octapharma

STATISTICAL ANALYSIS PLAN
LEX-211

FActor REplacement in Surgery

Four-Factor Prothrombin Complex Concentrate versus Frozen Plasma in Bleeding Adult Cardiac Surgical Patients ("FARES-II" Study)

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The contents of this document were approved by the following (approval date of document is the last signature date)

Name, function and Affiliation	Date and signature
[redacted] ERGOMED plc	_____
[redacted] Octapharma USA, Inc	_____
[redacted] Octapharma AG	_____

Document history

Version	Date	Author	Description
5.0	28-Oct-2024	[redacted]	- Updated definition of PP population to clarify not all major protocol deviations result in exclusion from PP population - Added age group and race as subgroups of interest - Added clarifications to endpoints in section 10.3 - Added AE summaries - Updated transformation of 1 apheresis unit of frozen plasma to allogeneic units
4.0	25-Apr-2023	[redacted]	- Per protocol update, updated secondary endpoint time from IMP initiation to leaving the operating room to time from IMP initiation to arrival at ICU room
3.0	29-Mar-2022	[redacted]	- Addition of inclusion criterion to specify that informed consent will be obtained prior to study enrolment in patients at the US study sites - Detailed description of interim analysis and sample size re-estimation procedures - Description of intercurrent events and estimands
2.0	02-Feb-2022	[redacted]	- Change of test statistics for primary endpoint to ensure maintenance of overall type I error in case that sample size re-estimation results in substantial imbalance between study stages, - Inclusion of details on estimands, - Explicitly adding a section on sensitivity analyses.
1.0	07-Sep-2021	[redacted]	New document

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1. List of Abbreviations

Term	Description
AE	Adverse Event
ABC	Allogenic Blood Component
ACB	Aortocoronary Bypass
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
APE	All Patients Enrolled
aPTT	Activated Partial Thromboplastin Time
ASD	Atrial Septal Defect
BMI	Body Mass Index
BW	Body Weight
CCA	Complete Case Analysis
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clotting Time
DMP	Data Management Plan
DOAC	Direct Oral Anticoagulant
EXTEM	ROTEM Test Assessing the Extrinsic Coagulation Pathway
FAS	Full Analysis Set
FCP	Failed Consent Patients
FIBTEM	Fibrin-Based ROTEM Test Extrinsically Activated with Tissue Factor and Containing the Platelet Inhibitor Cytochalasin D
FP	Frozen Plasma
GLIM	Generalised Linear Interactive Modelling
IABP	Intra-Aortic Balloon Pump
ICU	Intensive Care Unit
ID	Identification
IDSMC	Independent Data and Safety Monitoring Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ITT	Intention-To-Treat
IU	International Units
MACE	Major Adverse Cardiovascular Event

Term	Description
MCF	Maximum Clot Firmness
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of patients/events in a set
n	Number of patients/events contributing to a particular output
PCC	Prothrombin Complex Concentrate
POD	Postoperative Day
PPS	Per-Protocol Set
PT	Prothrombin Time
RBC	Red Blood Cell Concentrate
ROTEM	Rotational Thromboelastometry
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-Related Acute Lung Injury
TEAE	Treatment-Emergent Adverse Event
TEE	Thromboembolic Event
TLF	Tables, Listings, Figures
UDPB	Universal Definition of Perioperative Bleeding

2. Introduction

Cardiac surgery is frequently complicated by coagulopathic bleeding that often leads to excessive blood loss, blood product transfusion and bleeding-related complications [1-4]. Coagulopathy during cardiac surgery is caused by several factors, including the contact of blood with the cardiopulmonary bypass (CBP) circuit, which activates the intrinsic and extrinsic coagulation pathways (despite the use of heparin and heparin-coated circuits), causing excessive clot formation and breakdown. Other contributory factors include haemodilution, hypothermia, blood loss, surgical trauma and use of foreign substances such as aortic grafts causing the consumption of coagulation factors [5-9].

Replacement of coagulation factors is an important aspect of a multimodal approach to coagulopathy to reduce bleeding and transfusion [4, 10]. To replenish depleted coagulation factors and improve thrombin generation, two therapeutics, frozen plasma (FP) and prothrombin complex concentrate (PCC), are available. FP is currently the mainstay of therapy for patients with acquired coagulopathies in North America whereas PCC is the mainstay of therapy in much of Europe [11].

The purpose of the LEX-211 study is to determine whether the PCC, *Octaplex,* is clinically non-inferior to FP with respect to haemostatic effectiveness when used to treat bleeding in cardiac surgical patients requiring coagulation factor replacement. Haemostatic management in bleeding surgical patients is evolving from empirical therapy with non-purified allogeneic blood products to targeted therapy with purified products that have undergone treatment with pathogen reduction

technologies [12]. The proposed study, by comparing two currently available but distinctly different therapies for treating bleeding surgical patients requiring coagulation factor replacement, is well aligned with this change.

Given the potential advantages of PCC over FP, including viral inactivation, ease of administration, standardised dosing/predictable effect and substantially lower risk of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) due to smaller volume, as well as the haemostatic superiority signals detected in observational studies and the recently completed FARES pilot randomised trial [13], a large multicentre trial adequately powered to establish haemostatic superiority or non-inferiority is warranted. The need for such a trial was highlighted in a recent editorial [14], as it will have a profound impact on clinical practice, potentially altering the long-established practice of administering FP for coagulation factor replacement in bleeding patients. If the study is positive, it will lead to the adoption of PCC over FP as first-line therapy for the management of bleeding surgical patients requiring coagulation factor replacement. If it is negative, on the other hand, it will prevent the inappropriate adoption of PCC over FP for this indication. Thus, the study will inform clinical practice and promote the rationale use of healthcare resources.

3. Study Objectives

3.1. Primary Objective

1. To demonstrate that the 4-factor prothrombin complex concentrate (PCC) *Octaplex* is clinically non-inferior to frozen plasma (FP) with respect to haemostatic effectiveness, as measured by the need for post-therapy haemostatic interventions.

3.2. Secondary Objectives

1. To compare global haemostatic response between the *Octaplex* and FP groups, as measured by a composite of the need for post-therapy haemostatic interventions and drop in haemoglobin.
2. To compare the amount of bleeding as measured by the amount of chest tube drainage between the *Octaplex* and FP groups.
3. To compare the incidence of severe to massive bleeding between the *Octaplex* and FP groups.
4. To compare efficacy in terms of the total number of allogeneic blood components transfused between the *Octaplex* and FP groups.
5. To compare efficacy in terms of the incidence and number of individual allogeneic blood components transfused between the *Octaplex* and FP groups.
6. To compare the incidence of use of other coagulation factor products between the *Octaplex* and FP groups.
7. To compare the incidence of other bleeding-related clinical endpoints, i.e., intracerebral haemorrhage, gastrointestinal haemorrhage and surgical re-exploration, between the *Octaplex* and FP groups.
8. To compare the effect of *Octaplex* versus FP administration on the international normalised ratio (INR) between the *Octaplex* and FP groups.
9. To compare the effect of *Octaplex* versus FP administration on other coagulation parameters.

10. To compare time from Investigational Medicinal Product (IMP) initiation to arrival in the ICU between the *Octaplex* and FP groups.
11. To compare safety as measured by serious treatment-emergent adverse events (TEAEs) between the *Octaplex* and FP groups.
12. To compare other secondary safety endpoints including duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalisation, incidence of death and days alive and out of hospital between the *Octaplex* and FP groups.

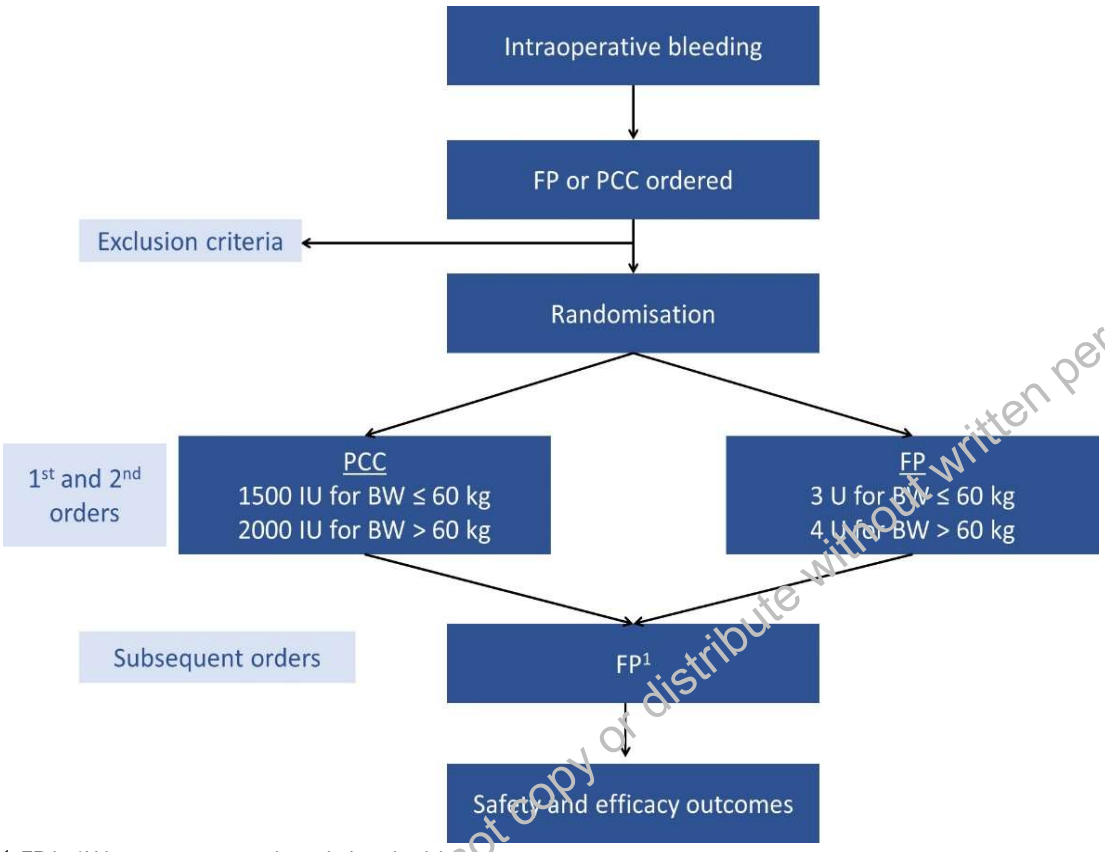
4. Study Design

This is a multicentre, randomised, active-control, prospective, Phase 3 study in adult cardiac surgery patients. Approximately 12 hospitals will participate, and the study will require approximately two years to complete. The study is planned to start in quarter 4, 2022 and to be completed in quarter 4, 2024.

The study will include adult (≥18 years old) patients who undergo cardiac surgery on CPB and require coagulation factor replacement due to bleeding post-CPB and after adequate reversal of heparin with protamine during surgery, and who have a known or suspected coagulation factor deficiency. Patients will be randomised to receive either 4-factor PCC (*Octaplex*) or FP when the blood bank/pharmacy receives the first order for coagulation factor replacement from the operating room and patient eligibility is confirmed. IMP will be administered once treatment indications are met. Patients will be treated according to their assigned group until the maximum dose of IMP is administered during the treatment period, which represents 24 hours after IMP initiation. If additional treatment is required after the maximum dose of IMP is administered or the treatment period has elapsed, patients in both groups will receive FP (**Figure *1***).

Other aspects of coagulation management will be according to a standardised transfusion algorithm. Measurements of INR and haemoglobin will be performed at preestablished time points, if not available already. No other aspects of care will be modified.

Figure 1. Study flow



[1] FP in 1U increments as per the ordering physician

PCC, prothrombin complex concentrate; FP, frozen plasma; BW, body weight; IU, international units

4.1. Inclusion/Exclusion

4.1.1. Inclusion Criteria

Patients meeting the following criteria will be eligible for inclusion in the study:

1. Adult (≥18 years old) patients undergoing any index cardiac surgery employing CPB
2. Coagulation factor replacement with PCC or FP ordered in the operating room for:
    a. Management of bleeding, or
    b. Anticipated bleeding in a patient who has been on-pump for >2 hours or has undergone a complex procedure (e.g., aortocoronary bypass [ACB] plus aortic valve replacement)
3. Coagulation factor deficiency, either known to exist (e.g., as indicated by elevated EXTEM clotting time [CT] or INR) or suspected based on the clinical situation
4. Patients who have given written informed consent[1]

[1] US sites only; in Canada informed consent will be obtained in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans.

4.1.2. Exclusion Criteria

Patients who meet any of the following criteria are *not* eligible for the study:

1. Undergoing heart transplantation, insertion or removal of ventricular assist devices (not including intra-aortic balloon pump [IABP]) or repair of thoracoabdominal aneurysm
2. Critical state immediately before surgery with high probability of death within 24 hours of surgery (e.g., acute aortic dissection, cardiac arrest within 24 hours before surgery)
3. Severe right heart failure (clinical diagnosis ± echocardiography)
4. Known contraindications to heparin
5. PCC required for reversal of warfarin or direct oral anticoagulant (DOAC; dabigatran, rivaroxaban, apixaban or edoxaban) within 3 days prior to or during surgery
6. Known thromboembolic event (TEE) within 3 months prior to surgery
7. History of severe allergic reactions to PCC or FP
8. Individuals who have immunoglobulin A (IgA) deficiency with known antibodies against IgA
9. Refusal of allogeneic blood products
10. Known pregnancy
11. Currently enrolled in any other interventional clinical trials

4.2. Sample Size

The analysis of the primary efficacy endpoint will involve comparison of haemostatic treatment response to IMP, defined as ‘effective’ if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

Patients categorised as having an ‘ineffective’ haemostatic treatment response to IMP, due to requiring administration of any haemostatic intervention in the time window from 60 minutes to 24 hours after initiation of the first IMP dose, will be considered as treatment failures.

Of the more than 100 patients studied in the FARES pilot study, approximately 75% of patients in the PCC group and 65% in the FP group demonstrated haemostatic treatment response from 60 minutes to 24 hours after initiation of the first IMP dose [13]. Using a more conservative estimate of 70% versus 65%, it is estimated that 410 patients will be required to demonstrate non-inferiority with a one-sided α of 0.025, power of ≥90% and non-inferiority margin of 0.10 when using a Farrington-Manning score test.

It is anticipated that up to 20% of randomised patients may not meet administration criteria (based on objective Bleeding Severity Scale and INR) due to cessation of haemorrhage between randomisation and delivery of IMP to the operating room and therefore will not receive the therapy or will withdraw consent.

An administrative interim analysis will be carried out after approximately 50% of the target number of evaluable patients have been randomised and treated (100 patients enrolled in each group) and will be used to re-estimate the sample size or stop for futility (non-binding) (**Section**

7.4). The sample size in the second stage is limited to 210–800 evaluable patients. Accounting for dropouts as described above, the total sample size will range between 513–1250 if the study is not stopped for futility at the interim (see table below).

	Stage 1	**Stage 2 – Minimum**	**Stage 2 – Maximum**	**Total - Maximum**
Evaluable patients	200	210	800	1000
Sample size including 20% dropouts	250	263	1000	1250

4.3. Randomisation

Eligible patients will be randomly assigned to receive either *Octaplex* or FP. Randomisation lists using a permuted-block, randomisation scheme (stratified by site) will be prepared by the biostatistician. Sealed randomisation envelopes based on the randomisation lists will then be provided to the blood banks/pharmacies of the participating centres who will be responsible for providing the IMP.

Patients will be identified using a sequential numbering system within the centre. Randomisation will then be performed in sequential order of the patient IDs.

4.4. Study Assessments

An overview of all assessments during the study is contained in Table 1 of the study protocol. For further details, observations and procedures per visit are described in section 6.1 and study assessments are described in sections 7.1 to 7.3 of the study protocol.

5. Endpoints

5.1. Primary Endpoint

1. Comparison of haemostatic treatment response to *Octaplex* versus FP, defined as 'effective' if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

5.2. Secondary Endpoints

Efficacy endpoints

1. Comparison of global haemostatic response to *Octaplex* versus FP, defined as 'positive' if no additional haemostatic intervention (as per the primary endpoint) is required and haemoglobin levels decrease by <30% (after accounting for red cell transfusions) from 60 minutes to 24 hours after initiation of the first dose of IMP.
2. Comparison of the total amount of chest tube drainage at 12 and 24 hours after chest closure between the *Octaplex* and FP groups.

3. Comparison of the incidence of severe to massive bleeding, using a modification of the universal definition of perioperative bleeding (UDPB) in cardiac surgery and its individual components during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
4. Comparison of the mean number of total allogeneic blood components – including red cells, platelets and all (IMP and non-IMP) FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.
5. Comparison of the mean number of total non-IMP allogeneic blood components – including red cells, platelets and non-IMP FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.
6. Comparison of the mean number of total non-IMP allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after IMP initiation, between the *Octaplex* and FP groups.
7. Comparison of the mean number of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
8. Comparison of the incidence of transfusion of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
9. Comparison of the incidence of administration of non-IMP coagulation factor products – including fibrinogen concentrate and activated recombinant factor VII – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
10. Comparison of the incidence of intracerebral haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
11. Comparison of the incidence of gastrointestinal haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
12. Comparison of the incidence of surgical re-exploration during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
13. Comparison of the change in INR, from within 30 minutes before to within 60 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups; INR reduction will be considered successful if the magnitude of the reduction is >1.0 or the post-treatment level drops below 1.5.
14. Comparison of the changes in other coagulation parameters, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen activity, ROTEM EXTEM CT and maximum clot firmness (MCF) and platelets, from within 75 minutes before to within 75 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups.
15. Comparison of time elapsed from initiation of the first dose of IMP to arrival at the ICU room between the *Octaplex* and FP groups.

Safety endpoints

All adverse events (AEs) and serious AEs (SAEs) will be collected from beginning of surgery (defined as entry into operating room) to postoperative day (POD)-30.

1. Comparison of the incidence of serious treatment-emergent adverse events (TEAEs), individually and as composite where appropriate (e.g., TEEs and major adverse cardiac events [MACE]), between the *Octaplex* and FP groups.
2. Comparison of the duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days) up to POD-30 between the *Octaplex* and FP groups.
3. Comparison of the duration of ICU stay up to POD-30 between the *Octaplex* and FP groups.
4. Comparison of the duration of hospitalisation up to POD-30 between the *Octaplex* and FP groups.
5. Comparison of the incidence of death up to POD-30 between the *Octaplex* and FP groups.
6. Comparison of the number of days alive and out of hospital at POD-30 between the *Octaplex* and FP groups.

6. Analysis Populations

US Study Sites:

At the US study sites, voluntarily given, written informed consent will be obtained from the patient before any study-related procedures are conducted.

Canadian Study Sites:

At the Canadian study sites, informed consent will be obtained from the patient or the patient's legally authorised representative (LAR) as soon as possible after surgery. If neither the patient nor the LAR is reachable for consent during the follow-up period, a family member who is not a LAR is to be provided with an opportunity to object to the patient's participation in the study.

Due to the emergency nature of the condition being studied (i.e., bleeding during surgery) the trial will include only patients who are incapable of providing informed consent at the time the therapy is needed and in whom delays in obtaining surrogate consent can be severely detrimental to their well-being. Thus, this study qualifies for alteration to consent requirement before randomisation, in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans. Patient or LAR consent from all patients, including those untreated, will be obtained at the earliest possible opportunity after surgery.

It is not possible to predict which patients will bleed due to coagulation factor deficiency, and once identified, any delays in therapy will lead to patient harm. The entire process from termination of CPB to administration of the blood products is around 50 minutes. However, the time frame for therapy decision, and consequently for seeking consent from a LAR for the patient to participate in the trial (meaning consent to randomisation and all study procedures thereafter), is even shorter, as it consists of the 5–10 minutes in which coagulation assays are reviewed and a call is placed to the blood bank to order coagulation factors. Even if it were possible to contact a LAR to seek consent during this time, the acuity of the situation would likely be highly stressful to the LAR, which could preclude them from effectively making an informed decision regarding consent. These factors make it essentially impossible to obtain prospective informed consent from a LAR during the surgery.

As a rule, only data from randomised and treated patients with informed consent will be analysed. Consented and randomised but untreated patients will not be included in the efficacy or safety analyses but will be followed for 30 days to determine between-group comparability in baseline characteristics and outcomes.

To ensure that the safety reporting is complete, all haemostatic therapy and SAE data will be collected in cases where consent for remaining in the study cannot be obtained from Canadian sites due to logistical issues (e.g., patient died and a legally authorised representative could not be reached) and REB approval is obtained to collect the information. For Canadian patients who refuse consent, only treatment allocation data will be collected, and patients will not be included in any analyses.

Hence, the disposition of patients will be displayed according to the following analysis populations:

- All Patients population (APP)
  - Patients consented at the US study sites (US APP)
  - Patients randomised at the Canadian study sites (Canadian APP)
- Failed Consent Patients (FCP) population
- Full Analysis Set (FAS) population
- Safety (SAF) population
- Per-Protocol Set (PPS)

A final decision about the classification of protocol deviations and their consequences regarding assignment of patients to analysis populations will be made during the data review meeting prior to the final analyses. All protocol deviations documented during the conduct of the study or identified at the data review process prior to database lock will be reviewed and classified as minor or major and with respect to their significance for the planned analyses. This classification of protocol deviations is the joint responsibility of the clinical project manager, the study statistician, and Octapharma's responsible medical expert, and will be agreed and documented before the database is locked and the statistical analyses are performed.

6.1. All Patients Population (APP)

The AP population will include all patients regardless of the consent status. This population will only be used for displays of patient disposition. This population will also be separated by the country where patients are enrolled, i.e., into the US APP, containing all patients screened and consented at US sites, and the Canadian APP, containing all patients randomised to treatment at the Canadian sites.

6.2. Failed Consent Patients (FCP) Population

The FCP population will consist of all randomised Canadian patients who receive at least one treatment with either PCC or FP for whom consent cannot be obtained (due to logistical reasons and if approved by the REBs). This population will only be used for displays of haemostatic therapy and serious adverse events.

6.3. Full Analysis Set (FAS) Population

The full analysis set (FAS) will be defined according to the intention-to-treat (ITT) principle and will consist of all randomised patients who provide consent and receive any amount of the intervention.

The FAS will serve as the primary analysis set. For patients who withdraw consent, data will be used up until the time consent is withdrawn.

6.4. Safety (SAF) Population

The safety analysis population (SAF) will be identical to the FAS.

For patients who refuse consent only treatment allocation data will be collected and they will not be included in any of the analyses.

6.5. Per-Protocol Set (PPS)

The per-protocol set (PPS) will exclude all patients in the FAS with major deviations that may have an impact on the primary endpoint (e.g., patients who receive an IMP different to the IMP assigned by randomisation; patients who receive <50% of the planned dose; and patients who significantly violate inclusion/exclusion criteria).

6.6. Subgroup Analysis

The following subgroups will be analysed: sex (male/female); age group (<65 years/ ≥65 years), race, urgency (elective/non-elective surgery); and complexity (simple/complex surgery [procedures other than isolated ACB, single valve or repair of Atrial Septal Defect (ASD)]). Moreover, the impact of CPB duration on effectiveness will be evaluated by assessing treatment effect based on CPB duration increments (≤120 minutes, 121-180 minutes, >180 minutes).

6.7. Protocol Deviations

No specific protocol deviations will be considered as this is a randomised, active-control, Phase 3 study.

Classification of protocol deviations as minor and major will be defined a priori. Patients with major protocol deviations that may have an impact on the primary endpoint will be excluded from the per-protocol analyses. The Sponsor and Independent Data and Safety Monitoring Committee (IDSMC) will review the number and nature of major protocol deviations and take appropriate measures to minimise the impact on the study.

A complete listing of protocol deviations (documented as well as derived ones) and the judgement for assessment of patient disposition will be signed before clinical database lock. A description of protocol violations that led to exclusion from any analysis sets will be included in the table part of the Clinical Study Report.

7. Statistical Methods

All statistical analyses will be performed using the SAS® software (Version 9.4 or later).

The analysis of safety will be based on the FAS population.

The primary evaluation of overall efficacy will be performed on the FAS population. In addition, selected efficacy analyses will also be presented for the PPS population.

If not stated otherwise, the following standard descriptive statistics will be presented:

- Descriptive statistics for continuous data

Number (N), mean, standard deviation (SD), min, lower quartile, median, upper quartile and max will be presented. These descriptive statistics will be determined for measured values and optionally for differences to baseline.

- Descriptive statistics for categorical data

Absolute frequencies and percentages will be presented. Percentage bases (denominators) will be identified in the table title or footnote (i.e., all patients at risk, all non-missing cases, all cases). For changes from baseline, shift tables may be generated.

- Exploratory statistics

Although statistical methods are primarily descriptive, two-sided 95% confidence intervals may be presented for selected parameters (e.g., incidences of adverse events) in an exploratory manner.

- Listings

All recorded data will be listed by patient. Identification variable will be the patient ID.

Derived data will be stored in special analysis data sets and will be calculated as outlined in **Appendix 1**.

7.1. Conventions

7.1.1. Baseline definition

Baseline will be defined as the last value on or prior to the first IMP administration.

7.1.2. Missing data

In general, missing data will not be imputed. Due to the nature of the study, important variables are expected to have few missing data. Only for the primary efficacy endpoint in addition to presentation of the primary and secondary endpoints for different analysis sets, multiple imputation methods, may be used to impute missing values.

7.2. IMP exposure, compliance

Dose and frequency of IMP administrations of PCC or FP will be summarised in appropriate tables (summary statistics or frequency tables) for the FAS and PPS populations.

7.2.1. Medical history

Medical history findings will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus in the version current at the time of study start. Coding will be performed by the CRO and agreed upon with the Sponsor before database lock (cf. Data Management Plan [DMP]). The summary tables will display the medical history findings for pre-specified conditions by MedDRA System Organ class (SOC) and Preferred term. Displays will be presented for the FAS and PP populations. Other medical history texts will only be listed.

7.3. Prior and concomitant medication

Medications will be coded using the WHO Drug Global thesaurus in the version current at the time of study start. Coding will be performed by the CRO and agreed upon with the Sponsor before database lock (cf. DMP). For concomitant medications, tables will show the frequencies of patients by WHO preferred term. Prior medication will only be listed.

7.4. Interim Analysis

An administrative unblinded interim analysis will be carried out when approximately 50% of the target number of evaluable patients have been randomised and treated (100 evaluable patients in each treatment group) by an independent statistician. Unblinded information will be communicated only to the IDSMC. Possible outcomes of this analysis are:

- The study may be stopped for futility after an evaluation of the sample size calculation at the interim analysis.

- The sample size will be re-estimated by the independent statistician.

The study cannot be stopped for efficacy at the interim analysis.

The sample size re-estimation will be based on the evaluation of the conditional power, calculated as described in section 7.3 of [15] making use of the observed response rates and inverse normal combination test statistic with equal weights given by

$$(\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2))/\sqrt{2},$$

where p_1 and p_2 denote the p-values for testing the non-inferiority null hypothesis for the first and the second stage of the trial, respectively. The aspired conditional power used for the new intended sample size will be 90%.

A 20% dropout rate will be added to the re-estimated sample size of evaluable patients to receive the number of patients to be enrolled in the second stage.

The minimum number of patients for the second stage is 210 evaluable subjects (even if the re-estimated sample size is below this number) or 263 including dropouts. The sample size for the second stage cannot exceed 1250 patients (dropouts included). If the dropout adjusted re-estimated sample size exceeds this threshold, the IDSMC may recommend to either stop the trial for futility or to enrol the maximum number of additional 1250 patients.

7.5. Software and analyses

All study data will be transferred to a SAS database (version 9.4 or later) for statistical analysis purposes. Data will be imported from an Electronic Data Capture System via validated SAS programs. If applicable, external data will also be transferred to SAS for presentation of these data in the statistical analyses.

The SAP will be finalised before any unblinded analysis, after agreement with the Sponsor.

8. Demographics and Baseline Characteristics

All available demographic data (sex, age, height and body mass index [BMI]) will be summarised in appropriate tables (summary statistics or frequency tables) for the SAF, FAS and PPS populations.

9. Evaluation of Treatment Compliance and Exposure

All study treatment will be administered on-site by study-site staff, and all doses are to be documented in the electronic CRF. Administered doses of *Octaplex* or FP will be recorded for every infusion, including dates, times and batch numbers; the batch numbers will be reported in the final study report. Individual compliance will be derived from these entries and presented as a percentage relative to the recommended dose. Summary statistics for treatment compliance will be displayed.

10. Evaluation of Efficacy

10.1. Estimand

The components of the estimand are presented in

Table *1* below.

Table 1. Description of the primary estimand

Population	Bleeding cardiac surgery patients with valid informed consent requiring coagulation factor replacement randomized and treated with PCC or FP as defined by in- and exclusion criteria for this study
Endpoint	Haemostatic effectiveness, defined as the absence of any additional haemostatic interventions during the period from 60 minutes to 24 hours after administration of the first treatment

	Yes/No response	
Intercurrent events (ICE)	**Event**	**Strategy**
	Discontinuation from study or death	Composite variable strategy: Haemostatic efficacy will be set to 'No', if the patient discontinues for any reason or dies before end of 24-hour period. If discontinuation occurs after the 24-hour period, the response will be considered a valid response.
	Receipt of study medication different from randomisation schedule	Treatment policy strategy: Patients with this ICE will be followed until the end of the 24-hour period and their response will contribute to the analysis as collected and assigned to the randomised treatment group (ITT principle).
	Partial administration of study treatment	Treatment policy strategy: Patients with this ICE will be followed until the end of the 24-hour period and their response will contribute to the analysis as collected.
Population level summary	Difference in proportions of patients with haemostatic effectiveness between the PCC and FP treatment group	

10.2. Primary Endpoint

The primary population for the analysis of the efficacy of the IMPs will be the FAS.

The analysis of efficacy will focus on the following primary endpoint:

P1. Comparison of haemostatic treatment response to *Octaplex* versus FP, defined as 'effective' if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

The non-inferiority of the primary endpoint 'haemostatic response' will be tested between the treatment groups by means of a one-sided Farrington-Manning score test with non-inferiority margin 0.10 at a significance level of 2.5%, testing the null hypothesis as follows:

H_0: $p(PCC) \leq p(FP) - 0.10$ will be tested against the alternative H_1: $p(PCC) > p(FP) - 0.10$

where p(PCC) and p(FP) denote the haemostatic response proportions in the PCC and FP treatment groups, respectively.

At the end of the trial, the inverse normal test statistic with equal weights given by

$$(\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2))/\sqrt{2}$$

is calculated, where p_1 and p_2 denote the p-values for testing the non-inferiority null hypothesis for the first and the second stage of the trial, respectively. If the test statistic exceeds the value 1.96, non-inferiority is demonstrated (see [15]).

Only in case that non-inferiority is demonstrated, i.e., the null hypothesis is rejected at the one-sided 2.5% level of significance, superiority of PCC with regard to the primary endpoint will be investigated:

H_0: p(PCC) ≤ p(FP) will be tested against the alternative H_1: p(PCC) > p(FP)

The Farrington-Manning score test will be used to calculate a two-sided 95% confidence interval based on the inverse normal test statistic as given above. This confidence interval corresponds with the test decision for showing non-inferiority and/or superiority [16]. This hierarchical test procedure allows to perform the superiority test at the full alpha of 2.5%.

10.3. Secondary Endpoints

The following secondary efficacy endpoints will be explored:

S1. Comparison of global haemostatic response to *Octaplex* versus FP, defined as 'positive' if no additional haemostatic intervention (as per the primary endpoint) is required and haemoglobin levels decrease by <30% (after accounting for red cell transfusions) from 60 minutes to 24 hours after initiation of the first dose of IMP. The 24-hour haemoglobin result will be reduced by 1 g/dL for each unit of RBC transfused from 60 minutes to 24 hours.

S2. Comparison of the total amount of chest tube drainage at 12 and 24 hours after chest closure between the *Octaplex* and FP groups.

S3. Comparison of the incidence of severe to massive bleeding, using a modification of the universal definition of perioperative bleeding (UDPB) in cardiac surgery and its individual components during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.

S4. Comparison of the mean number of <u>total</u> allogeneic blood components – including red cells, platelets and all (IMP and non-IMP) FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.

S5. Comparison of the mean number of <u>total non-IMP</u> allogeneic blood components – including red cells, platelets and non-IMP FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.

S6. Comparison of the mean number of total non-IMP allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after IMP initiation, between the *Octaplex* and FP groups.

S7. Comparison of the mean number of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.

S8. Comparison of the incidence of transfusion of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.

S9. Comparison of the incidence of administration of non-IMP coagulation factor products – including fibrinogen concentrate and activated recombinant factor VII – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.

S10. Comparison of the incidence of intracerebral haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.

S11. Comparison of the incidence of gastrointestinal haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.

S12. Comparison of the incidence of surgical re-exploration for bleeding during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.

S13. Comparison of the change in INR, from within 30 minutes before to within 60 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups; INR reduction will be considered successful if the magnitude of the reduction is >1.0 or the post-treatment level drops below 1.5.

S14. Comparison of the changes in other coagulation parameters, including PT, aPTT, fibrinogen activity, ROTEM EXTEM CT and MCF and platelets, from within 75 minutes before to within 75 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups. For a given parameter, if there are multiple results in the window within 75 minutes before to initiation of IMP administration, the most recent result before IMP initiation will be used. If there are multiple results in the window within 75 minutes after the initiation of IMP administration, the earliest result after IMP administration will be used.

S15. Comparison of time elapsed from initiation of the first dose of IMP to arrival at the ICU room between the *Octaplex* and FP groups. Patients in the ICU at the time of first dose of IMP will be excluded from this analysis.

The following analysis methods will be applied to the different endpoints, according to their data type:

The analysis of categorical variables (S1, S3, S8, S9, S10, S11, S12) will present relative frequency tables and estimates of the proportions with 95% confidence intervals separately in the treatment groups. The proportions will be compared between the treatment groups in the context of a logistic regression model.

The analysis of continuous variables (S2, S13, S14, S15) will present descriptive statistics of the sampling distribution and the differences between treatment groups. Also, 95% confidence intervals and results of F-test of the treatment group differences will be reported in the context of an ANOVA model.

The analysis of integer count variables (S4, S5, S6, S7) will present descriptive statistics of the sampling distribution and the differences between treatment groups. Treatment group comparisons for variables (S4, S5, S6, S7) will be performed in the context of a counting regression model for the ABCs and their components (SAS PROC GENMOD with Negative-Binomial distribution). Tests and 95% confidence intervals for the treatment group differences will be derived from this statistical model and reported.

10.4. Sensitivity Analyses

The analysis results for the primary endpoint will be presented in different contexts. This will include those involving the different multiple imputation procedures for missing data, if needed. The analysis of the primary endpoint will be presented for the PPS. Haemostatic treatment response will also be summarized descriptively by study site.

11. Safety Analysis

All safety analyses will be based on the FAS population. If the SAF population differs from the FAS population, then only AE information will additionally be displayed for the SAF.

All AEs and SAEs will be collected from beginning of surgery (defined as entry into OR) to POD-30.

The analysis of safety will study the following endpoints:

1. Comparison of the incidence of serious treatment-emergent adverse events (TEAEs), individually and as composite where appropriate (e.g., TEEs and MACE), between the *Octaplex* and FP groups.
2. Comparison of the duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days) up to POD-30 between the *Octaplex* and FP groups.
3. Comparison of the duration of initial ICU stay up to POD-30 between the *Octaplex* and FP groups.
4. Comparison of the duration of hospitalisation up to POD-30 between the *Octaplex* and FP groups.
5. Comparison of the incidence of death up to POD-30 between the *Octaplex* and FP groups.
6. Comparison of the number of days alive and out of hospital at POD-30 between the *Octaplex* and FP groups.

11.1. Adverse events

AEs will be coded according to the MedDRA. Coding will be agreed upon with the Sponsor before database lock (cf. DMP).

All AEs recorded for patients in the SAF will be listed in the appendix of the study report, differentiated by treatment-emergent and non-treatment-emergent AEs.

Only treatment-emergent AEs (TEAE) will be analysed, i.e., all new and worsening pre-existing AEs occurring after first IMP administration up to POD-30. It is assumed that for each increase in intensity of an AE a new entry of the AE will be recorded by the investigator; hence, such cases will be analysed like different phases of the same AE.

A descriptive analysis will be performed. This analysis will comprise the following set of tables, separated by treatment group and time of first occurrence (within 48 hours, 7 days and 30 days post-surgery):

- Global incidence
- Incidences by primary system organ classes (SOC) and incidences of preferred term within primary SOC sorted according to the Internationally Agreed Order

Global incidences of primary SOC and preferred terms will be calculated for

- All TEAE irrespective of the causality assessment
- TEAE by relationship (probable, possible, unlikely, not related and unclassified)
- TEAEs by worst severity
- Serious TEAEs
- TEAEs possibly or probably related per PI assessment
- TEAEs possibly or probably related per sponsor assessment
- TEAEs possibly or probably related per PI and/or sponsor assessment
- TEEs per PI assessment
- TEEs per MedDRA SMQ
- TEEs per sponsor assessment
- Treatment-emergent major adverse cardiac events (MACE)

Multiple counts within a preferred term or SOC (repeated or different included terms or changes in descriptors) will be counted only once for the calculation of incidences.

A listing of 'special cases' containing patient ID, age, sex, AE descriptors and start and end of treatment will be prepared for the following types of TEAEs:

- Fatal SAEs
- AEs which led to discontinuation
- Myocardial infarction
- Stroke
- Acute liver injury
- Acute kidney injury
- TEEs
- MACE
- TRALI
- TACO

The number of patients who died will be summarised. A possible difference between treatment groups will be estimated by the risk ratio with 95% confidence interval. Kaplan-Meier estimates for the time to death distribution will be calculated and graphically presented. The incidence of death up to POD-30 will be calculated, as well as the incidence of death within 48 hours or 7 days, and special cause mortality.

11.2. Laboratory variables

In case of derived items in the database (e.g., after transformation to standard units, see DMP), only the derived items will be analysed. Results of all individual laboratory tests will be listed in original and standard units in appendix 16.2 to the clinical trial report.

The following laboratory parameters will be analysed (as available from local laboratories):

Coagulation profile	Point-of-care INR, PT, aPTT, INR, fibrinogen activity via Clauss assay, ROTEM EXTEM CT, ROTEM EXTEM MCF, ROTEM FIBTEM MCF, PlateletWorks platelet count and function
Haematology	Standard panel as per local laboratory
Clinical chemistry	Standard panel as per local laboratory
Safety laboratory analyses	Troponin, ALT/ALP, bilirubin, creatinine

All laboratory values will be classified as normal or abnormal according to the laboratories' reference ranges and indicated as clinically significant or not clinically significant by the investigator on specified ranges. The following approaches will be taken for each laboratory parameter for the statistical analysis:

Quantitative data will be examined for trends using descriptive analysis (number of patients, number of missing values, mean, SD, median, quartiles, minimum, maximum) of actual values at each scheduled time point and changes from baseline to each scheduled time point. In addition, mean concentration vs. time profiles (including standard deviations) will be plotted by treatment to illustrate any time trends.

Qualitative data based on reference ranges will be described according to the categories (i.e., low, normal, high).

Shift tables will be generated illustrating changes with respect to the laboratories' reference ranges between baseline and a defined scheduled time point.

Patient listings will be provided showing individual laboratory abnormalities.

12. Data Derivations and Data Transfer

The results of all data transformations and derivations will be stored in analysis data sets.

Laboratory data received electronically will be integrated into the database.

13. Tables, Figures and Lists

A complete List of Tables, Listings, Figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The List will serve as a reference for the Sponsor, the Trial Statistician and the statistical programmer and describes the entire set of statistical output to be produced. Therefore, this List will be versioned and approved by both Ergomed and the Sponsor before commencing the statistical programming.

Each output page will have an appropriate heading specifying the study ID and abbreviated study title.

Each output page will show a common date and page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output. The output pages will not contain any other sequential page numbering.

All statistical output will identify the underlying analysis set(s) and indicate the number of patients/events in this set (N) and the number of patients/events actually contributing to the particular output (n).

All patient listings will contain, in addition to the patient ID, the treatment arm and the analysis set.

14. Changes from Analyses Specified in the Protocol

The described statistical analyses match those pre-specified in the study protocol.

15. Quality Control

The SAP was reviewed by the Trial Statistician before signature. In particular, the Trial Statistician has checked the consistency of the described methods and outputs with the actual version of the study protocol. In addition, a Sponsor representative has reviewed the SAP before final approval.

Log files of all SAS® programs used in the analysis will be checked for errors, warnings and suspicious notes by the statistical programmer. All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by the program author or an independent statistical programmer, depending on the requested validation level selected in the List of TLFs.

The agreement of the program outputs with the SAP and their consistency and plausibility will be checked by the Trial Statistician. Moreover, the Trial Statistician will review the outputs regarding completeness, readability and comprehensibility.

The described process is associated with the 'normal' level of program validation. Additional levels of quality control can be specified in the List of TLFs (**Section 14**) for individual outputs.

16. References

1. Stokes ME, Ye X, Shah M, Mercaldi K, Reynolds MW, Rupnow MF, et al. Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. BMC Health Serv Res. 2011;11:135.
2. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion. 2004;44(10):1453-62.
3. Karkouti K, Arellano R, Aye T, Dupuis JY, Kent B, Lee TW, et al. Off-label use of recombinant activated factor VII in surgical and non-surgical patients at 16 Canadian hospitals from 2007 to 2010 (Canadian Registry Report). Can J Anaesth. 2014;61(8):727-35.
4. Society of Thoracic Surgeons Blood Conservation Guideline Task F, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg. 2011;91(3):944-82.
5. Hartmann M, Sucker C, Boehm O, Koch A, Loer S, Zacharowski K. Effects of cardiac surgery on hemostasis. Transfus Med Rev. 2006;20(3):230-41.
6. Parr KG, Patel MA, Dekker R, Levin R, Glynn R, Avorn J, et al. Multivariate predictors of blood product use in cardiac surgery. J Cardiothorac Vasc Anesth. 2003;17(2):176-81.
7. Johansson PI, Solbeck S, Genet G, Stensballe J, Ostrowski SR. Coagulopathy and hemostatic monitoring in cardiac surgery: an update. Scand Cardiovasc J. 2012;46(4):194-202.
8. Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. Transfusion. 2008;48(1 Suppl):2S-30S.
9. Bevan DH. Cardiac bypass haemostasis: putting blood through the mill. Br J Haematol. 1999;104(2):208-19.
10. Ghadimi K, Levy JH, Welsby IJ. Perioperative management of the bleeding patient. Br J Anaesth. 2016;117(suppl 3):iii18-30.
11. Chowdary P, Tang A, Watson D, Besser M, Collins P, Creagh MD, et al. Retrospective Review of a Prothrombin Complex Concentrate (Beriplex P/N) for the Management of

Perioperative Bleeding Unrelated to Oral Anticoagulation. Clin Appl Thromb Hemost. 2018;24(7):1159-69.
12. Fries D. The early use of fibrinogen, prothrombin complex concentrate, and recombinant-activated factor VIIa in massive bleeding. Transfusion. 2013;53 (Suppl 1):91S-5S.
13. Karkouti K, Bartoszko J, Grewal D, Bingley C, Armali C, Carroll J, et al. Comparison of 4-Factor Prothrombin Complex Concentrate With Frozen Plasma for Management of Hemorrhage During and After Cardiac Surgery: A Randomized Pilot Trial. JAMA Netw Open. 2021;4(4):e213936.
14. Thalji NK, Patel PA. Out of Control: Why Randomized Trials of Factor Concentrates are So Elusive. J Cardiothorac Vasc Anesth. 2021;[Online ahead of print.]: doi.org/10.1053/j.jvca.2021.06.011.
15. Wassmer G, Brannath W. Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. Switzerland: Springer, Cham; 2016.
16. Bauer P, Kieser M. A Unifying Approach for Confidence Intervals and Testing of Equivalence and Difference. Biometrika. 1996;83(4):934-7.

Appendix 1. Transformations/Derivations

Formulas for derived variables:

Variable	Definition / Derivation
Response (24h) (Treatment response)	= 'Effective' ('Yes') if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP. = 'Ineffective' ('No') otherwise.
Response (24h) (Global response)	= 'Positive' ('Yes') if no additional haemostatic intervention (as per the primary endpoint) is required and haemoglobin levels decrease by <30% (after accounting for red cell transfusions) from 60 minutes to 24 hours after initiation of the first dose of IMP. = 'Negative' ('No') otherwise.
ABC(time frame)	= Mean number of total Allogenic Blood Components (RBCs, Platelets and all [IMP and non-IMP] FP) transfused in specified time frame.
Non-IMP ABC(time frame)	= Mean number of total non-IMP Allogenic Blood Components (RBCs, Platelets, Cryoprecipitate and non-IMP FP) transfused in specified time frame.
Individual ABC(time frame)	= Mean number of individual Allogenic Blood Components (RBCs, Platelets, Cryoprecipitate and non-IMP FP) transfused in specified time frame.
Incidence of ABC(time frame)	= Incidence of transfusion of individual Allogenic Blood Components (RBCs, Platelets, Cryoprecipitate and non-IMP FP) in specified time frame.

Transformations to be applied

In order that the sim of Allogenic Blood Products and its constituents adequately represent the exposure to donors, the following transformations will be applied before any derivations:

Platelets	
1 apheresis unit	= 4 allogeneic units,
1 non-apheresis unit	= 4 allogeneic units
Frozen plasma (used in transfusions):	
1 apheresis unit	= 1 allogeneic unit,
1 non-apheresis unit	= 1 allogeneic unit

Transfusion units without any information about apheresis are handled as apheresis units.