data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the JRMO SOP 20 Archiving.

17.1 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 onto the screening log. The participant's 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 authorized research staff. This information will be kept on the screening log. The initials of any patient who has been screened but does not provide consent to enrol in the trial must be redacted within 90 days as required by the CAG.

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, i.e. develop bleeding or are anticipated to bleed within 24 hours of the start of surgery and receive either the control or intervention, 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.

17.2 National Data Opt-out

The research team staff responsible for assessing eligibility of patients in the pre-surgery assessment clinics will check the national opt out register prior to approaching potential patients about taking part in the trial'.

More information on the national data opt-out can be found here: National data opt-out - NHS England Digital

18.0 Monitoring, Audit, and Inspection

18.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the Sponsor and Chief Investigator based on the Sponsor's risk assessment, which will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan. The Sponsor has delegated NHSBT CTU to monitor participating UK sites as per agreed Trial Monitoring Plan including specifically: Protocol compliance, Informed consent, SAE reporting, Standard Data Verification. NHSBT CTU will provide periodical Monitoring Summary Reports to the Sponsor (research.safety@qmul.ac.uk).

18.2 Auditing and Inspection

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.

19.0 Compliance

The CI will ensure that the protocol and trial are conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), GCP guidelines, the World Medical Association Declaration of Helsinki, the Sponsor's and trial specific SOPs, and other regulatory requirements.

The trial will not commence until Sponsor permission to activate sites is received.

Sites will be individually activated by the CI and CTU trial management; this will not occur until site approval is granted.

19.1 Non-Compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. Non-compliances will be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. Protocol non-compliance will be identified and managed by the CI and CTU coordinating team in the first instance and documented on a protocol deviation form and captured on a Site deviation Log.

The CI and the CTU coordinating team will assess the non-compliances and action in a timeframe in which they need to be dealt with. This assessment will include the need to escalate to the Sponsor. Any event with the potential to affect participant safety or data integrity will be reported to the Sponsor within 24 hours of the Coordinating team becoming aware.

The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated.

Where applicable corrective and preventative actions will be assigned. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, including an on-site audit.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used (e.g. it is not acceptable to enroll a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol). Accidental

protocol deviations can happen at any time. However, they will be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, and will require review with the CI and a corrective and preventative action plan implemented. If such deviations continue, or participant safety is affected, these will be escalated to the Sponsor for review and could potentially be classified as a serious breach.

Systematic failure of both the CI and the trial staff not adhering to SOPs/protocol/ICH-GCP and UK regulations, which leads to prolonged collection of deviations, will result in reporting of serious breaches or suspected fraud.

19.2 Notification of Serious Breaches to GCP and/or the protocol

A 'serious breach' is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

The site PI is responsible for reporting any potential serious breaches to the Sponsor (research.safety@qmul.ac.uk) and the NHSBT CTU (prophesy2trial@nhsbt.nhs.uk) within **24 hours** of becoming aware of the event.

Please note email address can be changed if agreed with GCP team Sponsorship submission.

The Chief Investigator is responsible for reporting any potential serious breaches to the NHSBT CTU and to JRMO as Sponsor **within 24 hours** of becoming aware of the event.

The Sponsor has delegated NHSBT CTU to determine whether a potential serious breach constitutes a serious breach, and to work with the CI to investigate and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach. The Sponsor (research.safety@qmul.ac.uk) should be included in any relevant conversation.

20.0 Declaration of interests

Co-applicants Professor Laura Green, Professor Simon Stanworth, Dr Josephine McCullagh and Helen Thomas 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 have received educational grant funding, honoraria or travel expenses from Fisher & Paykel, Pharmacosmos, Massimo and Nordic Pharma.
All competing interests will be held in the Trial Master File. Please address enquiries to prophesy2trial@nhsbt.nhs.uk

21.0 Peer review

The trial was peer reviewed by four independent experts as part of the NHIR HTA funding application. The trial protocol has been reviewed by the NHSBT CTU and Blizard Institute (CI's institute).

22.0 Public and Patient Involvement (PPI)

Involvement: Ms Sarah Murray (SM), a lay member and a chair of National Cardiac Surgery Clinical Trials Initiative, is a member of the Trial Management Group. A patient representative will sit on the Trial Steering Committee. Both will lead the trial PPI activities, supported and coordinated by Professor Julie Sanders (JS). SM and JS are also experienced and internationally published in supporting the representation of women in cardiovascular trials.

A Patient Researcher will be appointed from the Equality, Diversity and Inclusion (EDI) group based at Queen Mary University of London (QMUL). The Patient Researcher will sit on the TMG and will advise the trial team on recruitment processes ensuring that cultural, educational, and language barriers for undeserved communities are mitigated.

The PPI representative in the TMG, Patient Researcher, Professor Julie Sanders and the CI will for the PPI/EDI (equality diversity and inclusion) panel that will meet regularly. The panel will work with local and national stakeholder groups that have PPI representation in cardiac surgery, such as: EDI initiatives for clinical trials in cardiac surgery, Cardiovascular Care Partnership UK, Society of Cardiothoracic Surgery (chaired by SM), British Heart Foundation (BHF) Clinical Research Collaborative and NHSBT PPI group). Bespoke trial-dedicated training will be provided for all PPI members and the Patient Researcher during the set-up period.

Stakeholder webinars: During the set-up phase, we will host national webinars to reach out to stakeholders across all regions of the country where recruitment will take place. This will be coordinated by the NHSBT Clinical Trial Unit, with support by Cardiovascular Care Partnership UK and BHF Clinical Research to discuss patient information documentations and consent.

Engagement: The PPI members and the Patient Researcher will actively contribute to the trial accountability for patient and stakeholder engagement, including advising and ensuring representation and inclusion throughout the trial. They will be involved in developing the patient information leaflets, webinars, other trial research materials (for example, website, videos) and events.

PPI lead: Professor JS will be the overall PPI lead, working closely with SM and the Patient Researcher. JS has extensive experience with managing and coordinating the PPI activities, including patient co-authorship in a recent cardiovascular outcome study with SM. She will have oversight of PPI activities and support the PPI members and Patient Researcher in the PPI plan/strategy. JS will be responsible on all PPI activities, the training of PPI members and Patient researcher, the PPI webinars, and communicating to public the trial status and its results.

23.0 Indemnity/ Insurance

The insurance that Queen Mary University of London has in place provides cover for the design and management of the trial as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm. Clinical trial indemnity cover (NHSBT staff activities) is provided by NHSBT CTU.

24.0 Trial committees

The trial will be Sponsored by Queen Mary University of London. The NHS Blood and Transplant (NHSBT) Clinical Trials Unit (UKCRC registration Nr 57) will be the trial-coordinating centre and the data-coordinating centre.

The CI and the CTU will undertake trial management responsibilities for the trial. The committees for this trial are detailed below.

24.1 Trial Management Group (TMG)

The 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 will be 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.

24.2 Trial Steering Committee (TSC)

The role of the TSC will be 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 continuation of the trial lies with the TSC. The TSC will meet bi-annually and will be chaired by an independent member.

24.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee will consist of 3 members. 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 members will include two independent clinicians with an interest in bleeding, cardiac surgery or transfusion, and one statistician. It is anticipated that the DMC will meet 6 monthly, or more frequently if required. The trial statistician will provide data analyses and reports for the committee, and meetings will be minuted and filed in the TMF maintained at the NHSBT CTU.

25.0 Publication and dissemination policy

25.1 Publication

The main trial findings will be published in a peer-review journal of broad readership, together with presentations at scientific meetings in the fields of cardiac surgery, transfusion and anaesthesia/critical care.

Authorship for any publications arising from this trial will follow the rules set out by the International Committee of Medical Journal Editors definitions of Authorship and Contributorship.

For the main report of this trial submitted for publication, the members of the TSC and DMC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication. Further, the support of the funders and the Sponsor will be acknowledged in all publications/presentations.

The full trial report will be accessible via ISRCTN within one year of the End of the Trial Notification.

25.2 Dissemination policy

Ownership of the data arising from this trial reside with the Sponsor. 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 PROPHESY-2 Trial Management Group.

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. All presentations and publications related to the trial must be authorised by the TMG.

Participants will be able to access the results through the PROPHESY-2 trial website.

No data may be made public before publication and without agreement from the CI and Sponsor.

25.3 Access to the final trial dataset

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.

26.0 Archiving

During the course of the research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research project is complete, it is a requirement of the Sponsor that the records are kept for a further 25 years. Sites will be given instruction at the end of the trial period relating to archiving. All site PIs must be able to access the data for the duration of the archiving period.

Site files from other sites must be archived for 25 years at the external site and will not be stored at the Barts Health Modern Records Centre or within Queen Mary.

Destruction of essential documents will require authorisation from the Sponsor.

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