A pragmatic pilot randomized phase II controlled trial of Prothrombin Complex Concentrates (PCC) versus Fresh Frozen Plasma (FFP) in adult patients who are Undergoing Heart Surgery (PROPHESY)

Laura Green (laura.green@qmul.ac.uk)
Queen Mary University of London https://orcid.org/0000-0003-4063-9768
Neil Roberts
Barts Health NHS Trust
Jackie Cooper
Queen Mary University of London
Jane Field
Queen Mary University of London
Ravi Gill
Southampton Genral Hospital
Andrew Klein
Papworth Hospital, Cambridge
Seema Agarwal
Manchester Royal Infirmary, Manchester
Simom Stanworth
NHS Blood and Transplant, Oxford
Atholl Johnston
Queen Mary University of London
Vivienne Monk
Queen Mary University of London
Ben O'Brien
Barts NHS Trust

Study protocol

Keywords: Cardiac Surgery, bleeding, Fresh Frozen Plasma, Prothrombin Complex Concentrate, randomized control trial, pilot study

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Abstract

Background Fresh Frozen Plasma (FFP) is the accepted standard treatment for clotting factor replacement in bleeding patients during, or immediately after cardiac surgery. In the United Kingdom (UK) prothrombin complex concentrate (PCC) is not licensed in this setting although it is being used in Europe, because it has a higher concentration of clotting factor levels, and it can be administered rapidly and in small volume, resulting in less volume overload during cardiac surgery. Methods PROPHESY is a pragmatic single-centre, open-label, randomized, controlled pilot trial that will assess whether it is feasible to perform a large trial in the future that will compare PCC versus FFP in patients who are bleeding (not on warfarin) and who require blood transfusion. Over a 15-month period, 50 patients will be randomized to PCC versus FFP if they develop active bleeding within 24 hours of cardiac surgery, and for whom the clinician has decided to administer FFP for treatment of bleeding. Standard laboratory and Point-of-Care assessments will be performed as per routine practice, and additional research blood samples will be taken at three time-points to assess haemostasis. Subjects will be assessed daily up to hospital discharge or 30 days or death (whichever occurs first) and will be followed up for 90 days after surgery to assess for thromboembolic complications, and hospital re-admission since discharge. Quality of life assessment will be performed pre-surgery and at 90 days. We will also perform qualitative research with clinical experts and patients to explore the understanding and experience with the interventions, and adherence to study procedures and protocol. Discussion There have been no randomized control trials that have compared the safety and efficacy of FFP versus PCC in cardiac surgery in patients who are bleeding. This pilot study will assess if individual components of a large trial are deliverable to assess the safety and efficacy of the two blood products in the future.

Background

Approximately 30,000 cardiac procedures are performed each year in the UK, and it is estimated that approximately 10% of all blood supplied by the national blood service is used during these procedures. Bleeding after cardiac surgery that requires blood transfusion is associated with significant morbidity and mortality, resulting in substantial costs to healthcare systems [1]. The national comparative audit in the UK in 2011, which incorporated data from 66% of all UK cardiac centres, showed that the overall blood transfusion rate was high across all procedures, with Fresh Frozen Plasma (FFP) being administered in over 20% of patients undergoing valve replacement or repair surgeries, and 30% of patients undergoing combined Coronary Artery Bypass Grafts (CABG) + valve repair/replacement surgeries [2].

FFP is the accepted standard treatment for replacement of clotting factors in bleeding patients undergoing cardiac surgery, yet in a recent Cochrane review only one study, out of 14 trials (n=738 participants) identified, has evaluated the FFP efficacy in bleeding patients, and this was underpowered to determine outcomes in mortality [3]. Taking into consideration that blood transfusion is not without risks, other haemostatic agents, such as Prothrombin Complex Concentrate (PCC) are being explored by clinicians for management of bleeding, including in the perioperative phase for patients undergoing cardiac surgery.

Potential advantages of PCC over FFP include increased concentration of clotting factors leading to faster and more sustained reversal of coagulopathy; improved ease and speed of administration; reduced fluid volume (20 – 40mL compared to up to 1000mL with FFP); and reduced incidence of immune modulatory side effects.

However, to date there have been no randomized controlled trials (RCT) that have compared the clinical efficacy and safety of PCC versus FFP in bleeding cardiac surgery patients, who are not taking vitamin K antagonists (like warfarin), and this was highlighted in a recent systematic review [4]. Several observational studies have demonstrated that PCC is safe in this setting, and that its administration is associated with reduced blood transfusion requirements, albeit with no difference in other outcomes [5, 6]. However, clinical equipoise and the lack of high-quality evidence means that an RCT is required to determine how PCC compares with FFP. Prior to such a trial, a pilot study is required to determine if a large scale randomized controlled trial is possible and this is the hypothesis of this single centre RCT.

Full Text

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Dr Laura Green, Blizard Institute, Queen Mary University of London, NHS Blood and Transplant and Barts Health NHS Trust. 4 Newark St, Whitechapel, London E1 2AT laura.green@qmul.ac.uk

Mr Neil Roberts,* St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE. neil.roberts@bartshealth.nhs.uk

Jackie Cooper, Barts Cardiovascular Clinical Trials Unit (CVCTU), William Harvey Research Institute, Heart Centre, Barts and The London School of Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ Jackie.cooper@qmul.ac.uk

Jane Field, Barts Cardiovascular Clinical Trials Unit (CVCTU), William Harvey Research Institute, Heart Centre, Barts and The London School of Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ jane.field@qmul.ac.uk

Dr Ravi Gill, Southampton General Hospital, Tremona Road, SO16 6YD ravi@gill-taylor.com

Dr Andrew Klein, Papworth Hospitals NHS Foundation Trust, Papworth Everard, Cambridge, CB23 3RE andrew.klein@nhs.net

Dr Seema Agarwal, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL seema.agarwal@nhs.net

Professor Simon Stanworth, Oxford University Hospitals NHS Foundation Trust, Headley Way, Oxford, OX3 9BQ. Simon.stanworth@nhsbt.nhs.uk

Professor Atholl Johnston, William Harvey Research Institute, Heart Centre, Barts and The London School of Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ. a.johnston@qmul.ac.uk

Dr Vivienne Monk, Barts Cardiovascular Clinical Trials Unit (CVCTU), William Harvey Research Institute, Heart Centre, Barts and The London School of Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ v.monk@qmul.ac.uk

Professor Ben O'Brien, St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE

Outcomes Research Consortium, Cleveland Clinic, OH, USA. ben.obrien@bartshealth.nhs.uk

*Joint first author

Corresponding Author – Dr Laura Green laura.green@qmul.ac.uk

Abstract

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Methods: PROPHESY is a pragmatic single-centre, open-label, randomized, controlled pilot trial that will assess whether it is feasible to perform a large trial in the future that will compare PCC versus FFP in patients who are bleeding (not on warfarin) and who require blood transfusion. Over a 15-month period, 50 patients will be randomized to PCC versus FFP if they develop active bleeding within 24 hours of cardiac surgery, and for whom the clinician has decided to administer FFP for treatment of bleeding. Standard laboratory and Point-of-Care assessments will be performed as per routine practice, and additional research blood samples will be taken at three time-points to assess haemostasis. Subjects will be assessed daily up to hospital discharge or 30 days or death (whichever occurs first) and will be followed up for 90 days after surgery to assess for thromboembolic complications, and hospital re-admission since discharge. Quality of life assessment will be performed pre-surgery and at 90 days. We will also perform qualitative research with clinical experts and patients to explore the understanding and experience with the interventions, and adherence to study procedures and protocol.

Discussion: There have been no randomized control trials that have compared the safety and efficacy of FFP versus PCC in cardiac surgery in patients who are bleeding. This pilot study will assess if individual

components of a large trial are deliverable to assess the safety and efficacy of the two blood products in the future.

Trial Registration: PROPHESY has been registered on the EudraCT database (2018-003041-41) and with Clinicaltrials.gov (NCT03715348) on 29 July 2018.

Keywords

Cardiac Surgery, bleeding, Fresh Frozen Plasma, Prothrombin Complex Concentrate, randomized control trial, pilot study

Background

Approximately 30,000 cardiac procedures are performed each year in the UK, and it is estimated that approximately 10% of all blood supplied by the national blood service is used during these procedures. Bleeding after cardiac surgery that requires blood transfusion is associated with significant morbidity and mortality, resulting in substantial costs to healthcare systems [1]. The national comparative audit in the UK in 2011, which incorporated data from 66% of all UK cardiac centres, showed that the overall blood transfusion rate was high across all procedures, with Fresh Frozen Plasma (FFP) being administered in over 20% of patients undergoing valve replacement or repair surgeries, and 30% of patients undergoing combined Coronary Artery Bypass Grafts (CABG) + valve repair/replacement surgeries [2].

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However, to date there have been no randomized controlled trials (RCT) that have compared the clinical efficacy and safety of PCC versus FFP in bleeding cardiac surgery patients, who are not taking vitamin K antagonists (like warfarin), and this was highlighted in a recent systematic review [4]. Several observational studies have demonstrated that PCC is safe in this setting, and that its administration is associated with reduced blood transfusion requirements, albeit with no difference in other outcomes [5, 6]. However, clinical equipoise and the lack of high-quality evidence means that an RCT is required to

determine how PCC compares with FFP. Prior to such a trial, a pilot study is required to determine if a large scale randomized controlled trial is possible and this is the hypothesis of this single centre RCT.

Methods

Study design

The study design is a single centre (at Barts Health NHS Trust), open label, non-blinded, pragmatic, pilot randomized control trial (see Figure 1 for study flow chart).

Figure 1: Study Flowchart

Aim and Objectives

To determine if it is feasible to deliver a large trial in the future that will compare FFP versus PCC in cardiac surgery patients who are bleeding within 24 hours of surgery.

Primary objective

Evaluate the recruitment rate, defined as the proportion of subjects who consent to the study (out of all those eligible), and receive the intervention.

Secondary objectives

Assess the delivery of different components of the trial, assess protocol compliance and violation, and the ability to collect outcome data.

Compare the impact of FFP and PCC on the haemostatic capacity of bleeding patients, through the use of standard clotting tests and other global clotting tests,

Obtain input from patients, members of the public and healthcare professionals on the design/running of the large trial, as well as identify the most important primary/secondary outcomes for the larger trial.

Primary Outcome:

The proportion of participants who receive intervention within 24 hours of surgery, out of all eligible participants.

Secondary Endpoint

Time to administration of study drug (PCC) or control (FFP) to patient - defined as time in minutes from telephoning laboratory to first administration to patient.

Proportion of patients for whom clinical outcome data were collected up to 90 days, or death, whichever occur first

Proportion of patients who consent and randomised within 24 hours of surgery

Proportion of patients who consent and are not randomised within 24 hours of surgery

Proportion of patients for whom timing of administration, and completion of intervention(s) were documented

Proportion of patients where there was protocol adherence, and protocol violation

Proportion of patients who do not consent to intervention, but agree to consenting of their de-identified data for up to 24 hours after surgery

Obtain data on event rates in both groups to help estimate the sample size for the large trial

Study population

A total of 50 patients will be randomized over a 15-month period, with a follow-up at 90 days or death, whichever occurs first. Consent will be obtained from all patients prior to participation in the trial.

Inclusion criteria: Adult patients (>18years), Able to give consent, Undergoing elective or non-elective cardiac surgery, excluding procedures given under exclusion criteria,

Exclusion criteria: Unable to consent, Patients refusing blood transfusion for any reason, First time isolated coronary artery bypass grafts, First time isolated aortic valve replacement (excluding active endocarditis), Thoraco-abdominal surgeries, Minor surgeries that do not involve cardiopulmonary bypass, use of warfarin within four days, use of direct oral anticoagulants (i.e. dabigaran, rivaroxban, apixaban or edoxaban) within 48 hrs or 72 hours depending on estimated glomerular filtration rate, inherited bleeding disorder, pregnancy, known or suspected allergy to FFP, LG-Octaplas or PCC, known or suspected allergy to heparin, Sodium citrate dihydrate, sodium dihydrogenphosphate dihydrate and Glycine, history of Heparin-induced thrombocytopenia, IgA deficiency with known antibodies against IgA, documented venous thromboembolism in the last three months, documented antiphospholipid syndrome, severe protein S deficiency, participation in another clinical trial, where the patient has received Investigational Medicinal Product (IMP) in the last 3 months

For women of childbearing age (<50 years old) a urine pregnancy test will be performed for eligibility purposes. There will be no other study specific screening procedures.

To determine the bleeding rate, routine clinical data will also be collected for up to 24 hours on: a) eligible participants who have consented to take part in the study, but are not randomized because they did not develop bleeding; and b) eligible participants who have not consented to take part in the main study, but have consented to the collection of de-identified routine data.

Randomization process

The pragmatic nature means that the decision on whether to administer intervention will be based on clinicians' judgement, so that when a patient is actively bleeding within 24 hours of surgery and a clinician has decided that FFP is needed to treat the bleeding, the patient will be randomized by the transfusion laboratory to either a single dose of FFP (Fresh Frozen plasma or LG-Octaplas) or 4-factor PCC (Octaplex) using a web-based electronic database. In the UK it is recommended that individuals born after 1st of January 1996 should be transfused non-UK plasma, as a variant CJD risk reduction measure and this has been the practice since 1999 [7]. At the study site, LG-Octaplas is the standard of care for management of such patients who are bleeding. Doses of intervention will be calculated according to subject weight, and as per the dosing schedules below:

Subject Weight

FFP or LG-Octaplas

< 60 kg

3 units

61 – 90 kg

4 units

> 90 kg

5 units

Subject Weight

Octaplex (IU)

< 60 kg

500 (1 vial)

61 – 90 kg

1000 (2 vials)

> 90 kg

1,500 (3 vials)

If the subject continues to bleed after this first single dose of study treatment, standard care for the treatment of bleeding will continue as per hospital protocol, and this may include having additional FFP. However, no further PCC will be administered to subjects.

Study assessments

Subjects will have laboratory assessments with standard routine care tests and thromboelastography (TEG). Research blood samples will also be taken at 3 time points (pre-intervention, 1 hour and 24 hours post intervention) to perform a more detailed analysis of haemostatic capacity of subjects (see table 1 under Appendix).

Clinical data that will be collected include: age, gender, ethnicity, previous medical history, drug history, type of surgery, date/time of intervention. For those who have received intervention, daily and weekly (24 hrs, 7, 14, 21, 30 days, or on discharge, or death – whichever is first) assessments will be performed for: Amount of blood lost through the chest drains, blood components transfused (RBC, RBC, FFP, Platelets and cryoprecipitate), any other haemostatic agents administered (such as recombinant Factor VIIa, fibrinogen concentrate), total days in Intensive Care Unit (level 3); High Dependency Units (Level 2), any organ failure (e.g. acute lung injury, acute respiratory distress syndrome renal failure, liver failure etc.), thrombosis (arterial and venous thrombosis), acute transfusion reaction, Infections, duration of organ support (i.e. ventilatory support, cardiovascular support, and renal replacement therapy) and mortality. At 90 days, or death – whichever is first the following data will be collected: mortality, re-hospitalization, thromboembolic event (arterial and venous), number of days alive and out of hospital since operation and QOL questionnaire.

Statistics

Sample size calculation

Over a 15-month period, we expect 638 patients to be eligible – this would allow us to estimate a consent rate of 30% within a 95% confidence interval of +/- 3.5%. Assuming that 30% of the eligible patients consent, we will have a sample of 191 patients on which to estimate the proportion of consented patients who bleed and are administered FFP/PCC. From the national and local cardiac audit data, the rate of FFP transfusion in the eligible study patients is just over 30%, so we have estimated that 30% of consented patients will go on to develop bleeding during surgery that requires FFP transfusion. A sample size of 191 would allow us to estimate a proportion of 30% within a 95% confidence interval of +/- 6.5%. Based on the above 30% rate, around 57 patients would be randomized within 15 months giving an expected final sample size of 50 patients completing the study after allowing for 10% drop out or loss to follow up. This sample would be analyzed for assessment of the secondary endpoints. No formal interim analysis for efficacy is planned. Numbers recruited, eligibility and consent rates will be considered by the Data Safety Monitoring Committee (DSMC). Safety analysis including reporting of adverse events will be undertaken biannually for review by the DSMC. Other interim analysis may be undertaken at the request of the DSMC. Tables will be prepared by the study statistician.

The primary analysis will use data from the eligible patient population (for consent rate estimation) and the consenting patients (for estimation of the percentage who are randomized and receive study treatment). The proportion of patients who agree to collection of their de-identified data for up to 24 hours

after surgery will be obtained analyzing the population of eligible patients who do not consent to enter the main trial. The intention-to-treat population will be used to analyze secondary endpoints relating to the delivery of the intervention, clinical outcome data and hemostatic capacity of patients. Full details of the statistical considerations are given in the study Statistical Analysis Plan.

Discussion

There has been no randomized controlled trial (RCT) that has compared the clinical efficacy and safety of PCC versus FFP in patients undergoing cardiac surgery, who are bleeding and have not been on a vitamin K antagonist in the perioperative phase. Observational studies have suggested that PCC is safe in this setting: however, clinical equipoise and the lack of high-quality evidence mean that a large RCT is required to determine how PCC compares with FFP. Prior to such a trial, it is important that feasibility of recruitment, as well as different aspects of delivering the large trial are assessed, and this is the aim of this pragmatic, pilot randomized control trial.

The pragmatic nature means that the decision on whether to administer intervention will be based on 'real-world' practice, rather than a specific algorithm. One reason for choosing this approach is because it is vital that the results produced from the study are applicable to everyday practice in the future. Further, a recent RCT phase III trial in a cardiac surgery setting that compared fibrinogen concentrate with placebo, highlighted some of the challenges with trials using complex algorithms to administer intervention [8]. Difficulties in implementing such algorithms during trials can result in a number of shortcomings such as low proportion of patients being actually randomized, high rate of non-adherence to the study protocol, high proportion of patients being given intervention when they did not fulfill the study criteria, and consequently greater costs incurred.

Furthermore, the pragmatic nature of the trial reflects real world current practice and does not add pre-intervention tests that could delay the issuing of FFP or PCC in a clinical scenario that requires rapid action. The pilot study will collect pre-intervention clotting profile data, but this will not be used as entry criteria to allow intervention to take place. There is no current bedside test with 100% sensitivity and specificity to identify the need for blood products after cardiac surgery, and as such the trial reflects real world practice and current clinical judgement. There is no set limit for the amount of blood loss to define bleeding, as although this is possible with a closed chest and chest drains on an intensive care unit, this is not possible to define in the operating room before chest closure when swabs and suction are being used.

Another important aspect of this pilot trial are the surveys with different experts across disciplines (cardiac surgeons, anaesthetists, intensivists, transfusion laboratory scientists etc.) and patient and public groups to reach a consensus on the outcome measures for the large trial. In 2015 Benstoem and colleagues [9] performed a systematic review of the literature to identify the main outcomes that have been measured in cardiac surgery intervention trials in adult – in this review a total of 121 outcomes identified, which were collapsed into 36 outcome domains. Using the results of the above review, in 2017 Bentoem and colleagues [10] performed an international three-round eDelphi exercise to reach a consensus on core

outcomes sets that should be measured and reported, as a *minimum*, in clinical trials of cardiac surgery trials. Of the 36 outcome variables identified from the systematic review, the panel reached consensus on four core outcome sets which were: mortality, Quality of Life, hospitalization, and cerebrovascular complications. Currently in the UK there a national database that collects clinical outcomes for patients who have undergone cardiac surgery, and of the four core outcome sets agreed in the Delphi consensus [10], Quality of Life is the only outcome that is not collected by the national database, and of the 36 outcome variables identified from the systematic review [9] a total of seven variables are collected in the UK. In order to obtain patient and public opinion about the outcome measures for the large trial, we will conduct surveys with patients and UK healthcare professionals, using the results of the above Delphi survey and the outcomes measured by the national database. Further, we will also conduct interviews with patients and clinicians who have been involved with the study to explore understanding of, and experience with, the intervention delivered, get their input on how best to optimize recruitment of participants, and how to improve adherence of the trial protocols. All these will allow for a more cost-effective and informative trial in the future.

Trial status

Protocol V2.0, 27 November 2018. Start date of subject recruitment: 01 March 2019. Project recruitment completion date: 30 June 2020

The study was peer-reviewed by three independent experts as part of the BHF funding application and underwent Barts Heart Centre independent Peer review. The study protocol has been reviewed by the Barts Cardiovascular Clinical Trials Unit (CVCTU) Scientific committee and the Blizard Institute, MHRA and NHS Research Ethics Committees.

The Barts Cardiovascular Clinical Trials Unit (CVCTU) will oversee the management and conduct of the trial, and will be responsible for Pharmacovigilance and safety reporting, coordination of trial committees, statistical analysis and reporting, and database management and CRF design. The study Sponsor will be responsible for trial monitoring. When the research trial is complete, it is a sponsor requirement that the records are kept for a further 20 years in a secure, long-term storage facility as per the Sponsor policy.

Data will be captured in REDCap, a web-based electronic database, for all study participants and the database will be held on a secure server at Queen Mary University of London (QMUL). Participants eligible for the study will be given a screening number, and this number will be used to identify them throughout their study duration. The screening number will be identified on all electronic Case Report Forms (eCRFs) and study documentation, e.g. questionnaires, lab reports, enrollment and dispensing logs. Only authorized users approved by the Chief Investigator (CI) will have access to the REDCap electronic database, and each user will be assigned specific user roles and rights. Sponsor representatives and CVCTU team members will have read-only access to the data. The study Research Nurse will be the primary person with delegated responsibility for data entry and CRF completion. The transfusion laboratory team will have access to the

eCRF to complete randomization. The CI will have overall responsibility for data captured in the eCRF and be able to review, lock and electronically sign the completed eCRFs.

List of abbreviations

ACT Activated Clotting Time

APTT Activated Partial Thromboplastin Time

CABG Coronary Artery Bypass Graft

CI Chief Investigator

CRF Case Report Form

CTIMP Clinical Trial of Investigational Medicinal Product

CVCTU Cardiovascular Clinical Trials Unit

DSMC Data Safety Monitoring Committee

EudraCT European Clinical Trials Database

FBC Full Blood Count

FFP Fresh Frozen Plasma

GCP Good Clinical Practice

IMP Investigational Medicinal Product

ICU Intensive Care Unit

MHRA Medicines and Healthcare products Regulatory Agency

NHSBT National Health Service Blood and Transplant

PCC Prothrombin Complex Concentrates

PI Principal Investigator

PT Prothrombin time

QOL Quality of Life

QMUL Queen Mary University of London

RCT Randomized Control Trial

RBC Red Blood Cells

REC Research Ethics Committee

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SOP Standard Operating Procedure

TEG Thromboelastography

TSC Trial Steering Committee

Declarations

Ethics approval and consent to participate

The trial was granted clinical trials authorization by the Medicines and Healthcare products Regulatory Authority (MHRA), and has received NHS Research Ethics approval from the London-Fulham REC (18/LO/1726) and Health Research Authority approval (IRAS Nr. *250632)*. All subjects participating in the trial will provide written informed consent.

Consent for publication

All relevant data from this study will be submitted to peer review journals for publication following the termination of the study in line with sponsor trust publication policy. Data will be captured for all study participants, and no patient identifiable data will be used in any publications. The sponsor retains the right to review all publications prior to submission or publication. Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator.

Availability of data and material

The datasets used and/or analyzed during the current study will be available from the Chief Investigator on reasonable request. All data generated or analyzed during this study will be included in future publications.

Competing interests

. The authors declare that they do not have any competing interests, apart from SA who has previously completed consultancy work for Octapharma. Financial and competing interests information will be collected and documented over the duration of the study.

Funding

The study is funded by the British Heart Foundation (BHF). The funder has reviewed the funding application, and will have oversight of study progress, but has no role in the collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

LG, NR and BO wrote the manuscript. All authors contributed to the design of the study and writing of the final manuscript.

Acknowledgements

We acknowledgement the support of the Joint Research Management Office, Queen Mary University of London as sponsor for the study. The sponsor's contacts are as follow: Joint Research Management Office, 5 Walden Street, London, E1 2EF. Email: research.governance@qmul.ac.uk

The trial is managed and run by Barts Cardiovascular Clinical Trials Unit (CVCTU) at William Harvey Research Institute, QMUL, a UKCRN registered unit (4). The Barts CVCTU will be responsible for Pharmacovigilance and safety reporting, coordination of trial committees, statistical analysis and reporting, and database management and case report form design. The study Sponsor (QMUL) will be responsible for trial monitoring. When the research trial is complete, it is a sponsor requirement that the records are kept for a further 20 years in a secure, long-term storage facility as per the Sponsor policy.

Trial committees have been established to oversee and monitor the trial conduct and patient safety.

The Trial Steering Committee (TSC) is chaired by an independent cardiac surgeon (Mr Justin Nowell, St. Georges Hospital), with 3 other independent members (Dr Nick Fletcher, Consultant Anaesthetist, St. Georges Hospital, UK; Dr Nicola Curry, Consultant Haematologist, Oxford University Hospital NHS Trust, UK; and Mr Steve Stevenson, Lay representative). The TSC provides overall supervision of the trial, and ensures that it is being conducted according to the protocol, good clinical practice and relevant regulations. This committee also monitors trial progress in relation to recruitment, data capture and completeness, protocol deviations and subject withdrawals. Committee meet every 6 months.

The Data Safety Monitoring Committee (DSMC), is chaired by an independent haematologist (Prof Mike Laffan, Imperial College London, UK), with an independent anesthetist (Dr Paul Diprose, University of Southampton, UK) and statistician (Dr Phil Edwards, London School of Hygiene and Tropical Medicine, UK). The DSMC is responsible for reviewing the trial data throughout the study and assessing whether there are any safety issues that need to be brought to the attention of the TSC, or any ethical reasons, why the trial should not continue.

Study data is collected and managed using REDCap (research electronic data capture) tools [11] hosted at Barts Cancer Centre, QMUL. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data

entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [11].

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Appendix

Table1.Assessments for Randomised subjects

Study Procedure

Screening

Pre-op

Prior to surgery (time 0)

Prior to randomisation – Intervention

One hour post study intervention

24hr post surgery

Day 7, 14, 21

Day 30 (discharge/death)

Day 90 (discharge/ death)

Visit Windows

-14 days

Day 0

Day 0

Day 0

Day 1

+/- 1 days

+/- 2 days

+/- 7 days

Screening - Assess eligibility (includes urine pregnancy test)

X

Informed consent

X

Patient Characteristics

X

Assessment by surgical team

X

Assessment by Anaesthesiologist

X

Bloods [1] – FBC

X

X

X

X

Bloods[1] - group and screen samples

X

X

Bloods[1] – Liver and renal function tests

X

X

Routine coagulation tests (PT, APTT and fibrinogen) [1]

X

X

X

X

Additional clotting assays[2]

X

X

X

Thromboelastography (TEG) assessment[1]

X

X

X

Inform transfusion laboratory of need for FFP

X

Randomisation & Intervention – PCC or LG-Octaplas/FFP

X

Time of Intervention (start & stop)

X

Weekly ITU assessment

X

X

Thromboembolic AE/SAE

X

X

X

X

X

Transfusion AE/SAE

X

X

X

X

Hospital re-admission since discharge

X

Quality of Life – EQ5D

X

X

90 day survival status - End of study form (telephone or clinic visit)

X

FBC; full blood count; PT: prothrombin time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; ITU: intensive care unit; AE: adverse events; SAE: serious adverse events

Methods

Study design

The study design is a single centre (at Barts Health NHS Trust), open label, non-blinded, pragmatic, pilot randomized control trial (see Figure 1 for study flow chart).

Aim and Objectives

To determine if it is feasible to deliver a large trial in the future that will compare FFP versus PCC in cardiac surgery patients who are bleeding within 24 hours of surgery.

Primary objective

Evaluate the recruitment rate, defined as the proportion of subjects who consent to the study (out of all those eligible), and receive the intervention.

Secondary objectives

1. Assess the delivery of different components of the trial, assess protocol compliance and violation, and the ability to collect outcome data.
2. Compare the impact of FFP and PCC on the haemostatic capacity of bleeding patients, through the use of standard clotting tests and other global clotting tests,
3. Obtain input from patients, members of the public and healthcare professionals on the design/running of the large trial, as well as identify the most important primary/secondary outcomes for the larger trial.

Primary Outcome:

The proportion of participants who receive intervention within 24 hours of surgery, out of all eligible participants.

Secondary Endpoint

Time to administration of study drug (PCC) or control (FFP) to patient - defined as time in minutes from telephoning laboratory to first administration to patient.

Proportion of patients for whom clinical outcome data were collected up to 90 days, or death, whichever occur first

Proportion of patients who consent and randomised within 24 hours of surgery

Proportion of patients who consent and are not randomised within 24 hours of surgery

Proportion of patients for whom timing of administration, and completion of intervention(s) were documented

Proportion of patients where there was protocol adherence, and protocol violation

Proportion of patients who do not consent to intervention, but agree to consenting of their de-identified data for up to 24 hours after surgery

Obtain data on event rates in both groups to help estimate the sample size for the large trial

Study population

A total of 50 patients will be randomized over a 15-month period, with a follow-up at 90 days or death, whichever occurs first. Consent will be obtained from all patients prior to participation in the trial.

Inclusion criteria: Adult patients (>18years), Able to give consent, Undergoing elective or non-elective cardiac surgery, excluding procedures given under exclusion criteria,

Exclusion criteria: Unable to consent, Patients refusing blood transfusion for any reason, First time isolated coronary artery bypass grafts, First time isolated aortic valve replacement (excluding active endocarditis), Thoraco-abdominal surgeries, Minor surgeries that do not involve cardiopulmonary bypass, use of warfarin within four days, use of direct oral anticoagulants (i.e. dabigaran, rivaroxban, apixaban or edoxaban) within 48 hrs or 72 hours depending on estimated glomerular filtration rate, inherited bleeding disorder, pregnancy, known or suspected allergy to FFP, LG-Octaplas or PCC, known or suspected allergy to heparin, Sodium citrate dihydrate, sodium dihydrogenphosphate dihydrate and Glycine, history of Heparin-induced thrombocytopenia, IgA deficiency with known antibodies against IgA, documented venous thromboembolism in the last three months, documented antiphospholipid syndrome, severe protein S deficiency, participation in another clinical trial, where the patient has received Investigational Medicinal Product (IMP) in the last 3 months

For women of childbearing age (<50 years old) a urine pregnancy test will be performed for eligibility purposes. There will be no other study specific screening procedures.

To determine the bleeding rate, routine clinical data will also be collected for up to 24 hours on: a) eligible participants who have consented to take part in the study, but are not randomized because they did not develop bleeding; and b) eligible participants who have not consented to take part in the main study, but have consented to the collection of de-identified routine data.

Randomization process

The pragmatic nature means that the decision on whether to administer intervention will be based on clinicians' judgement, so that when a patient is actively bleeding within 24 hours of surgery and a clinician has decided that FFP is needed to treat the bleeding, the patient will be randomized by the transfusion laboratory to either a single dose of FFP (Fresh Frozen plasma or LG-Octaplas) or 4-factor PCC (Octaplex) using a web-based electronic database. In the UK it is recommended that individuals born after 1st of January 1996 should be transfused non-UK plasma, as a variant CJD risk reduction measure and this has been the practice since 1999 [7]. At the study site, LG-Octaplas is the standard of care for management of such patients who are bleeding. Doses of intervention will be calculated according to subject weight, and as per the dosing schedules below:

Subject Weight	FFP or LG-Octaplas
≤ 60 kg	3 units
61 – 90 kg	4 units
> 90 kg	5 units

Subject Weight	Octaplex (IU)
≤ 60 kg	500 (1 vial)
61 – 90 kg	1000 (2 vials)
> 90 kg	1,500 (3 vials)

If the subject continues to bleed after this first single dose of study treatment, standard care for the treatment of bleeding will continue as per hospital protocol, and this may include having additional FFP. However, no further PCC will be administered to subjects.

Study assessments

Subjects will have laboratory assessments with standard routine care tests and thromboelastography (TEG). Research blood samples will also be taken at 3 time points (pre-intervention, 1 hour and 24 hours post intervention) to perform a more detailed analysis of haemostatic capacity of subjects (see table 1 under Appendix).

Clinical data that will be collected include: age, gender, ethnicity, previous medical history, drug history, type of surgery, date/time of intervention. For those who have received intervention, daily and weekly (24 hrs, 7, 14, 21, 30 days, or on discharge, or death – whichever is first) assessments will be performed for: Amount of blood lost through the chest drains, blood components transfused (RBC, RBC, FFP, Platelets and cryoprecipitate), any other haemostatic agents administered (such as recombinant Factor VIIa, fibrinogen concentrate), total days in Intensive Care Unit (level 3); High Dependency Units (Level 2), any organ failure (e.g. acute lung injury, acute respiratory distress syndrome renal failure, liver failure etc.), thrombosis (arterial and venous thrombosis), acute transfusion reaction, Infections, duration of organ support (i.e. ventilatory support, cardiovascular support, and renal replacement therapy) and mortality. At 90 days, or death – whichever is first the following data will be collected: mortality, re-hospitalization, thromboembolic event (arterial and venous), number of days alive and out of hospital since operation and QOL questionnaire.

Statistics

Sample size calculation

Over a 15-month period, we expect 638 patients to be eligible – this would allow us to estimate a consent rate of 30% within a 95% confidence interval of +/- 3.5%. Assuming that 30% of the eligible patients consent, we will have a sample of 191 patients on which to estimate the proportion of consented patients who bleed and are administered FFP/PCC. From the national and local cardiac audit data, the rate of FFP transfusion in the eligible study patients is just over 30%, so we have estimated that 30% of consented patients will go on to develop bleeding during surgery that requires FFP transfusion. A sample size of 191 would allow us to estimate a proportion of 30% within a 95% confidence interval of +/- 6.5%. Based on the above 30% rate, around 57 patients would be randomized within 15 months giving an expected final sample size of 50 patients completing the study after allowing for 10% drop out or loss to follow up. This sample would be analyzed for assessment of the secondary endpoints. No formal interim analysis for efficacy is planned. Numbers recruited, eligibility and consent rates will be considered by the Data Safety Monitoring Committee (DSMC). Safety analysis including reporting of adverse events will be undertaken biannually for review by the DSMC. Other interim analysis may be undertaken at the request of the DSMC. Tables will be prepared by the study statistician.

The primary analysis will use data from the eligible patient population (for consent rate estimation) and the consenting patients (for estimation of the percentage who are randomized and receive study treatment). The proportion of patients who agree to collection of their de-identified data for up to 24 hours after surgery will be obtained analyzing the population of eligible patients who do not consent to enter the main trial. The intention-to-treat population will be used to analyze secondary endpoints relating to the

delivery of the intervention, clinical outcome data and hemostatic capacity of patients. Full details of the statistical considerations are given in the study Statistical Analysis Plan.

Discussion

There has been no randomized controlled trial (RCT) that has compared the clinical efficacy and safety of PCC versus FFP in patients undergoing cardiac surgery, who are bleeding and have not been on a vitamin K antagonist in the perioperative phase. Observational studies have suggested that PCC is safe in this setting: however, clinical equipoise and the lack of high-quality evidence mean that a large RCT is required to determine how PCC compares with FFP. Prior to such a trial, it is important that feasibility of recruitment, as well as different aspects of delivering the large trial are assessed, and this is the aim of this pragmatic, pilot randomized control trial.

The pragmatic nature means that the decision on whether to administer intervention will be based on 'real-world' practice, rather than a specific algorithm. One reason for choosing this approach is because it is vital that the results produced from the study are applicable to everyday practice in the future. Further, a recent RCT phase III trial in a cardiac surgery setting that compared fibrinogen concentrate with placebo, highlighted some of the challenges with trials using complex algorithms to administer intervention [8]. Difficulties in implementing such algorithms during trials can result in a number of shortcomings such as low proportion of patients being actually randomized, high rate of non-adherence to the study protocol, high proportion of patients being given intervention when they did not fulfill the study criteria, and consequently greater costs incurred.

Furthermore, the pragmatic nature of the trial reflects real world current practice and does not add pre-intervention tests that could delay the issuing of FFP or PCC in a clinical scenario that requires rapid action. The pilot study will collect pre-intervention clotting profile data, but this will not be used as entry criteria to allow intervention to take place. There is no current bedside test with 100% sensitivity and specificity to identify the need for blood products after cardiac surgery, and as such the trial reflects real world practice and current clinical judgement. There is no set limit for the amount of blood loss to define bleeding, as although this is possible with a closed chest and chest drains on an intensive care unit, this is not possible to define in the operating room before chest closure when swabs and suction are being used.

Another important aspect of this pilot trial are the surveys with different experts across disciplines (cardiac surgeons, anaesthetists, intensivists, transfusion laboratory scientists etc.) and patient and public groups to reach a consensus on the outcome measures for the large trial. In 2015 Benstoem and colleagues [9] performed a systematic review of the literature to identify the main outcomes that have been measured in cardiac surgery intervention trials in adult – in this review a total of 121 outcomes identified, which were

collapsed into 36 outcome domains. Using the results of the above review, in 2017 Bentoem and colleagues [10] performed an international three-round eDelphi exercise to reach a consensus on core outcomes sets that should be measured and reported, as a *minimum*, in clinical trials of cardiac surgery trials. Of the 36 outcome variables identified from the systematic review, the panel reached consensus on four core outcome sets which were: mortality, Quality of Life, hospitalization, and cerebrovascular complications. Currently in the UK there a national database that collects clinical outcomes for patients who have undergone cardiac surgery, and of the four core outcome sets agreed in the Delphi consensus [10], Quality of Life is the only outcome that is not collected by the national database, and of the 36 outcome variables identified from the systematic review [9] a total of seven variables are collected in the UK. In order to obtain patient and public opinion about the outcome measures for the large trial, we will conduct surveys with patients and UK healthcare professionals, using the results of the above Delphi survey and the outcomes measured by the national database. Further, we will also conduct interviews with patients and clinicians who have been involved with the study to explore understanding of, and experience with, the intervention delivered, get their input on how best to optimize recruitment of participants, and how to improve adherence of the trial protocols. All these will allow for a more cost-effective and informative trial in the future.

Trial Status

Protocol V2.0, 27 November 2018. Start date of subject recruitment: 01 March 2019. Project recruitment completion date: 30 June 2020

The study was peer-reviewed by three independent experts as part of the BHF funding application and underwent Barts Heart Centre independent Peer review. The study protocol has been reviewed by the Barts Cardiovascular Clinical Trials Unit (CVCTU) Scientific committee and the Blizard Institute, MHRA and NHS Research Ethics Committees.

The Barts Cardiovascular Clinical Trials Unit (CVCTU) will oversee the management and conduct of the trial, and will be responsible for Pharmacovigilance and safety reporting, coordination of trial committees, statistical analysis and reporting, and database management and CRF design. The study Sponsor will be responsible for trial monitoring. When the research trial is complete, it is a sponsor requirement that the records are kept for a further 20 years in a secure, long-term storage facility as per the Sponsor policy.

Data will be captured in REDCap, a web-based electronic database, for all study participants and the database will be held on a secure server at Queen Mary University of London (QMUL). Participants eligible for the study will be given a screening number, and this number will be used to identify them throughout their study duration. The screening number will be identified on all electronic Case Report Forms (eCRFs)

and study documentation, e.g. questionnaires, lab reports, enrollment and dispensing logs. Only authorized users approved by the Chief Investigator (CI) will have access to the REDCap electronic database, and each user will be assigned specific user roles and rights. Sponsor representatives and CVCTU team members will have read-only access to the data. The study Research Nurse will be the primary person with delegated responsibility for data entry and CRF completion. The transfusion laboratory team will have access to the eCRF to complete randomization. The CI will have overall responsibility for data captured in the eCRF and be able to review, lock and electronically sign the completed eCRFs.

Abbreviations

ACT	Activated Clotting Time
APTT	Activated Partial Thromboplastin Time
CABG	Coronary Artery Bypass Graft
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CVCTU	Cardiovascular Clinical Trials Unit
DSMC	Data Safety Monitoring Committee
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ICU	Intensive Care Unit
MHRA	Medicines and Healthcare products Regulatory Agency
NHSBT	National Health Service Blood and Transplant
PCC	Prothrombin Complex Concentrates
PI	Principal Investigator
PT	Prothrombin time

QOL	Quality of Life
QMUL	Queen Mary University of London
RCT	Randomized Control Trial
RBC	Red Blood Cells
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TEG	Thromboelastography
TSC	Trial Steering Committee

Declarations

- Ethics approval and consent to participate

The trial was granted clinical trials authorization by the Medicines and Healthcare products Regulatory Authority (MHRA), and has received NHS Research Ethics approval from the London-Fulham REC (18/LO/1726) and Health Research Authority approval (IRAS Nr. *250632)*. All subjects participating in the trial will provide written informed consent.

- Consent for publication

All relevant data from this study will be submitted to peer review journals for publication following the termination of the study in line with sponsor trust publication policy. Data will be captured for all study participants, and no patient identifiable data will be used in any publications. The sponsor retains the right to review all publications prior to submission or publication. Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator.

- Availability of data and material

The datasets used and/or analyzed during the current study will be available from the Chief Investigator on reasonable request. All data generated or analyzed during this study will be included in future publications.

- Competing interests

. The authors declare that they do not have any competing interests, apart from SA who has previously completed consultancy work for Octapharma. Financial and competing interests information will be collected and documented over the duration of the study.

- Funding

The study is funded by the British Heart Foundation (BHF). The funder has reviewed the funding application, and will have oversight of study progress, but has no role in the collection, analysis, and interpretation of data and in writing the manuscript.

- Authors' contributions

LG, NR and BO wrote the manuscript. All authors contributed to the design of the study and writing of the final manuscript.

- Acknowledgements

We acknowledgement the support of the Joint Research Management Office, Queen Mary University of London as sponsor for the study. The sponsor's contacts are as follow: Joint Research Management Office, 5 Walden Street, London, E1 2EF. Email: research.governance@qmul.ac.uk

The trial is managed and run by Barts Cardiovascular Clinical Trials Unit (CVCTU) at William Harvey Research Institute, QMUL, a UKCRN registered unit (4). The Barts CVCTU will be responsible for Pharmacovigilance and safety reporting, coordination of trial committees, statistical analysis and reporting, and database management and case report form design. The study Sponsor (QMUL) will be responsible for trial monitoring. When the research trial is complete, it is a sponsor requirement that the records are kept for a further 20 years in a secure, long-term storage facility as per the Sponsor policy.

Trial committees have been established to oversee and monitor the trial conduct and patient safety.

The Trial Steering Committee (TSC) is chaired by an independent cardiac surgeon (Mr Justin Nowell, St. Georges Hospital), with 3 other independent members (Dr Nick Fletcher, Consultant Anaesthetist, St.

Georges Hospital, UK; Dr Nicola Curry, Consultant Haematologist, Oxford University Hospital NHS Trust, UK; and Mr Steve Stevenson, Lay representative). The TSC provides overall supervision of the trial, and ensures that it is being conducted according to the protocol, good clinical practice and relevant regulations. This committee also monitors trial progress in relation to recruitment, data capture and completeness, protocol deviations and subject withdrawals. Committee meet every 6 months.

The Data Safety Monitoring Committee (DSMC), is chaired by an independent haematologist (Prof Mike Laffan, Imperial College London, UK), with an independent anesthetist (Dr Paul Diprose, University of Southampton, UK) and statistician (Dr Phil Edwards, London School of Hygiene and Tropical Medicine, UK). The DSMC is responsible for reviewing the trial data throughout the study and assessing whether there are any safety issues that need to be brought to the attention of the TSC, or any ethical reasons, why the trial should not continue.

Study data is collected and managed using REDCap (research electronic data capture) tools [11] hosted at Barts Cancer Centre, QMUL. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [11].

- Authors' information (optional)

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Tables

Table1. Assessments for Randomised subjects

Study Procedure	Screening Pre-op	Prior to surgery (time 0)	Prior to randomisation – Intervention	One hour post study intervention	24hr post surgery	Day 7, 14, 21	Day 30 (discharge/death)	Day 90 (discharge/ death)
Visit Windows	-14 days	Day 0	Day 0	Day 0	Day 1	+/- 1 days	+/- 2 days	+/- 7 days
Screening - Assess eligibility (includes urine pregnancy test)	X							
Informed consent	X							
Patient Characteristics	X							
Assessment by surgical team	X							
Assessment by Anaesthesiologist	X							
Bloods [1] – FBC	X		X	X	X			
Bloods[1] - group and screen samples	X	X						
Bloods[1] – Liver and renal function tests	X				X			
Routine coagulation tests (PT, APTT and fibrinogen) [1]	X		X	X	X			
Additional clotting assays[2]			X	X	X			
Thromboelastography (TEG) assessment[1]			X	X	X			
Inform transfusion laboratory of need for FFP			X					
Randomisation & Intervention – PCC or LG-Octaplas/FFP			X					
Time of Intervention (start & stop)			X					
Weekly ITU assessment					X	X		
Thromboembolic AE/SAE				X	X	X	X	X
Transfusion AE/SAE				X	X	X	X	
Hospital re-admission since discharge								X
Quality of Life – EQ5D	X							X
90 day survival status - End of study form (telephone or clinic visit)								X

FBC; full blood count; PT: prothrombin time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; ITU: intensive care unit; AE: adverse events; SAE: serious adverse events

Figures

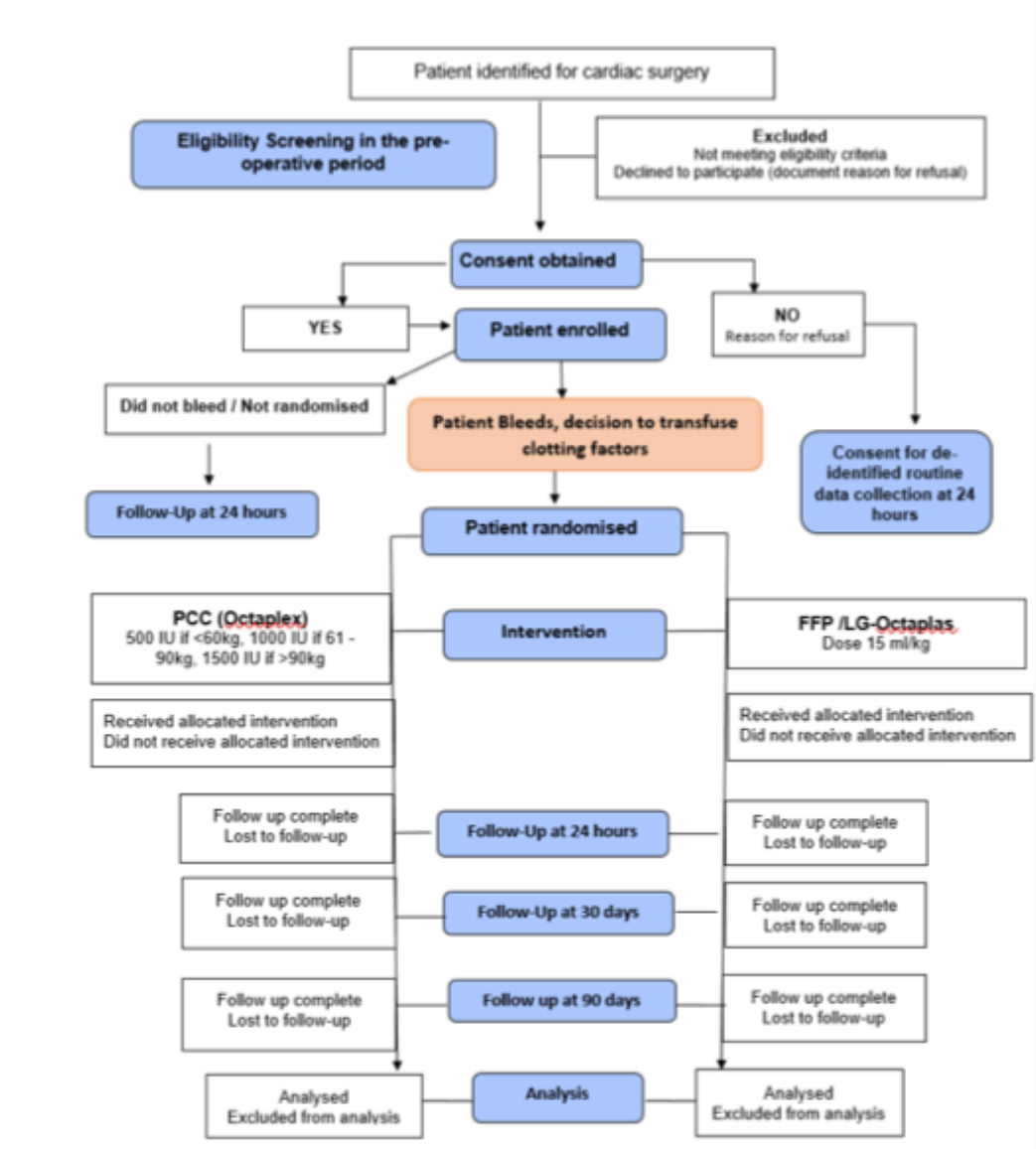

Figure 1

Study Flowchart

Supplementary Files

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