



FIBRES

Submission of Documents to JAMA



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CLINICAL STUDY PROTOCOL

FIBRES

FIBrinogen REplenishment in Surgery

Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients

Investigational Product:	<i>Octafibrin</i>
Indication:	Acquired fibrinogen deficiency
Study Design:	Prospective, multi-center, randomized, active-control, single-blinded non-inferiority study
Sponsor:	Keyvan Karkouti
Study Number:	FIBRES (FORMA-06)
EudraCT and/or IND Number:	TBD
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 4 2016
Planned Clinical End:	Quarter 4 2018
Date of Protocol:	24-Nov-2016
Version:	1.1
Coordinating Investigator:	Keyvan Karkouti MD Department of Anesthesia Toronto General Hospital 200 Elizabeth Street, 3EN Toronto, ON M5G 2C4 Canada

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090-CSP-FIBRES_FORMA-06 V 1.1 Nov_24_2016_fin

STUDY OUTLINE

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
Name of Investigational Product: <i>Octafibrin</i>	Protocol Identification Code: (FORMA-06)
Name of Active Ingredient: Human fibrinogen	Date of Final Protocol: 24-Nov-2016

Title of Study: Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients
Indication: Acquired fibrinogen deficiency
Number of Study Centre(s): Up to 12 Canadian hospitals
Objectives: Primary Objective: The primary objective of this study is to demonstrate that the fibrinogen concentrate <i>Octafibrin</i> is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products (ABPs) administered during the first 24 hours after termination of cardiopulmonary bypass (CPB). Secondary Objectives: The secondary objectives include: <ul style="list-style-type: none"> • Comparison of efficacy as measured by the total and individual number of ABPs transfused from the beginning of surgery up to postoperative day 7 • Comparison of the amount of bleeding during the first 24 hours after termination of CPB • Comparison of the effect on fibrinogen levels observed within 1 hour before and 1 hour after fibrinogen supplementation • Comparison of safety as measured by adverse events (AE) and serious adverse events (SAEs) during the first 28 days after termination of CPB • Comparison of other secondary safety endpoints including, duration of mechanical ventilation, dura-

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
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tion of intensive care unit (ICU) stay, duration of hospitalization.

Study Design:

This is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require up to 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank receives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB). No other aspects of care will be modified.

The primary efficacy outcome will be the number of ABPs (red blood cells [RBCs], pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB. Safety outcomes will be measured for the first 28 days after surgery, which is the duration of participation of each patient in the trial. Comparisons will be by intention-to-treat (ITT) (primary) and per-protocol (PP) analysis. One interim analysis will be conducted after 600 patients have been treated to determine whether the study should be terminated for safety reasons, demonstrated non-inferiority or futility reasons.

Name of Sponsor:

Keyvan Karkouti, Toronto General Hospital

Name of Investigational Product:

Octafibrin

Protocol Identification Code:

(FORMA-06)

Name of Active Ingredient:

Human fibrinogen

Date of Final Protocol:

24-Nov-2016

Number of Patients:

Total = 1200; randomized to two arms.

Patient Selection Criteria:

Inclusion Criteria:

1. Patients undergoing cardiac surgery with CPB in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).

Exclusion Criteria:

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

1. Receipt of fibrinogen-containing products, including concentrate or cryoprecipitate within 24 hours before surgery (to exclude patients with significant blood loss before surgery)
2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate
3. Refusal of fibrinogen concentrate or cryoprecipitate due to religious or other reasons
4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation, which is the upper limit of the normal range)
5. Known pregnancy

Test Product, Dose, and Mode of Administration:

Octafibrin and cryoprecipitate will be administered intravenously. Patients randomized to *Octafibrin* will receive 4 g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB. Patients randomized to cryoprecipitate will receive 10 units each time fibrinogen supplementation is ordered during the first 24 hours after the termination of CPB.

Duration of Treatment:

The first 24 hours after termination of CPB.

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint

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The primary endpoint, which is of efficacy, is the comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.

Secondary efficacy endpoints

- Comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.
- Comparison of major bleeding, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] during the first 24 hours after termination of CPB.
- Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) within 1 hour before and 1 hour after the first dose of fibrinogen supplementation.

Secondary safety endpoints:

- Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, will be compared between the groups up to postoperative day 28.
- Other secondary safety endpoints that will also be compared between groups are:
 - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
 - Duration of intensive care unit (ICU) stay up to postoperative day 28
 - Duration of hospitalization up to postoperative day 28

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Study Procedures:

First fibrinogen supplementation order from the surgical team received at the blood bank

The blood bank technologist confirms eligibility with the clinical team and will then randomize patients to fibrinogen or cryoprecipitate according to the randomization schedule and prepares and releases the product

Visit 1: First post-randomization visit (0 to 24 hours after termination of CPB)

Obtain consent from patient or surrogate
Collect baseline and surgical data
Collect laboratory, transfusion and bleeding data
Collect extubation time and LOS in the ICU
Collect concomitant medications
Collect AEs and SAEs

Visit 1a: 0–36 hours if any subsequent doses of IMP are given

Coagulation analyses
Collect laboratory, transfusion and bleeding data
Collect extubation time and LOS in the ICU
Collect concomitant medications
Collect AEs and SAEs

Visit 2: Postoperative day 7 (or at discharge if earlier)

Collect laboratory and transfusion data
Collect extubation time, LOS in the ICU and hospital (if applicable)
Collect AEs and SAEs

Visit 3: Postoperative day 28 (in person if in hospital or by phone)

Collect AEs and SAEs
Collect extubation time, LOS in the ICU, LOS in the hospital

Statistical Analysis Plan:

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses: $H_0: \mu_F / \mu_c \geq (1 + \delta)$ (inferiority) vs. $H_1: \mu_F / \mu_c < (1 + \delta)$ (non-inferiority) will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$ (μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively). Testing of the hypothesis in the final analysis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect. The test of the primary hypothesis in the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if

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the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the ITT population. A secondary analysis will be performed for the PP population. Only in case of demonstrated non-inferiority in the ITT and the PP population subsequently the pair of hypotheses: $H'_0: \mu_F / \mu_c \geq 1$ vs. $H'_1: \mu_F / \mu_c < 1$ will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary.

The safety analysis population (SAF) will include all patients who receive at least one dose of the IMP (if no randomization errors occur, this will be the same population as the ITT population). Safety outcomes will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

FLOW CHART OF ASSESSMENTS

Table 1 Flow Chart of Assessments Performed Throughout the Study

Procedures	Prior to enrollment	Visit 1 Post-randomization (0 to 24 h)	Visit 1a 0–36 h any additional IMP	Visit 2 POD7/DC	Visit 3 POD28
Blood bank receives fibrinogen order^a	x	(x) ^d			
Inclusion and exclusion criteria	x				
Randomization	x				
IMP administration^b		x			
Patient (surrogate) debriefing and consent		x	(x)	(x)	
Baseline data					
Demographics		x			
Medical history		x			
Preoperative medications		x			
Surgical data					
Intraoperative medications		x			
CPB time		x			
Cross-clamp time		x			
Circulatory arrest		x			
Vital signs		x			
Fluid in- and output monitoring		x			
Inotropes and vasopressors		x	x		
Laboratory assessments					
Chemistry ^f		x	x	x	
Hematology ^f		x ^c	x	x	
Coagulation profile ^f		x ^c	x	x	
Safety labs ^f		x	x	x	
Transfusion requirements^e					
RBCs		x	x	x	
Pooled and apheresis platelets		x	x	x	
Plasma		x	x	x	
Other hemostatic products		x	x	x	
Blood loss determination using UDPB		x	x	x	
Extubation time		x	(x)	(x)	(x)
ICU length of stay		x	(x)	(x)	(x)
Hospital length of stay				x	(x)
AEs and SAEs		x	x	x	x
Concomitant medications		x	x	x	x
Physical examination		x	x		

^a After the start of surgery and during or after CPB.

^b IMP will first be administered after start of surgery based on the physician's judgement. The first IMP dose can be administered before fibrinogen levels are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available).

^c Prior to and 60 minutes after IMP administration.

^d Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

^e 24 hours after IMP administration

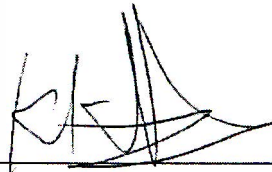
^f As per standard practice

() If needed

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol,
Good Clinical Practice and applicable regulatory requirements.

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14/Jan/2017

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABP	Allogeneic Blood Product
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CREA	Serum Creatinine
CRF	Case Report Form
CRO	Contract Research Organisation
DDAVP	Desmopressin
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IABP	Intra-Aortic Balloon Pump
IB	Investigator's Brochure
ICU	Intensive Care Unit
IDSMC	Independent Data Safety Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT	Intention-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating Room
PCC	Prothrombin Complex Concentrate
POD	Postoperative Day
POD7/DC	Postoperative Day 7 or at Discharge
PP	Per-Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
REB	Research Ethics Board

SAE	Serious Adverse Event
SAF	Safety Analysis Population
SDV	Source Data Verification
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Event
UDPB	Universal Definition of Perioperative Bleeding
WFI	Water for Injections
WNV	West Nile Virus

1 INTRODUCTION

1.1 Background

Human fibrinogen

Human fibrinogen is a plasma glycoprotein synthesized in the liver, and it circulates in the plasma at a concentration of 2.9–4.5 g/L. In healthy human adults, about 2–5 g of fibrinogen is synthesized daily, and the same amount is catabolized [2,3]. Fibrinogen is essential for primary and secondary hemostasis, wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen into fibrin, and often the interaction of fibrinogen with various proteins and cells. The plasma half-life of fibrinogen, under normal physiological conditions, has been estimated to be 3–5 days [4,5].

Acquired hypofibrinogenemia in cardiac surgery

Coagulopathy leading to excessive bleeding is a serious complication of cardiac surgery requiring cardiopulmonary bypass (CPB). Occurring in more than 10% of cases, it frequently necessitates the transfusion of large amounts of allogeneic blood products (ABPs) and is associated with an increased risk of adverse outcomes, such as multi-organ failure and death [6,7]. While the causes of coagulopathy are usually multifactorial, acute acquired hypofibrinogenemia – defined as an acute drop in fibrinogen plasma level – is believed to be the primary factor [8].

Fibrinogen is a critical component of the coagulation cascade as it is both a precursor for fibrin and a cofactor that enhances platelet aggregation [8,9,10,11]. Unlike other coagulation factors that have a large reserve margin [12], a modest drop in fibrinogen levels to <1.5–2.0 g/L impairs coagulation and increases bleeding complications [13,14,15,16,17,18,19,20,21].

Several factors predispose cardiac surgical patients to developing acquired hypofibrinogenemia. These include loss of fibrinogen due to surgical bleeding, dilution due to administration of fluids and CPB prime, and consumption due to activation of the coagulation cascade during CPB (despite anticoagulation with heparin) [21]. As a result, fibrinogen plasma level drops by an average of 40–50% during cardiac surgery [21], and the critical level of <1.5–2.0 g/L is reached in approximately 5% of patients [22]. It is in this group of patients that fibrinogen supplementation is crucial (and current standard of care) to prevent excessive hemorrhage, large-volume transfusion, and associated adverse outcomes [8,23].

Options available for fibrinogen supplementation

There are two primary options available for fibrinogen supplementation: cryoprecipitate and purified human-derived fibrinogen concentrate [8]. Cryoprecipitate is an ABP that is prepared by thawing fresh frozen plasma at 2 to 4° C, harvesting the resultant precipitate by centrifugation, and then re-freezing it at –20 °C.

Cryoprecipitate is currently the mainstay of therapy in North America, but it has several important limitations.

First, the amount of fibrinogen in each unit of cryoprecipitate is highly variable, ranging from 120 to 796 mg per unit [24], and the transfused fibrinogen is only about 50% recoverable [25,26]. As a result, the response to cryoprecipitate is limited and variable, ranging from an increase of 0.05–0.1 g/L in fibrinogen levels per unit transfused [24]. To achieve adequate fibrinogen plasma level for hemostasis, therefore, cryoprecipitate is typically administered in 10 unit pools, which exposes patients to the risks of multiple allogeneic units.

Second, thawing, reconstituting in plasma, and pooling of cryoprecipitate is time consuming and labor intensive, which precludes rapid therapy.

Third, cryoprecipitate is not a purified product and contains large amounts of contaminants such as fibronectin and platelet microparticles [24]. These contaminants are not benign and may cause adverse outcomes such as microvascular thrombosis and organ dysfunction [24,27]. In one observational study, cryoprecipitate was independently associated with a two-fold increase in the risk of death, which was larger than the risk associated with any other blood products [28].

Since cryoprecipitate is not purified, it also contains other pro-hemostatic factors in addition to fibrinogen, including coagulation factor VIII, von Willebrand factor, and coagulation factor XIII, which may be beneficial if the cause of bleeding is multifactorial and not solely due to fibrinogen deficiency [8,24]. This theoretical benefit, however, is not supported by existing data, which is not surprising given that these factors do not usually drop below critical levels during cardiac surgery unless there is massive bleeding, in which case patients would receive plasma transfusions that would contain these factors [21,29,30].

The second option for fibrinogen supplementation is to administer **purified human-derived fibrinogen concentrate**, which is currently the mainstay of therapy for acquired hypofibrinogenemia in much of Europe. In North America, however, this therapy is only approved for the treatment of *congenital* hypofibrinogenemia, and its use for acquired hypofibrinogenemia is currently off-label and therefore not widespread.

The fibrinogen concentrate that will be used for this study, *Octafibrin*, is similar to cryoprecipitate in that it is derived from human plasma, but it has several important advantages [31].

First, it undergoes several virus removal and inactivation steps (nanofiltration [20 nm filter] and solvent detergent treatment), which remove contaminants and inactivate viruses. Thus, it is likely to have a lower risk of transmission of infectious agents. Indeed, a Canadian consensus statement from 2008 recommends adoption of pathogen inactivation strategies once they become available to reduce the risk of transfusion transmissible diseases [32].

Second, it is a highly purified concentrate, containing a consistent amount of fibrinogen (approximately 1 g per vial), and the response to therapy is potentially more predictable and more robust than for cryoprecipitate [33,34,35,36].

Third, since (unlike cryoprecipitate) the product can be administered immediately after it is reconstituted with sterile water, it allows for rapid fibrinogen supplementation.

Review of the literature

The use of cryoprecipitate and fibrinogen concentrate in congenital hypofibrinogenemia is supported by several small, non-controlled studies [37,38,39]. Both therapies have also been shown to successfully increase fibrinogen levels and improve clot formation in various in vitro and in vivo models of fibrinogen deficiency [11,40,41,42,43,44,45]. There are also several observational studies showing improved outcomes when fibrinogen supplementation is used in bleeding patients with acquired hypofibrinogenemia, but the bulk of these studies only examined fibrinogen concentrate [46,47,48,49,50,51,52,53,54,55].

There are several studies that have explored the efficacy of fibrinogen concentrate as a ‘universal’ hemostatic agent i.e., not targeted specifically for patients with acquired hypofibrinogenemia – in cardiac and other types of surgery. While several early-stage trials were mostly positive [56,57,58,59,60,61,62,63], a Cochrane review found that they were inconclusive [64,65]. In a recently completed randomized multicentered trial, fibrinogen supplementation as first-line therapy in bleeding adult cardiac surgical patients was not efficacious, but this study had multiple limitations. It used fibrinogen supplementation as part of a rigid treatment algorithm that was not consistent with current best-practice, used fibrinogen concentrate as a universal hemostatic agent irrespective of other coagulation defects, and had several design flaws with very high post-randomization drop-outs and transfusion protocol violations [66].

Overall, therefore, the well-established practice of fibrinogen supplementation in bleeding patients with acquired hypofibrinogenemia is primarily based on mechanistic principles rather than high-grade clinical evidence. Yet, this practice is so entrenched that it is uniformly endorsed by existing guidelines [25,67,68,69,70,71,72,73,74], and most would agree that it is neither clinically nor ethically appropriate to withhold fibrinogen supplementation from bleeding patients with confirmed or presumed (in cases of severe bleeding) acquired hypofibrinogenemia [75], thus precluding the conduct of placebo-controlled trials.

To determine the most appropriate fibrinogen supplementation therapy, comparative randomized trials between cryoprecipitate and fibrinogen concentrate are needed, but there is a dearth of such trials. One experimental study found that cryoprecipitate and fibrinogen concentrate have similar abilities in correcting clot firmness in an in vitro model of hemodilution [40]. Two small retrospective observational studies found that fibrinogen concentrate results in a generally more robust fibrinogen response than cryoprecipitate in various groups of patients with acquired hypofibrinogenemia, but these studies were not equipped to compare the safety and effectiveness of the two therapies [33,34]. One randomized comparative clinical trial that included 63 children (<7 years old) who were bleeding after cardiac surgery and had a fibrinogen level of <1.0 g/L

found no differences between fibrinogen concentrate and cryoprecipitate in terms of efficacy and safety, but this study was in a pediatric population and was underpowered to prove non-inferiority [76].

Propensity-score matching and TACS study

As background work for the proposed trial, a retrospective comparison of fibrinogen concentrate versus cryoprecipitate was performed at Toronto General Hospital after a point-of-care-based transfusion algorithm for guiding coagulation management in bleeding cardiac surgical patients had been instituted in January 2013 [77].

For the treatment of acquired hypofibrinogenemia, cryoprecipitate was used during the first 11 months after the algorithm was introduced (n=51), and fibrinogen concentrate was used thereafter (n=99), resulting in a homogeneous cohort of patients allowing comparison of the two therapies using propensity-score matching. Despite the low power of the study, the results do suggest that the two therapies have similar risk-benefit profiles. These results have helped inform the appropriate outcome and the required sample size for the randomized trial presented in this protocol (Table 2 and Table 3).

Table 2 Transfusion data in propensity-score matched patients

Variables	Cryoprecipitate (n=43)	Fibrinogen concentrate (n=43)	p value
RBC transfusion			
n (%)	39 (91%)	34 (79%)	0.2
Units	6 (2–12)	4 (1–12)	0.2
Plasma transfusion			
n (%)	36 (84%)	30 (70%)	0.2
Units	4 (2–8)	4 (0–8)	0.2
Platelet transfusion			
n (%)	42 (98%)	35 (81%)	0.03
Pools	3 (1–5)	2 (1–4)	0.04
Total allogeneic units*	12 (7–27)	10 (4–21)	0.15
Severe/Massive bleeding**	30 (70%)	27 (63%)	0.5

*Number of transfused units of red blood cells (RBCs) + units of plasma + pools of platelets

**According to the universal definition of perioperative bleeding in cardiac surgery (occurrence of any of the following: 24-hour chest tube drainage >1L; RBC transfusion ≥5 units; plasma transfusion ≥5 units; rescue therapy with recombinant activated factor VII; or surgical re-exploration) [1]

Table 3 Adverse outcome data in propensity-score matched patients

Variables	Cryo-precipitate	Fibrinogen concentrate	p value
Acute kidney injury*	13 (30%)	10 (23%)	0.6
Hepatic dysfunction**	9 (21%)	5 (12%)	0.4
Stroke	3 (7%)	1 (2%)	0.6
Deep vein thrombosis and pulmonary embolism	0	0	–
Myocardial infarction	3 (7%)	1 (2%)	0.6
Death	9 (21%)	7 (16%)	0.8
Composite***	19 (44%)	12 (28%)	0.17

*>40% drop in estimated glomerular rate within one week of surgery [78]

**Alanine aminotransferase >150 U/L within one week of surgery [79]

***One or more of the listed complications

Further preliminary data was obtained from a recently completed multi-center trial (funded by the Canadian Institutes of Health Research) that assessed the effectiveness of a point-of-care coagulation management algorithm at 12 Canadian hospitals and included 7404 patients (TACS study; Circulation; In Press; ClinicalTrials.gov ID NCT02200419). During the 7-month trial, 447 (6%) patients received cryoprecipitate (n=394) or fibrinogen concentrate (n=61). Transfusion rates and adverse outcomes in these patients (Table 4) were similar to those in the propensity-matched single-center study described above.

Table 4 Outcomes of TACS study patients who received cryoprecipitate (n=394) or fibrinogen concentrate (n=61)

Variables	Received cryoprecipitate or fibrinogen concentrate (n=447/7404)
RBC transfusion	382 (85%)
Plasma transfusion	368 (82%)
Platelet transfusion	388 (87%)
Total allogeneic units	13 (7–23)
Severe/Massive bleeding	344 (77%)
Adverse outcome data	
Acute kidney injury	113 (26%)
Stroke	23 (5%)
Myocardial infarction	5 (1%)
Death	54 (12%)
Composite*	145 (32%)

*One or more of the listed complications

1.2 Rationale for Conducting the Study

The purpose of this study is to determine whether the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate with respect to efficacy when used to treat bleeding in cardiac surgical patients with acquired hypofibrinogenemia. Hemostatic management in bleeding surgical patients is evolving from empirical therapy with non-purified ABPs to targeted therapy with purified products [80]. The proposed study, by comparing two currently available but distinctly different therapies for treating acute acquired hypofibrinogenemia in bleeding surgical patients, non-purified cryoprecipitate versus purified human-derived fibrinogen concentrate, is well aligned with this change. Given the practical and theoretical advantages of purified fibrinogen concentrate over cryoprecipitate detailed above (improved safety, ease of administration, predictable and robust effect on fibrinogen plasma levels), we believe that a finding of non-inferiority will lead to the use of purified fibrinogen concentrate in place of cryoprecipitate in clinical practice.

This study uses a pragmatic approach for data collection leaving the surgical team to maintain the standard of care accepted by their institution. This is important since other multi-center studies that have included a very strict design so far have failed when studied in later phase trials because of the inability of the sites to accurately follow the specified design, which itself has been criticized for not being consistent with usual clinical practice.

1.3 Benefit-Risk Statement

Substituting either fibrinogen concentrate or cryoprecipitate for the other is not expected to pose any material risks to the participants. Patients will only be included in the trial when their clinicians have ordered fibrinogen supplementation for treatment of bleeding that is thought to be due to acquired hypofibrinogenemia. Thus, no patient will receive fibrinogen supplementation solely for the purposes of this study.

Octafibrin, the fibrinogen concentrate to be used in this study, is under development for the treatment of congenital afibrinogenemia and hypofibrinogenemia. *Octafibrin* has been shown to have comparable (and in some instances superior) pharmacokinetics, hemostatic effects, and safety profile to *Riastap* (CSL Behring), which is an approved (by Health Canada and FDA) purified human-derived fibrinogen concentrate. Ongoing studies looking at the treatment of bleeding and surgery in patients with congenital fibrinogen deficiency, have shown excellent efficacy and safety profile so far. *Octafibrin* has been submitted to EU, USA, and Canada for licensing approval in the indication named above.

The experience to date with this concentrate has shown an excellent safety profile that is in all likelihood superior to that of cryoprecipitate [8,75]. As discussed, fibrinogen concentrate is pathogen inactivated and can be administered in predictable doses, making its administration likely to be both safer than, and at least as efficacious as, cryoprecipitate.

1.4 Principal Investigator (Sponsor)

The Sponsor and Coordinating Investigator of this study is Keyvan Karkouti MD at the Department of Anesthesia, Toronto General Hospital, 200 Elizabeth Street, 3EN, Toronto, ON, Canada.

Octapharma AG will support the conduct of this study by awarding an unrestricted grant for study conduct supporting data management, statistical services, and supplying the fibrinogen concentrate.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate that the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of ABPs administered during the first 24 hours after termination of CPB.

2.2 Secondary Objectives

The secondary objectives include:

- Comparison of efficacy as measured by the total and individual number of ABPs transfused from the beginning of surgery up to postoperative day 7
- Comparison of the amount of bleeding during the first 24 hours after termination of CPB
- Comparison of the effect on fibrinogen levels observed within 1 hour before and 1 hour after fibrinogen supplementation
- Comparison of safety as measured by adverse events (AEs) and serious adverse events (SAEs) during the first 28 days after termination of CPB
- Comparison of other secondary safety endpoints including, duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalization.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary endpoint, which is of efficacy, is the comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.

3.1.2 Secondary Endpoints

Secondary efficacy endpoints

- Comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.
- Comparison of major bleeding, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] (**Section 7.2.3**) during the first 24 hours after termination of CPB.
- Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) within 1 hour before and 1 hour after the first dose of fibrinogen supplementation.

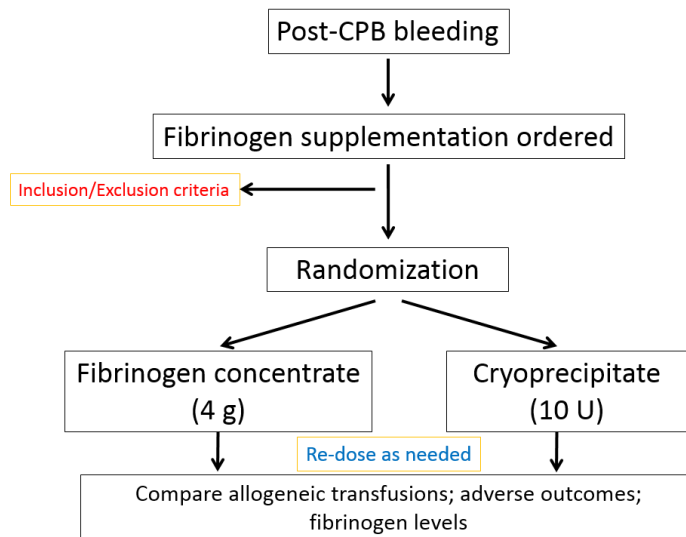
Secondary safety endpoints

- Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, will be compared between the groups up to postoperative day 28.
- Other secondary safety endpoints that will also be compared between groups are:
 - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
 - Duration of intensive care unit (ICU) stay up to postoperative day 28
 - Duration of hospitalization up to postoperative day 28

3.2 Overall Study Design and Plan

This is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require approximately 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank re-



ceives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB) [see flowchart below].

The primary efficacy outcome will be the number of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB, with the primary comparisons being by intention-to-treat (ITT).

Safety outcomes will be measured for the first 28 days, which is the duration of participation of each patient in the trial. One interim analysis will be conducted after 600 patients have been treated to determine whether the study should be terminated for safety, demonstrated non-inferiority or futility reasons.

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Non-inferiority Design

A non-inferiority rather than superiority design was selected because both products are used to supplement fibrinogen in acquired hypofibrinogenemia. However, purified fibrinogen concentrate has important advantages over cryoprecipitate (it is faster to prepare, easier to administer, has a more predictable response and a better safety profile) that would make it the preferred option if it was found to be non-inferior to cryoprecipitate [81].

3.3.2 Choice of Primary Endpoint

The primary efficacy endpoint is the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the 24 hours after termination of CPB. This is a clinically relevant outcome that has been used in previous randomized fibrinogen trials [57]. Moreover, it is a primary outcome that has been accepted by the European Medicines Agency (EMA) for a major multi-center clinical study (ClinicalTrials.gov Identifier: NCT01475669).

3.3.3 Major Bleeding as Secondary Endpoint

Major bleeding after the index surgery according to the UDPB in cardiac surgery is a secondary outcome [1]. This is a validated, prognostically important clinical outcome in cardiac surgery [1,82]. Kinnunen et al. found that patients with major bleeding according to this definition had a greater than four-fold increase in the risk-adjusted odds of death compared with all other patients [82]. In our preliminary data, major bleeding as per the UDPB definition was associated with a 31-fold increase in the risk-adjusted odds of death compared to those with insignificant bleeding. In terms of prognostic value, major bleeding was the second most prognostically important variable (superseded only by renal failure) in a model that included all SAEs.

3.3.4 Dose Rationale

Each time fibrinogen supplementation is ordered, patients will receive either cryoprecipitate (1 dose = 10 units = approximately 4 g) or purified fibrinogen concentrate (1 dose = 4 g) according to their group assignment.

The amount of fibrinogen in each unit of cryoprecipitate is estimated to be approximately 400 mg [24]. Thus, 4 g of fibrinogen concentrate will be dose-equivalent to 10 units of cryoprecipitate, which is the current recommended dose for fibrinogen supplementation in the setting of acute bleeding [81].

3.3.5 Choice of Comparator

The trial will not include a placebo arm because delaying fibrinogen supplementation in bleeding patients with acquired hypofibrinogenemia would expose them to the negative consequences of excessive blood loss, is not consistent with standard practice [83,84], and would withhold an effective treatment from patients and thus be unethical. Moreover, the question being addressed does not meet any of Freedman's five conditions that would justify the use of a placebo control, which are: 1) no standard treatment exists; 2) standard treatment is not better than placebo; 3) standard treatment is a placebo or no treatment; 4) new evidence has shown uncertainty of the risk-benefit profile of the standard treatment; and 5) effective treatment is not readily available due to cost or supply issues [84,85].

3.3.6 External Validity

This will be a multi-center study performed in up to 12 hospitals with different characteristics. Moreover, patients will be recruited and randomized after the clinical team orders fibrinogen supplementation and the only change to routine practice is the choice of fibrinogen supplementation; thus, patient management in the control arm will reflect current practice and in the intervention arm will reflect how fibrinogen concentrate will be used in practice. For these reasons, the study will have good external validity.

3.3.7 Randomization and Baseline Differences

Given the large size of the study and random patient assignment stratified by center, study groups should be well balanced with respect to important clinical variables. The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial, and neither the individual randomizing nor any of the health care providers will know which treatment will be assigned to the patient when fibrinogen supplementation is ordered.

3.3.8 Recruitment and Informed Consent

This is a pragmatic trial that compares two fibrinogen replacement sources that are currently within the standard-of-care for this procedure and poses no additional risks to patients and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (i.e., bleeding during or after 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 qualified for waiver of informed consent followed by a postoperative debriefing to patients (or their surrogate decision maker), providing them the opportunity to withdraw from the study. The waiver of consent request meets the criteria of the Tri-council policy statement for the ethical conduct for research involving humans, as is outlined in **Section 10.3**.

3.3.9 Blinding of Investigational Medicinal Product (IMP)

Given that the products have quite different physical differences, it is not possible to blind clinicians to group assignment. To minimize bias, clinicians will be blinded to group assignment until after the product is prepared and released by the blood bank. Moreover, clinicians outside of the operating room and outcome assessors will remain blinded by using a generic product label in the patient chart and/or the electronic product name (i.e., study fibrinogen product 4 g, rather than specifying type of product used).

3.3.10 Drop-outs and Crossovers

Drop-outs: We anticipate that the intervention will not be administered in <5% of randomized patients for whom fibrinogen supplementation was ordered. This is usually due to cessation of bleeding or identification of other causes of bleeding after the product is ordered but before it is administered. Patients may also drop out after having received the therapy if they (or their decision makers) do not provide consent for the study. These patients will be included in the analysis if they provide permission for the use of their data. Based on past experience, however, we do not anticipate a significant number of post-therapy drop-outs. Study sample size has been calculated to compensate for drop-outs.

Product switching: Other than the fibrinogen supplementation order being cancelled, all patients will be treated according to the randomization schedule for the entire treatment period (24 hours after termination of CPB). To ensure minimal product switching, instructions will be entered into the blood bank information system to dictate the randomization product for the 24 hours after randomization and will flag the laboratory technologists if attempts are made to override the instruction. In very rare circumstances (e.g., after catastrophic bleeding during which several doses of fibrinogen supplementation have already been administered), clinicians may opt to switch from one therapy to the other during the treatment period. The reasons for this request will be collected and described. The anticipated number of product switches will be very few (<1%).

3.3.11 Outcome Assessments and Independent Data and Safety Monitoring Committee (IDSMC)

An IDSMC will review accumulating safety, endpoint, and other study data (recruitment, retention and compliance, data quality and timeliness, risk vs. benefit). The function of the IDSMC will be to protect and serve the recruited patients particularly pertaining to patient safety as well as to assist and advise the Sponsor on medical questions and issues of study conduct and continuation. The IDSMC will be independent of the investigating team and the Sponsor in operating and formulating recommendations. The IDSMC full role will be detailed in the IDSMC Charter.

4 STUDY POPULATION

4.1 Population Base

Approximately 1,200 bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be enrolled into the study, with approximately 600 patients assigned to each of the two treatment groups.

4.1.1 Inclusion Criteria

1. Patients undergoing cardiac surgery with CPB in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).

4.1.2 Exclusion Criteria

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

1. Receipt of fibrinogen-containing products, including concentrate or cryoprecipitate within 24 hours before surgery (to exclude patients with significant blood loss before surgery)
2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate
3. Refusal of fibrinogen concentrate or cryoprecipitate due to religious or other reasons
4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation, which is the upper limit of the normal range)
5. Known pregnancy

4.2 Prior and Concomitant Therapy

Details on medications taken within 1 week before enrolment and any concomitant medications taken during the study must be recorded in the case report form (CRF).

4.2.1 Permitted Concomitant Therapy

Concomitant administration of any therapies required as part of standard patient care is permitted, but must be recorded in the CRFs. We will record all hemostatic drugs or products administered (e.g., heparin and protamine dose, antifibrinolytic drugs, desmopressin, recombinant activated factor VII, prothrombin complex concentrate, idarucizumab, andexanet alpha, or topical hemostatic agents), as well as all procedures that may influence amount of bleeding (e.g., retrograde autologous priming of CPB circuit, cell salvage).

In addition, concomitant medications used to treat SAEs will be reported throughout the duration of follow-up (up to postoperative day 28).

4.2.2 Forbidden Concomitant Therapy

Fibrinogen-containing products within 24 hours before surgery are not allowed.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study non-interpretable, unnecessary withdrawal of patients will be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

4.3.2 Patient Replacement Policy

Patients withdrawn from the study for safety reasons will not be replaced.

4.4 Assignment of Patients to Treatment Groups

Patients will be assigned to treatment with either *Octafibrin* or cryoprecipitate using a permuted-block, stratified (by center) random allocation scheme prepared by a biostatistician not involved in the conduct of the trial. Group allocation will apply to all fibrinogen supplementation orders during the treatment period (up to 24 hours after termination of CPB).

Subjects/patients are not permitted to re-enroll in the study.

4.5 Relevant Protocol Deviations

In the case of any major protocol deviation, the Investigator (Sponsor) will decide on the further participation of the patient in this study.

4.6 Subsequent Therapy

During the first 36 hours after termination of CPB, the patient will be treated as per the standard-of-care at the participating institution.

Additional infusions of the randomized IMP can be given if felt necessary by the clinical team. All information on subsequent dosing should be captured and the reason for these additional infusions should be documented in the patient record.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

5.1 Characterization of Investigational Products

5.1.1 Octafibrin

Octafibrin is a highly purified, lyophilized human plasma fibrinogen concentrate without added albumins. The manufacturing process of *Octafibrin* includes two dedicated virus inactivation/removal steps, i.e., solvent/detergent treatment and nanofiltration.

The solvent/detergent treatment mode of action causes enveloped viruses to be irreversibly destroyed. These include the most transfusion-relevant viruses, such as human immunodeficiency virus types 1 and 2 (human immunodeficiency virus [HIV]-1, HIV-2), hepatitis B virus (HBV) and hepatitis C virus (HCV), and many other adventitious agents, e.g., newly emerging enveloped viruses, such as West Nile virus (WNV).

The Planova 20N filter was specifically developed by Asahi Kasei Pharma Corp. to remove infectious agents from protein solutions on the basis of their size. Thus, this nanofiltration step is in principle effective for removing even very small enveloped and non-enveloped viruses. Nanofiltration may be the only method to date permitting efficient removal of enveloped and non-enveloped viruses under conditions where 90–95% of protein activity is recovered [86].

Composition of Octafibrin

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous (IV) use. Its ingredients are listed in Table 5.

Table 5 Composition of *Octafibrin*

Ingredients	Quantity per mL reconstituted solution, mean values	Standard
Active ingredient		
Fibrinogen as clottable protein	20 mg	Ph. Eur.
Excipients		
Sodium chloride	6 mg	Ph. Eur.
Sodium citrate dehydrate	1.5 mg	Ph. Eur.
Glycine	10 mg	Ph. Eur.
L-arginine hydrochloride	10 mg	Ph. Eur.

Ph. Eur. = Pharmacopoeia Europaea

Octafibrin is a powder for solution for injection supplied in labeled 100 mL vials and provided by Octapharma. *Octafibrin* will be reconstituted with 50 mL sterile water for injections (WFI) produced according to GMP and provided by the clinical site.

The final product will be released by the responsible Octapharma Quality Control Department, according to a defined final product specification.

Conditions for Storage and Use

The IMP has to be stored at room temperature (not more than 25°C) and protected from light. The product must not be frozen. The Investigator/authorized personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

Dose and Dosing Schedule

Patients randomized to *Octafibrin* will receive 4 g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB.

Preparation

Each vial of *Octafibrin* will be reconstituted with 50 mL WFI at room temperature (not more than 25°C). *Octafibrin* dissolves at room temperature to an almost colorless and slightly opalescent solution within 10 minutes. If the solution is cloudy or contains particulates, it should not be used.

Method of Administration

The 4g of *Octafibrin* will be administered immediately after reconstitution over 10 minutes through a free-flowing IV by syringe injection. *Octafibrin* should not be mixed with other medicinal products or crystalloid intravenous solutions.

Packaging and Labelling

Octafibrin will be packaged and labeled for the trial by Octapharma. The label will comply with the Canadian national requirements.

Several batches of IMP may be used throughout the study. The batch numbers will be recorded in the CRFs and reported in the final study report.

5.1.2 Cryoprecipitate

Patients randomized to cryoprecipitate will receive 10 units each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB to 24 hours. Cryoprecipitate will be stored, thawed, and pooled by the blood bank according to current standards. The cryoprecipitate will be infused as per standard hospital protocols at the participating institutions (i.e., infused over 10–30 minutes through standard 170 µm blood infusing set).

5.2 Blinding, Emergency Envelopes, and Breaking the Study Blind

This is a single-blind randomized study, with patients randomized to equivalent doses of cryoprecipitate (1 dose = 10 units) or *Octafibrin* (1 dose = 4 g) (see **Section 5.1**). Given the physical differences in the products, it is not possible to blind clinicians to the IMPs.

The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial (see **Section 9.3**). To minimize bias, neither the individual randomizing nor any of the health care providers will know which treatment will be assigned to a given patient when fibrinogen supplementation is ordered.

Patients and outcome assessors will be blinded by having the compatibility label that will be placed in the patients' paper or electronic chart state "Study fibrinogen product 4g" rather than the actual product used.

5.3 Treatment Compliance

5.3.1 Drug Dispensing and Accountability

A drug dispensing log and the inventory will be kept current by the Investigator, detailing the dates and quantities of fibrinogen concentrate dispensed to each patient. The inventory will be available to the monitor to verify drug accountability during the study. Any unused or partially used fibrinogen concentrate, including empty containers, will be accounted for.

Unused fibrinogen concentrate may be destroyed at the study site, however, only after drug accountability has been verified and fully re-conciliated and written approval from the Sponsor has been obtained.

5.3.2 Assessment of Treatment Compliance

Fibrinogen supplementation will be ordered and administered by the clinical team in the hospital and will not be dependent on patient compliance.

6 STUDY CONDUCT

All patients having cardiac surgery with CPB will be the source of potential patients in the study. Patients will be randomized if they bleed after termination of CPB and the clinical team determines that fibrinogen supplementation is required according to current clinical standards for up to 24 hours after termination of CPB. Once the clinical team orders fibrinogen supplementation, the blood bank technologist will confirm patient eligibility and randomize the patient (according to a prepared randomization schedule) to *Octafibrin* or cryoprecipitate and prepare the product.

Patients will be treated according to their group allocation for any subsequent doses for the duration of the treatment period, which is 24 hours after termination of CPB.

Standard coagulation measures, including fibrinogen plasma level, will be obtained within one hour before and one hour after each fibrinogen supplementation, as per standard practice. The first IMP dose can be administered before fibrinogen level are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available, which is the treatment threshold recommended by current guidelines for treatment of bleeding patients) [8,70,71].

All AEs and SAEs occurring after termination of CPB to postoperative day 28 will be recorded. Patients will be followed by research coordinators in each institution. All clinical outcomes will be obtained from patients' medical records and electronic records, history and physical where needed, and via phone contact during the follow-up visits.

The flow chart of assessments by study visit is given on page viii.

6.1 Study Procedure

6.1.1 Prior to Enrolment

First fibrinogen supplementation order from the surgical team received at the blood bank

The blood bank technologist will confirm the following:

- CPB has been terminated
- Inclusion and exclusion criteria are met
- Coagulation measures (coagulation profile) are available or have been collected

The blood bank technologist will then randomize patients to fibrinogen or cryoprecipitate according to the randomization schedule and prepares and releases the product

Subsequent fibrinogen supplementation orders for the next 24 hours

- In addition to repeating the procedures for the first dose, the blood bank technologist will also confirm that fibrinogen plasma level have been re-checked: If yes, record value and confirm <2.0 g/L (by the Clauss method), in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available.
- If no, ask for sample to be sent to the lab prior to the administration of IMP

- [Study drug should not be released at this point by the blood bank without lab confirmation]

Time of IMP infusion in the Operating Room (OR)

Nurse or coordinator will collect the following:

- What time was the IMP administration started?
- Time of coagulation analyses (coagulation profile). Samples to be sent to the laboratory prior to IMP infusion and at 60 min after IMP infusion (exact sampling time needs to be recorded).

6.1.2 Visit 1: First post-randomization visit (0 to 24 hours after termination of CPB)

Obtain consent from patient or surrogate

- Collect baseline data
 - Demographics
 - Medical history
 - Preoperative concomitant medications
- Collect surgical data
 - Intraoperative concomitant medications
 - CPB time
 - Cross-clamp time
 - Circulatory arrest
 - Vital signs
 - Fluid in- and output monitoring
 - Inotropes and vasopressors
- Collect laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile before and after IMP administration
 - Safety labs (creatinine, liver function tests [AST, ALT], troponin)
- Collect transfusion requirements (number and timing) for the 24 hour period after infusion
 - RBCs
 - Pooled or apheresis platelets
 - Plasma
- Collect bleeding components using the UDPB criteria
- Collect extubation time
- Collect length of stay in the ICU
- Collect concomitant medications
- Collect AEs and SAEs

6.1.3 Visit 1a: 0–36 hours if any subsequent doses of IMP are given

- Coagulation analyses (including coagulation profile). Samples to be sent to the laboratory prior to IMP infusion and at 60 min after IMP infusion (exact sampling time needs to be recorded).
- Collect laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile before and after IMP administration
 - Safety labs (creatinine, liver function tests [AST, ALT], troponin)
- Collect transfusion requirements (number and timing) for the 24 hour period after infusion
 - RBCs
 - Pooled or apheresis platelets
 - Plasma
- Collect bleeding components using the UDPB criteria
- Collect extubation time
- Collect length of stay in the ICU
- Collect concomitant medications
- Collect AEs and SAEs

6.1.4 Visit 2: Postoperative day 7 (or at discharge if earlier)

- Collect daily laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile
 - Safety labs (creatinine, liver function tests [AST, ALT], bilirubin, troponin)
- Collect transfusion requirements
- Collect extubation time (if applicable)
- Collect length of stay in the ICU and hospital (if applicable)
- Collect AEs and SAEs

6.1.5 Visit 3: Postoperative day 28 (in person if in hospital or by phone)

- Collect AEs and SAEs
- Collect extubation time (if applicable)
- Collect length of stay in the ICU (if applicable)
- Collect length of stay in the hospital (if hospital stay is extended)
- Collect concomitant medications

After Visit 3 or on postoperative day 28, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

6.1.6 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply:

Table 6 Time Windows Used in this Study

Time point	Time stated	Tolerance
Interval between visits		
Blood sampling	before IMP administration	≤ 30 minutes
	60 minutes after IMP administration	± 15 minutes
	Day 7	± 1 day
	Day 28	± 2 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The **duration of the treatment period** is 24 hours from the end of CPB.

The **duration of the study** for an individual patient is 28 days from patient enrollment when patients will be contacted in person or by phone post-discharge.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when 1,200 patients are randomized and have finalized day 28 (or early termination at the time of the interim analysis). It is estimated that the study will take approximately 2 years for recruitment.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor, in consultation with the Independent Data Safety Monitoring Committee (IDSMC), reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Investigators will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and research ethics boards (REBs) will be informed in accordance with national regulations.

Early termination of the study as a whole or by center may apply for the following reasons:

Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.

Early Termination at an Individual Study Center

At any time, the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The a priori determined required recruitment rate is not met.

Should the study be prematurely terminated, all remaining *Octafibrin* will be returned to Octapharma or locally destroyed.

7 ASSESSMENTS AND METHODS

7.1 Baseline Data

The baseline information and medical history will be recorded during Visit 1, i.e., as soon as possible after randomization.

7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are sex, age, height, weight, and Body Mass Index (BMI).

7.1.2 Medical History and Prior/Concomitant Medications

The medical history will be obtained by interviewing the patient or from the medical records.

Prior and concomitant medications will be obtained.

7.2 Study Assessments

7.2.1 Surgical and Surgery-Related Data

The following surgical data will be collected: details of procedure, CPB duration, CPB start-end times, cross-clamp duration, circulatory arrest duration, fluid intake and output, any medications administered, hemodynamic support (e.g., IABP), as well as any blood conservation methods used (e.g., hemoconcentration, retrograde prime, cell salvage).

In addition, extubation time, ICU length of stay, and hospital length of stay will be documented.

7.2.2 Transfusion Data

All blood products and hemostatic agents released from the blood bank and transfused will be collected from the blood bank databases. These include ABPs: RBCs, pooled or apheresis platelets, and plasma. Other hemostatic agents include: DDAVP, prothrombin complex concentrates (PCC), activated recombinant factor VII, idarucizumab, and andexanet alpha. For the purposes of the study, a unit will refer to 1 unit of RBCs, 1 dose of pooled or apheresis platelets, or 1 unit of plasma.

7.2.3 Bleeding Data

The comparison of ‘major’ bleeding based on the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] (Table 7) will be assessed as a secondary endpoint. The UDPB is a multistage definition for perioperative bleeding based on easily measured clinical end points, including total blood loss from chest tubes within 12 hours, ABPs transfused, surgical re-exploration including cardiac tamponade, delayed sternal closure, and the need for salvage treatment.

Depending on these components, bleeding is graded as insignificant, mild, moderate, severe, or massive. (Table 7) [1].

Table 7 Bleeding categories according to the UDPB in adult cardiac surgery (if different categories indicate mixed definitions of bleeding, the worst definition applies) [1]

Bleeding definition	Postoperative chest tube blood loss within 12 h (mL)	RBC (units)	FFP (units)	PLT (units)	Cryoprecipitate	PCCs	rFVI-Ia	Reexploration/tamponade
Class 0 (insignificant)	<600	0*	0	0	No	No	No	No
Class 1 (mild)	601–800	1	0	0	No	No	No	No
Class 2 (moderate)	801–1000	2–4	2–4	Yes	Yes	Yes	No	No
Class 3 (severe)	1001–2000	5–10	5–10	NA	NA	NA	No	Yes
Class 4 (massive)	>2000	>10	>10	NA	NA	NA	Yes	NA

FFP, fresh frozen plasma; NA, not applicable; PCCs, prothrombin complex concentrates; PLT, platelets; rFVIIa, recombinant activated factor VII; UDPB, universal definition for perioperative bleeding.

*Correction of preoperative anemia or hemodilution only; the number of RBCs used should only be considered in the UDPB when accompanied by other signs of perioperative bleeding.

7.3 Laboratory Assessments

7.3.1 Test Parameters and Laboratories

Table 8 summarizes all test parameters and the laboratories responsible for analysis.

Table 8 Test parameters and laboratories

Test	Material needed	Responsible laboratory
Coagulation profile		
(PT, PTT, INR, fibrinogen activity via Clauss technique)	Citrated blood	Local
ROTEM FIBTEM A10	Citrated blood	Local, if available
Hematology – standard panel as per local lab	Citrated blood	Local
Clinical chemistry – standard panel as per local lab	Serum	Local
Safety labs		
Troponin	Serum	Local
AST/ALT	Serum	Local
Bilirubin	Serum	Local
Creatinine	Serum	Local

7.3.2 Blood Sampling

All blood sampling will be performed as per standard practice at the local institution.

The *actual* time of blood sampling for fibrinogen will be recorded in the CRF.

7.3.3 Citrated Blood

Citrated blood as required by the local laboratory will be collected and processed in accordance with local requirements.

7.3.4 Serum

For the determination of clinical chemistry and safety labs (alanine aminotransferase, ALT; aspartate aminotransferase, AST; serum creatinine, CREA; troponin), where a serum blood sample has been collected.

7.3.5 Recording of Clinically Significant Abnormal Laboratory Values as AEs/ADRs

Other than abnormal laboratory values due to the underlying condition, the Investigator must assess the clinical significance of abnormal laboratory values outside the specified normal range (see **Section 7.4**). Any clinically significant abnormalities will be documented. All specified clinically significant abnormalities will be documented as AEs/SAEs and investigated.

Additional tests and other evaluations required to establish the significance or etiology of specified abnormalities or to monitor the course of an AE will be obtained if clinically indicated. Follow-up will persist until resolution or up to the Study Completion Visit, whichever occurs first.

7.4 Safety Assessments

7.4.1 Assessments for Safety Endpoints

The following drug safety information will be collected:

- AEs and SAEs temporally associated with the administration of IMP (for definitions and reporting requirements, see **Sections 7.4.2, 7.4.3, and 7.4.4**).
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see **Section 7.4.5**).

7.4.2 Adverse Events (AEs)

Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase ‘response to an IMP’ means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Principal Investigator (Sponsor).

Collection of AEs

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as “How have you been since the last visit/during the previous study period?”. In addition, the Investigator will check the patient records for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the CRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the likelihood that they were related to the IMP (causality). The Sponsor will be responsible for assessing the expectedness of each ADR (expected or unexpected).

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

Severity of AEs

The intensity/severity of AEs will be graded as follows:

Mild: an AE, usually transient, which causes discomfort but does not interfere with the patient’s routine activities

Moderate: an AE which is sufficiently discomforting to interfere with the patient’s routine activities

Severe: an AE which is incapacitating and prevents the pursuit of the patient’s routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

Probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient’s clinical state.

Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example be-

cause of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

Unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.

Not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

Unclassified: reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

Expected: an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.

Unexpected: an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved (by Study Completion visit)
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death will be fully documented and reported.

Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None

- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Principal Investigator (Sponsor).

7.4.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is another important medical event.

In this study a number of SAEs are expected because of the nature of the surgery. These events will not be considered as SAEs in this study.

NOTE: The term ‘life-threatening’ refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgement should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as an SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.4.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Sponsor:

Keyvan Karkouti MD

Department of Anesthesia
Toronto General Hospital
200 Elizabeth Street, 3EN
Toronto, ON
M5G 2C4
Canada

Phone: 1-416-340-5164
Fax: 1-416-340-3698

Email: keyvan.karkouti@uhn.ca

In addition, within 24 hours after recognition of the event, a Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

Fax: +43 1 61032-9949

Email: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

Waivers from the SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.4.5 Other Relevant Safety Information

Pregnancies

Patients who are known to be pregnant will not be included in the study. In patients of reproductive age, pregnancy is ruled out prior to the cardiac surgery as part of standard of care.

Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as an SAE.

a) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

b) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

c) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the electronic CRF (eCRF) must be supported by source data in the patient records, with exceptions listed in **Section 8.1.2**.

The Investigator will permit study-related monitoring, audit(s), REB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (e.g., sub-investigators, clinical research coordinators/assistants, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms

Study site staff (e.g., blood bank technologist, research coordinator/assistant) will be responsible for completing a CRF for each patient enrolled. All site personnel will be trained on CRF completion. The site is also provided with the approved CRF Completion Guidelines which will assist in data entry and data issues/questions. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or to change CRF data must be listed in the Delegation of Authority Log.

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An Investigator's Brochure (IB) will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of *Octafibrin*.

The IB will be updated at regular intervals by Octapharma and whenever relevant new information concerning the IMP becomes available. This will be delivered by Octapharma to the Principal Investigator who will distribute to the approved study sites.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing CRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

At each study site the Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the site investigators will supply the Sponsor or designate, such as the monitors with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Safety Monitoring Committee

An IDSMC will be established by the Sponsor. The IDSMC will be composed of recognized experts in the field of statistics, perioperative medicine, and hematology who are not actively recruiting patients.

The IDSMC will review relevant data periodically (approximately after every 100 patients have been recruited) during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific charter will define in detail the composition, responsibilities, and procedures of the IDSMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external statistician. The principal statistical methodology is described in this section. Further specifics regarding the statistical analysis will be provided in the Statistical Analysis Plan (SAP).

9.1 Determination of Sample Size

The statistical analysis of the primary efficacy variable, i.e., the amount of ABPs, will be based on the mean number of ABP units within the first 24 hours after termination of CPB (μ_F and μ_C).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to the treatment with cryoprecipitate with respect to the mean number of ABP units, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \mu_F / \mu_C \geq (1 + \delta) \quad \text{vs.} \quad H_1: \mu_F / \mu_C < (1 + \delta)$$

will be carried out with a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_C denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term), with treatment group as main effect.

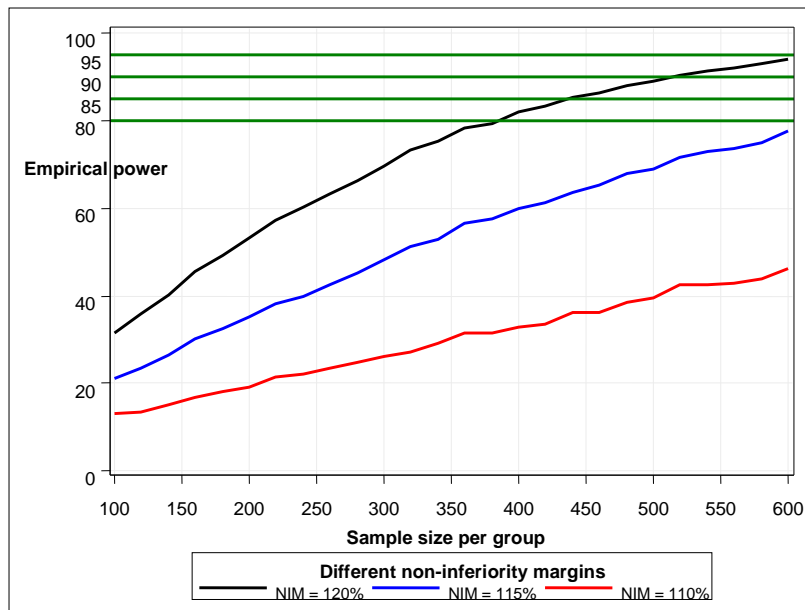
The test of the primary hypothesis in the planned interim and the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_C derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

Based on this method, a one-sided overall type I error probability $\alpha = 0.025$ and a non-inferiority margin of $\delta = 0.20$, simulations have been performed to study the power of the test for different sample sizes.

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units. The empirical distribution function with these sample characteristics was chosen based on results of the TACS study (see **Section 1.1**) with the same endpoint in the same indication and similar treatment.

10,000 studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

The plot below displays the empirical power curves for the test of H_0 vs. H_1 using the Poisson counting regression model analyzed with SAS PROC GENMOD for different sample sizes and values of δ .



As the diagram shows, an empirical power of >90% can be expected with a sample size of at least 550 patients per treatment group if a δ of 0.20 is chosen. For smaller values of δ , no sufficient power can be attained with operationally feasible sample sizes. The choice of the non-inferiority margin $\delta = 0.20$ is also motivated by the large variation of the primary endpoint that is to be expected from previous studies reflecting current clinical practice.

Therefore, it is planned to conduct the study with a maximum sample size of 600 patients in each treatment group and a non-inferiority margin of $\delta = 0.20$.

Assuming that a proportion of about 10% randomized patients will not be treated after randomization or for whom the endpoint cannot be obtained, this would ensure that data on at least 550 patients per treatment group in the ITT population will be available for the statistical analysis as derived from the sample size calculation.

9.2 Statistical Analysis

For the statistical analysis of the efficacy parameters the following analysis populations will be considered:

The ITT population: All randomized patients who agree to remain in the study after debriefing. In the event that a patient receives treatment that is not in concordance with the randomization schedule, the treatment group will be defined according to the randomization (rather than the actual treatment received).

If no randomization errors are observed the ITT population will be identical to the safety analysis population (SAF), which will be all randomized patients who opted to remain in the study and who received at least one dose of IMP.

The per-protocol (PP) population: This analysis population will consist of all patients in the ITT population, excluding patients with major protocol deviations. The following patients will be excluded:

- Patients who do not receive an IMP after randomization

- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 80% of the planned dose
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meeting prior to unblinding for the interim and final analyses. Decisions and outcome will be approved by the Principal Investigator (Sponsor) in consultation with the collaborator (Octapharma).

The ITT analysis population is considered the primary population for analysis of the primary efficacy objective. The evaluation of the primary efficacy endpoint will additionally be performed for the PP population.

9.2.1 Efficacy Analysis Plan

Primary endpoint: total amount of ABP units

The primary efficacy variable is the total number of ABP units (RBCs, pooled and apheresis platelets and plasma) used within 24 hours after termination of CPB.

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses:

$$\begin{aligned} H_0: & \quad \mu_F / \mu_c \geq (1 + \delta) \text{ (inferiority)} \\ \text{vs. } H_1: & \quad \mu_F / \mu_c < (1 + \delta) \text{ (non-inferiority)} \end{aligned}$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect.

The test of the primary hypothesis in the final analysis will be based on the one-sided CI for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the ITT population. A secondary analysis will be performed for the PP population.

Only in case of demonstrated non-inferiority in the ITT and the PP population subsequently the pair of hypotheses:

$$\begin{aligned} H'_0: & \quad \mu_F / \mu_c \geq 1 \\ \text{vs. } H'_1: & \quad \mu_F / \mu_c < 1 \end{aligned}$$

will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary.

Secondary endpoints

The following measurements will be considered exploratory secondary endpoints in the analysis of efficacy of the study treatments:

- Total number of units of ABPs administered from start of cardiac surgery until 7 days after surgery or discharge.
- Distribution of major bleeding type, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery.
- Change in fibrinogen plasma level (measured using the Clauss assay) within 1 hour before and 1 hour after fibrinogen supplementation for first and subsequent doses.
- Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets and plasma.
- Primary analysis of secondary endpoints will be based on the ITT population. Additionally, the same analyses will be done on the PP population.
- The total number of ABPs within 7 days/discharge and the different subtypes of ABPs will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.
- Frequency distributions of the major bleeding type according to UDPB will be presented for each treatment group.
- Change in fibrinogen plasma level will be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the *Octafibrin* and cryoprecipitate treatment groups and the corresponding 95% CI will be calculated.

Further exploratory endpoints

Exploratory analyses will include comparisons of length of hospital stay, ICU stay, and ventilation time.

Data collected as part of this study will be used for an economic analysis to be conducted at a later date.

Subgroup analyses for efficacy

The following subgroups will be analyzed: non-elective surgery; complex surgery (procedures other than isolated ACB, single valve, or repair of ASD).

9.2.2 Safety Analysis Plan

The safety analysis population (SAF) will include all patients who receive at least one dose of the IMP (if no randomization errors occur, this will be the same population as the ITT population). Safety outcomes will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

Adverse events, including thromboembolic events

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version as specified in the Data Management Plan. The analysis will focus on treatment emergent adverse events (TEAEs), i.e., AEs that started or worsened after start of infusion with IMP.

All TEAEs, related TEAEs (i.e., AEs probably or possibly related to the IMP), and serious TEAEs will be summarized and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in withdrawal from the study, respectively, will be tabulated using frequency tables if a reasonable number of events of this type are observed.

Analogous frequency tables for thromboembolic events (TEEs, identified using MedDRA SMQs) will be provided.

Patient listings will be provided for patients with SAEs, TEEs, AEs leading to withdrawal from study, and AEs leading to death. These listings will also include patients enrolled but not randomized.

Mortality

The number of patients who died will be summarized. A possible difference between treatment groups will be estimated by a risk ratio with 95% CI. Kaplan-Meier estimates for the time to death distribution will be calculated and graphically presented.

Routine laboratory data

All laboratory values will be classified as normal or abnormal according to the laboratories' normal 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
- Qualitative data based on reference ranges will be described according to the categories (i.e., low, normal, high)
- Shift tables illustrating changes with respect to the laboratories' normal ranges between baseline and a defined scheduled time point
- Number and frequency of patients with clinically significant laboratory values. A separate patient listing will be provided

9.2.3 Handling of Missing Data

In general, missing data will not be imputed. Due to the nature of the study, important variables will have few missing data.

9.3 Randomization, Stratification, and Code Release

Eligible patients will be randomly assigned to receive either *Octafibrin* or cryoprecipitate. Randomization lists using a permuted-block, randomization scheme (stratified by site) will be prepared by the biostatistician and integrated in to the eCRF system. The randomization lists will then be provided to the blood banks of the participating centers who will be in charge of providing the IMP to the OR.

Patients will be identified using a sequential numbering system.

9.4 Interim Analysis

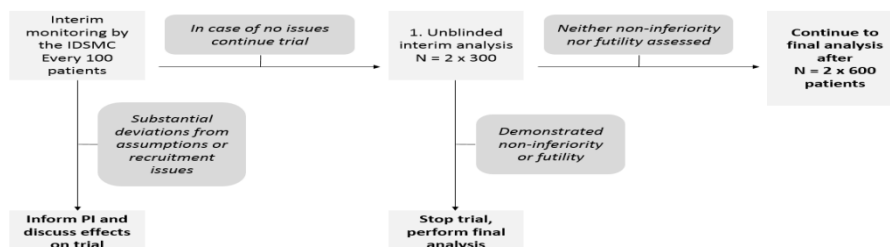
The study employs a group-sequential design that involves one pre-planned interim analysis after 600 patients have completed the study.

In addition, the IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study. This data monitoring serves the purpose of an ongoing assessment of recruitment problems as well as the compatibility of the accumulating data with the assumptions made at study start. The extent of the information to be reviewed will be defined in the IDSMC charter. The IDSMC will keep all these data monitoring results in strict confidence. Only in case of identified issues during their data monitoring the IDSMC will advise the Principal Investigator (Sponsor) in a non-treatment-disclosing manner on the problems.

The interim analysis will be an unblinded interim analysis with an adjusted type I error rate according to the O'Brien-Fleming method after 600 patients have been enrolled. After this interim analysis, a positive outcome may be claimed and enrolment may be stopped if the test of H_0 vs. H_1 in the ITT population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$ rejects the null hypothesis (efficacy stop). A full final analysis including all study data will be performed and reported if enrolment is stopped after the interim analysis. Also at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

Otherwise, the study will continue until the maximum sample size of $n = 2 \times 600$ patients, is reached. The final analysis will be performed as described above, but with an adjusted one-sided significance level of $\alpha_2 = 0.02242$ to maintain the overall one-sided significance level of $\alpha = 0.025$.

The flow chart below illustrates the decision process underlying the interim analyses. Further details of the interim analyses will be described in the respective sections of the SAP.



10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an REB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO).

10.2 Approval of Study Documents

The study protocol, a sample of the debriefing form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate REB and the Regulatory Authority. The study must be approved by the REB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Waiver of Consent

This is a pragmatic trial that compares two fibrinogen replacement sources that are currently within the standard-of-care for this procedure, is unlikely to pose additional risks to patients, and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (i.e., bleeding during or after 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. In addition, this complication occurs infrequently and cannot be predicted before surgery. Thus, while it is technically possible to obtain informed consent before all surgeries, it is simply ‘impracticable’ to do so for this specific study, thereby rendering such a study simply unfeasible.

Importantly, the study compares two substitutable therapies that are used as part of routine clinical care, and there is no compelling theoretical basis or any types of data that patients would be placed at risk by participating in the study. The results of this study, on the other hand, would have important societal benefits, as it will help the Canadian Blood Services to determine which of the two products should be supplied in the future. If fibrinogen concentrate is proven to be non-inferior, it will likely be the treatment of choice because it has a lower theoretical risk of viral transmission, improves the efficiency of the blood system (for every unit of cryoprecipitate produced, one unit of platelets, which is often in short supply, is diverted from the blood supply), and allows for more rapid, targeted therapy of bleeding.

The study meets the criteria stated in Article 3.7A of the 2014 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans for identifying situations in which exceptions may be sought for the requirement to seek prior consent.

We will obtain consent from the patient or a surrogate decision maker as soon as possible after randomization for collection and analysis of patient data. The Investigator (or delegate as appropriate) will obtain freely given written consent from each patient (or surrogate) after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the decision to continue to participate. The informed consent form must be signed, with name and date and time noted by the patient (or surrogate), before the patient is exposed to any further study-related procedures, namely evaluation and data collection.

The Investigator (or delegate) will explain that the patients are completely free to withdraw from the study at any time, without any consequences for their further care and without the need to justify. Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any amendments will be submitted to the competent REB and any authority as required by applicable regulations.

REB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective or design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor or REB and regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been captured.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines) will be prepared by the Sponsor after completion of the study. The Coordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study will be published and may be presented at scientific meetings.

In accordance with standard editorial and ethical practice, the Investigator will publish the multi-center data only in their entirety and not as individual center data. Authorship will be determined by mutual agreement. Any subsequent publications based on subsets of the data will require approval from the Sponsor.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Investigators and or their institutions will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

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15 APPENDICES

Not applicable.

CLINICAL STUDY PROTOCOL

FIBRES

FIBrinogen REplenishment in Surgery

Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients

Investigational Product:	<i>Octafibrin</i>
Indication:	Acquired fibrinogen deficiency
Study Design:	Prospective, multi-center, randomized, active-control, single-blinded non-inferiority study
Sponsor:	Keyvan Karkouti
Study Number:	FIBRES (FORMA-06)
Clinicaltrials.gov Registration	NCT03037424
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 4 2016
Planned Clinical End:	Quarter 4 2018
Date of Original Protocol:	24-Nov-2016 V1.1
Date of Amendment:	03-July-2018 V2.4
Coordinating Investigator:	Keyvan Karkouti MD Department of Anesthesia Toronto General Hospital 200 Elizabeth Street, 3EN Toronto, ON M5G 2C4 Canada

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FIBRES Protocol 2.4_Clean_03-July-2018

STUDY OUTLINE

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
Name of Investigational Product: <i>Octafibrin</i>	Protocol Identification Code: (FORMA-06)
Name of Active Ingredient: Human fibrinogen	Date of Final Protocol: 03-July-2018 V2.4

Title of Study: Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients
Indication: Acquired fibrinogen deficiency
Number of Study Centre(s): Up to 12 Canadian hospitals
Objectives: Primary Objective: The primary objective of this study is to demonstrate that the fibrinogen concentrate <i>Octafibrin</i> is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products (ABPs) administered during the first 24 hours after termination of cardiopulmonary bypass (CPB). Secondary Objectives: The secondary objectives include: <ul style="list-style-type: none">• Comparison of efficacy as measured by the total and individual number of ABPs transfused from the beginning of surgery up to postoperative day 7• Comparison of the amount of bleeding during the first 24 hours after termination of CPB• Comparison of the effect on fibrinogen levels observed before and after the first dose of fibrinogen supplementation

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
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- Comparison of safety as measured by adverse events (AE) and serious adverse events (SAEs) during the first 28 days after termination of CPB
- Comparison of other secondary safety endpoints including, duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalization.

Study Design:

This is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require up to 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank receives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB). No other aspects of care will be modified.

The primary efficacy outcome will be the number of ABPs (red blood cells [RBCs], pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB. Safety outcomes will be measured for the first 28 days after surgery, which is the duration of participation of each patient in the trial. Comparisons will be by modified intention-to-treat (mITT) (primary) and per-protocol (PP) analysis. One interim analysis will be conducted after 600 patients have been enrolled to determine whether the study should be terminated for safety reasons, demonstrated non-inferiority or futility reasons.

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
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Number of Patients: Total = 1200; randomized to two arms.
<p>Patient Selection Criteria:</p> <p>Inclusion Criteria: Patients undergoing index cardiac surgery with CPB in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).</p> <p>Exclusion Criteria: Patients who meet any of the following criteria are <i>not</i> eligible for the study:</p> <ol style="list-style-type: none"> 1. Receipt of fibrinogen-rich products (fibrinogen concentrate or cryoprecipitate) within 24 hours before surgery 2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate 3. Refusal of ABPs, fibrinogen concentrate or cryoprecipitate due to religious or other reasons 4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation) 5. Known pregnancy
<p>Test Product, Dose, and Mode of Administration:</p> <p><i>Octafibrin</i> and cryoprecipitate will be administered intravenously. Patients randomized to <i>Octafibrin</i> will receive 4 g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB. Patients randomized to cryoprecipitate will receive 10 units each time fibrinogen supplementation is ordered during the first 24 hours after the termination of CPB.</p>
<p>Duration of Treatment:</p> <p>The first 24 hours after termination of CPB.</p>

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint

The primary endpoint, which is of efficacy, is the comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.

Secondary efficacy endpoints

- Comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.
- Comparison of major bleeding, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] during the first 24 hours after termination of CPB.
- Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) before and after the first dose of fibrinogen supplementation.

Secondary safety endpoints:

- Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, will be compared between the groups up to postoperative day 28.
- Other secondary safety endpoints that will also be compared between groups are:
 - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
 - Duration of intensive care unit (ICU) stay up to postoperative day 28
 - Duration of hospitalization up to postoperative day 28

Study Procedures:

First fibrinogen supplementation order from the surgical team received at the blood bank

The blood bank technologist confirms eligibility with the clinical team and will then randomize patients to fibrinogen or cryoprecipitate according to the randomization schedule and prepares and releases the product

Visit 1: First post-randomization visit (0 to 24 hours after termination of CPB)

Obtain consent from patient or surrogate
Collect baseline and surgical data
Collect laboratory, transfusion and bleeding data
Collect extubation time and LOS in the ICU
Collect concomitant medications
Collect AEs and SAEs

Visit 2: Postoperative day 7 (or at discharge if earlier)

Obtain consent from patient or surrogate (if not already done)
Collect laboratory and transfusion data
Collect extubation time, LOS in the ICU and hospital (if applicable)
Collect AEs and SAEs

Visit 3: Postoperative day 28 (in person if in hospital or by phone)

Obtain consent from patient or surrogate (if not already done)
Collect AEs and SAEs
Collect extubation time, LOS in the ICU, LOS in the hospital

Statistical Analysis Plan:

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses: $H_0: \mu_F / \mu_c \geq (1 + \delta)$ (inferiority) vs. $H_1: \mu_F / \mu_c < (1 + \delta)$ (non-inferiority) will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$ (μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively). Testing of the hypothesis in the final analysis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect. The test of the primary hypothesis in the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the modified intention to treat (mITT) population, which will include all randomized patients who agree to remain in the study after debriefing. Randomized patients who did not undergo cardiac surgery or received no IMP will be excluded from the analysis.

A secondary analysis will be performed for the PP population, which will exclude all patients with major deviations. Only in case of demonstrated non-inferiority in the mITT and the PP population subsequently the pair of hypotheses: $H'_0: \mu_F / \mu_c \geq 1$ vs. $H'_1: \mu_F / \mu_c < 1$ will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated

previously, no adjustment of type I error is necessary.

The safety analysis population (SAF) will include all patients who opted to remain in the study and received at least one dose of the IMP. Safety outcomes will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

FLOW CHART OF ASSESSMENTS

Table 1 Flow Chart of Assessments Performed Throughout the Study

Procedures	Prior to enrollment	Visit 1 Post-randomization (0 to 24 h)*	Visit 2 POD7/DC	Visit 3 POD28
Blood bank receives fibrinogen order ^a	x	(x) ^d		
Inclusion and exclusion criteria	x			
Randomization	x			
IMP administration ^b		x		
Patient (surrogate) debriefing and consent		x	(x)	(x)
Baseline data				
Demographics		x		
Medical history		x		
Preoperative medications		x		
Surgical data				
Intraoperative medications		x		
CPB time		x		
Cross-clamp time		x		
Circulatory arrest		x		
Vital signs		x		
Fluid in- and output monitoring		x		
Inotropes and vasopressors		x		
Laboratory assessments				
Chemistry ^f		x	x	
Hematology ^f		x	x	
Coagulation profile ^f		x ^c	x	
Safety labs ^f		x	x	
Transfusion requirements^e				
RBCs		x	x	
Pooled and apheresis Platelets		x	x	
Plasma		x	x	
Other hemostatic products		x	x	
Blood loss determination using UDPB		x	x	
Extubation time		x	(x)	(x)
ICU length of stay		x	(x)	(x)
Hospital length of stay			x	(x)
AEs and SAEs		x	x	x
Concomitant medications		x	x	x
Physical examination		x		

*For any activities not completed during this visit, additional visits will be undertaken to complete activities

^a After the start of surgery and during or after CPB.

^b IMP can be administered after termination of CPB based on the physician's judgement and/or fibrinogen levels. .

^c Before and after IMP administration.

^d Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

^e 24 hours after IMP administration


^f As per standard practice

() If needed

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol,
Good Clinical Practice and applicable regulatory requirements.

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July 13/18

Coordinating Investigator and Sponsor

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABP	Allogeneic Blood Product
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CREA	Serum Creatinine
CRF	Case Report Form
CRO	Contract Research Organisation
DDAVP	Desmopressin
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IABP	Intra-Aortic Balloon Pump
IB	Investigator's Brochure
ICU	Intensive Care Unit
IDSMC	Independent Data Safety Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
mITT	Modified Intention-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating Room
PCC	Prothrombin Complex Concentrate
POD	Postoperative Day
POD7/DC	Postoperative Day 7 or at Discharge
PP	Per-Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
REB	Research Ethics Board

SAE	Serious Adverse Event
SAF	Safety Analysis Population
SDM	Substitute Decision Maker
SDV	Source Data Verification
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Event
UDPB	Universal Definition of Perioperative Bleeding
WFI	Water for Injections
WNV	West Nile Virus

1 INTRODUCTION

1.1 Background

Human fibrinogen

Human fibrinogen is a plasma glycoprotein synthesized in the liver, and it circulates in the plasma at a concentration of 2.9–4.5 g/L. In healthy human adults, about 2–5 g of fibrinogen is synthesized daily, and the same amount is catabolized [2,3]. Fibrinogen is essential for primary and secondary hemostasis, wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen into fibrin, and often the interaction of fibrinogen with various proteins and cells. The plasma half-life of fibrinogen, under normal physiological conditions, has been estimated to be 3–5 days [4,5].

Acquired hypofibrinogenemia in cardiac surgery

Coagulopathy leading to excessive bleeding is a serious complication of cardiac surgery requiring cardiopulmonary bypass (CPB). Occurring in more than 10% of cases, it frequently necessitates the transfusion of large amounts of allogeneic blood products (ABPs) and is associated with an increased risk of adverse outcomes, such as multi-organ failure and death [6,7]. While the causes of coagulopathy are usually multifactorial, acute acquired hypofibrinogenemia – defined as an acute drop in fibrinogen plasma level – is believed to be the primary factor [8].

Fibrinogen is a critical component of the coagulation cascade as it is both a precursor for fibrin and a cofactor that enhances platelet aggregation [8,9,10,11]. Unlike other coagulation factors that have a large reserve margin [12], a modest drop in fibrinogen levels to <1.5–2.0 g/L impairs coagulation and increases bleeding complications [13,14,15,16,17,18,19,20,21].

Several factors predispose cardiac surgical patients to developing acquired hypofibrinogenemia. These include loss of fibrinogen due to surgical bleeding, dilution due to administration of fluids and CPB prime, and consumption due to activation of the coagulation cascade during CPB (despite anticoagulation with heparin) [21]. As a result, fibrinogen plasma level drops by an average of 40–50% during cardiac surgery [21], and the critical level of <1.5–2.0 g/L is reached in approximately 5% of patients [22]. It is in this group of patients that fibrinogen supplementation is crucial (and current standard of care) to prevent excessive hemorrhage, large-volume transfusion, and associated adverse outcomes [8,23].

Options available for fibrinogen supplementation

There are two primary options available for fibrinogen supplementation: cryoprecipitate and purified human-derived fibrinogen concentrate [8]. Cryoprecipitate is an ABP that is prepared by thawing fresh frozen plasma at 2 to 4° C, harvesting the resultant precipitate by centrifugation, and then re-freezing it at –20 °C.

Cryoprecipitate is currently the mainstay of therapy in North America, but it has several important limitations.

First, the amount of fibrinogen in each unit of cryoprecipitate is highly variable, ranging from 120 to 796 mg per unit [24], and the transfused fibrinogen is only about 50% recoverable [25,26]. As a result, the response

to cryoprecipitate is limited and variable, ranging from an increase of 0.05–0.1 g/L in fibrinogen levels per unit transfused [24]. To achieve adequate fibrinogen plasma level for hemostasis, therefore, cryoprecipitate is typically administered in 10 unit pools, which exposes patients to the risks of multiple allogeneic units.

Second, thawing, reconstituting in plasma, and pooling of cryoprecipitate is time consuming and labor intensive, which precludes rapid therapy.

Third, cryoprecipitate is not a purified product and contains large amounts of contaminants such as fibronectin and platelet microparticles [24]. These contaminants are not benign and may cause adverse outcomes such as microvascular thrombosis and organ dysfunction [24,27]. In one observational study, cryoprecipitate was independently associated with a two-fold increase in the risk of death, which was larger than the risk associated with any other blood products [28].

Since cryoprecipitate is not purified, it also contains other pro-hemostatic factors in addition to fibrinogen, including coagulation factor VIII, von Willebrand factor, and coagulation factor XIII, which may be beneficial if the cause of bleeding is multifactorial and not solely due to fibrinogen deficiency [8,24]. This theoretical benefit, however, is not supported by existing data, which is not surprising given that these factors do not usually drop below critical levels during cardiac surgery unless there is massive bleeding, in which case patients would receive plasma transfusions that would contain these factors [21,29,30].

The second option for fibrinogen supplementation is to administer **purified human-derived fibrinogen concentrate**, which is currently the mainstay of therapy for acquired hypofibrinogenemia in much of Europe. In North America, however, this therapy is only approved for the treatment of *congenital* hypofibrinogenemia, and its use for acquired hypofibrinogenemia is currently off-label and therefore not widespread.

The fibrinogen concentrate that will be used for this study, *Octafibrin*, is similar to cryoprecipitate in that it is derived from human plasma, but it has several important advantages [31].

First, it undergoes several virus removal and inactivation steps (nanofiltration [20 nm filter] and solvent detergent treatment), which remove contaminants and inactivate viruses. Thus, it is likely to have a lower risk of transmission of infectious agents. Indeed, a Canadian consensus statement from 2008 recommends adoption of pathogen inactivation strategies once they become available to reduce the risk of transfusion transmissible diseases [32].

Second, it is a highly purified concentrate, containing a consistent amount of fibrinogen (approximately 1 g per vial), and the response to therapy is potentially more predictable and more robust than for cryoprecipitate [33,34,35,36].

Third, since (unlike cryoprecipitate) the product can be administered immediately after it is reconstituted with sterile water, it allows for rapid fibrinogen supplementation.

Review of the literature

The use of cryoprecipitate and fibrinogen concentrate in congenital hypofibrinogenemia is supported by several small, non-controlled studies [37,38,39]. Both therapies have also been shown to successfully increase fibrinogen levels and improve clot formation in various in vitro and in vivo models of fibrinogen deficiency [11,40,41,42,43,44,45]. There are also several observational studies showing improved outcomes when fibrinogen supplementation is used in bleeding patients with acquired hypofibrinogenemia, but the bulk of these studies only examined fibrinogen concentrate [46,47,48,49,50,51,52,53,54,55].

There are several studies that have explored the efficacy of fibrinogen concentrate as a ‘universal’ hemostatic agent i.e., not targeted specifically for patients with acquired hypofibrinogenemia – in cardiac and other types of surgery. While several early-stage trials were mostly positive [56,57,58,59,60,61,62,63], a

Cochrane review found that they were inconclusive [64,65]. In a recently completed randomized multi-centered trial, fibrinogen supplementation as first-line therapy in bleeding adult cardiac surgical patients was not efficacious, but this study had multiple limitations. It used fibrinogen supplementation as part of a rigid treatment algorithm that was not consistent with current best-practice, used fibrinogen concentrate as a universal hemostatic agent irrespective of other coagulation defects, and had several design flaws with very high post-randomization drop-outs and transfusion protocol violations [66].

Overall, therefore, the well-established practice of fibrinogen supplementation in bleeding patients with acquired hypofibrinogenemia is primarily based on mechanistic principles rather than high-grade clinical evidence. Yet, this practice is so entrenched that it is uniformly endorsed by existing guidelines [25,67,68,69,70,71,72,73,74], and most would agree that it is neither clinically nor ethically appropriate to withhold fibrinogen supplementation from bleeding patients with confirmed or presumed (in cases of severe bleeding) acquired hypofibrinogenemia [75], thus precluding the conduct of placebo-controlled trials.

To determine the most appropriate fibrinogen supplementation therapy, comparative randomized trials between cryoprecipitate and fibrinogen concentrate are needed, but there is a dearth of such trials. One experimental study found that cryoprecipitate and fibrinogen concentrate have similar abilities in correcting clot firmness in an in vitro model of hemodilution [40]. Two small retrospective observational studies found that fibrinogen concentrate results in a generally more robust fibrinogen response than cryoprecipitate in various groups of patients with acquired hypofibrinogenemia, but these studies were not equipped to compare the safety and effectiveness of the two therapies [33,34]. One randomized comparative clinical trial that included 63 children (<7 years old) who were bleeding after cardiac surgery and had a fibrinogen level of <1.0 g/L found no differences between fibrinogen concentrate and cryoprecipitate in terms of efficacy and safety, but this study was in a pediatric population and was underpowered to prove non-inferiority [76].

Propensity-score matching and TACS study

As background work for the proposed trial, a retrospective comparison of fibrinogen concentrate versus cryoprecipitate was performed at Toronto General Hospital after a point-of-care-based transfusion algorithm for guiding coagulation management in bleeding cardiac surgical patients had been instituted in January 2013 [77].

For the treatment of acquired hypofibrinogenemia, cryoprecipitate was used during the first 11 months after the algorithm was introduced (n=51), and fibrinogen concentrate was used thereafter (n=99), resulting in a homogeneous cohort of patients allowing comparison of the two therapies using propensity-score matching. Despite the low power of the study, the results do suggest that the two therapies have similar risk-benefit profiles. These results have helped inform the appropriate outcome and the required sample size for the randomized trial presented in this protocol (

Table 2 and Table 3).

Table 2 Transfusion data in propensity-score matched patients

Variables	Cryoprecipitate (n=43)	Fibrinogen concentrate (n=43)	p value
RBC transfusion			
n (%)	39 (91%)	34 (79%)	0.2
Units	6 (2–12)	4 (1–12)	0.2
Plasma transfusion			
n (%)	36 (84%)	30 (70%)	0.2
Units	4 (2–8)	4 (0–8)	0.2
Platelet transfusion			
n (%)	42 (98%)	35 (81%)	0.03
Pools	3 (1–5)	2 (1–4)	0.04
Total allogeneic units*	12 (7–27)	10 (4–21)	0.15
Severe/Massive bleeding**	30 (70%)	27 (63%)	0.5

*Number of transfused units of red blood cells (RBCs) + units of plasma + pools of platelets

**According to the universal definition of perioperative bleeding in cardiac surgery (occurrence of any of the following: 24-hour chest tube drainage >1L; RBC transfusion ≥5 units; plasma transfusion ≥5 units; rescue therapy with recombinant activated factor VII; or surgical re-exploration) [1]

Table 3 Adverse outcome data in propensity-score matched patients

Variables	Cryo- precipitate	Fibrinogen concentrate	p value
Acute kidney injury*	13 (30%)	10 (23%)	0.6
Hepatic dysfunction**	9 (21%)	5 (12%)	0.4
Stroke	3 (7%)	1 (2%)	0.6
Deep vein thrombosis and pulmonary embolism	0	0	–
Myocardial infarction	3 (7%)	1 (2%)	0.6
Death	9 (21%)	7 (16%)	0.8
Composite***	19 (44%)	12 (28%)	0.17

*>40% drop in estimated glomerular rate within one week of surgery [78]

**Alanine aminotransferase >150 U/L within one week of surgery [79]

***One or more of the listed complications

Further preliminary data was obtained from a recently completed multi-center trial (funded by the Canadian Institutes of Health Research) that assessed the effectiveness of a point-of-care coagulation management algorithm at 12 Canadian hospitals and included 7404 patients (TACS study; Circulation; In Press; Clinical-Trials.gov ID NCT02200419). During the 7-month trial, 447 (6%) patients received cryoprecipitate (n=394) or fibrinogen concentrate (n=61). Transfusion rates and adverse outcomes in these patients (

Table 4) were similar to those in the propensity-matched single-center study described above.

Table 4 Outcomes of TACS study patients who received cryoprecipitate (n=394) or fibrinogen concentrate (n=61)

Variables	Received cryoprecipitate or fibrinogen concentrate (n=447/7404)
RBC transfusion	382 (85%)
Plasma transfusion	368 (82%)
Platelet transfusion	388 (87%)
Total allogeneic units	13 (7–23)
Severe/Massive bleeding	344 (77%)
Adverse outcome data	
Acute kidney injury	113 (26%)
Stroke	23 (5%)
Myocardial infarction	5 (1%)
Death	54 (12%)
Composite*	145 (32%)

*One or more of the listed complications

1.2 Rationale for Conducting the Study

The purpose of this study is to determine whether the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate with respect to efficacy when used to treat bleeding in cardiac surgical patients with acquired hypofibrinogenemia. Hemostatic management in bleeding surgical patients is evolving from empirical therapy with non-purified ABPs to targeted therapy with purified products [80]. The proposed study, by comparing two currently available but distinctly different therapies for treating acute acquired hypofibrinogenemia in bleeding surgical patients, non-purified cryoprecipitate versus purified human-derived fibrinogen concentrate, is well aligned with this change. Given the practical and theoretical advantages of purified fibrinogen concentrate over cryoprecipitate detailed above (improved safety, ease of administration, predictable and robust effect on fibrinogen plasma levels), we believe that a finding of non-inferiority will lead to the use of purified fibrinogen concentrate in place of cryoprecipitate in clinical practice.

This study uses a pragmatic approach for data collection leaving the surgical team to maintain the standard of care accepted by their institution. This is important since other multi-center studies that have included a very strict design so far have failed when studied in later phase trials because of the inability of the sites to accurately follow the specified design, which itself has been criticized for not being consistent with usual clinical practice.

1.3 Benefit-Risk Statement

Substituting either fibrinogen concentrate or cryoprecipitate for the other is not expected to pose any material risks to the participants. Patients will only be included in the trial when their clinicians have ordered fibrinogen supplementation for treatment of bleeding that is thought to be due to acquired hypofibrinogenemia. Thus, no patient will receive fibrinogen supplementation solely for the purposes of this study.

Octafibrin, the fibrinogen concentrate to be used in this study, is under development for the treatment of congenital afibrinogenemia and hypofibrinogenemia. *Octafibrin* has been shown to have comparable (and in some instances superior) pharmacokinetics, hemostatic effects, and safety profile to *Riastap* (CSL Behring), which is an approved (by Health Canada and FDA) purified human-derived fibrinogen concentrate. Ongoing studies looking at the treatment of bleeding and surgery in patients with congenital fibrinogen deficiency, have shown excellent efficacy and safety profile so far. *Octafibrin* has been submitted to EU, USA, and Canada for licensing approval in the indication named above.

The experience to date with this concentrate has shown an excellent safety profile that is in all likelihood superior to that of cryoprecipitate [8,75]. As discussed, fibrinogen concentrate is pathogen inactivated and can be administered in predictable doses, making its administration likely to be both safer than, and at least as efficacious as, cryoprecipitate.

1.4 Principal Investigator and Sponsor

The Sponsor and Coordinating Investigator of this study is Keyvan Karkouti MD at the Department of Anesthesia, Toronto General Hospital, 200 Elizabeth Street, 3EN, Toronto, ON, Canada.

Octapharma AG will support the conduct of this study by awarding an unrestricted grant for study conduct and supporting data management, statistical services, and supplying the fibrinogen concentrate.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate that the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of ABPs administered during the first 24 hours after termination of CPB.

2.2 Secondary Objectives

The secondary objectives include:

- Comparison of efficacy as measured by the total and individual number of ABPs transfused from the beginning of surgery up to postoperative day 7
- Comparison of the amount of bleeding during the first 24 hours after termination of CPB
- Comparison of the effect on fibrinogen levels observed before and after the first dose of fibrinogen supplementation
- Comparison of safety as measured by adverse events (AEs) and serious adverse events (SAEs) during the first 28 days after termination of CPB
- Comparison of other secondary safety endpoints including, duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalization.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary endpoint, which is of efficacy, is the comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.

3.1.2 Secondary Endpoints

Secondary efficacy endpoints

- Comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.
- Comparison of major bleeding, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] (**Section 7.2.3**) during the first 24 hours after termination of CPB.
- Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) before and after the end of the first dose of fibrinogen supplementation.

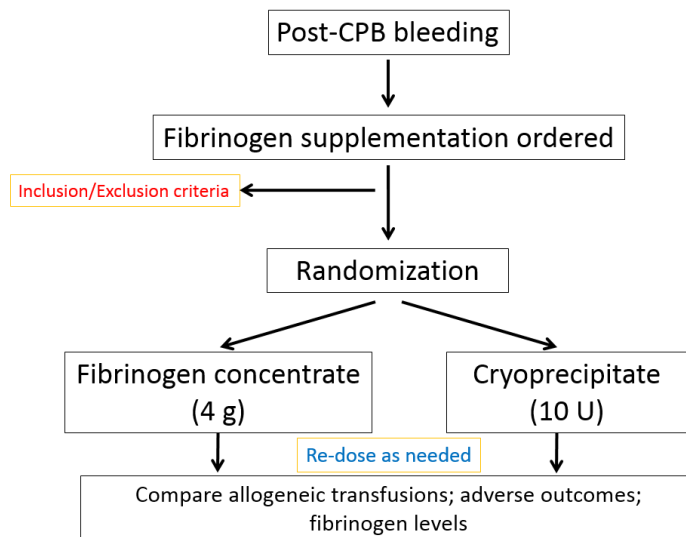
Secondary safety endpoints

- Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, will be compared between the groups up to postoperative day 28.
- Other secondary safety endpoints that will also be compared between groups are:
 - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
 - Duration of intensive care unit (ICU) stay up to postoperative day 28
 - Duration of hospitalization up to postoperative day 28

3.2 Overall Study Design and Plan

This is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require approximately 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank re-



ceives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB) [see flowchart below].

The primary efficacy outcome will be the number of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB, with the primary comparisons being by modified intention-to-treat (mITT; see Section 9.2).

Safety outcomes will be measured for the first 28 days, which is the duration of participation of each patient in the trial. One interim analysis will be conducted after 600 patients have been enrolled to determine whether the study should be terminated for safety, demonstrated non-inferiority or futility reasons.

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Non-inferiority Design

A non-inferiority rather than superiority design was selected because both products are used to supplement fibrinogen in acquired hypofibrinogenemia. However, purified fibrinogen concentrate has important advantages over cryoprecipitate (it is faster to prepare, easier to administer, has a more predictable response and a better safety profile) that would make it the preferred option if it was found to be non-inferior to cryoprecipitate [81].

3.3.2 Choice of Primary Endpoint

The primary efficacy endpoint is the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the 24 hours after termination of CPB. This is a clinically relevant outcome that has been used in previous randomized fibrinogen trials [57]. Moreover, it is a primary outcome that has been accepted by the European Medicines Agency (EMA) for a major multi-center clinical study (ClinicalTrials.gov Identifier: NCT01475669).

3.3.3 Major Bleeding as Secondary Endpoint

Major bleeding after the index surgery based on the UDPB in cardiac surgery is a secondary outcome [1]. This is a validated, prognostically important clinical outcome in cardiac surgery [1,82]. Kinnunen et al. found that patients with major bleeding according to this definition had a greater than four-fold increase in the risk-adjusted odds of death compared with all other patients [82]. In our preliminary data, major bleeding as per the UDPB definition was associated with a 31-fold increase in the risk-adjusted odds of death compared to those with insignificant bleeding. In terms of prognostic value, major bleeding was the second most prognostically important variable (superseded only by renal failure) in a model that included all SAEs.

3.3.4 Dose Rationale

Each time fibrinogen supplementation is ordered, patients will receive either cryoprecipitate (1 dose = 10 units = approximately 4 g) or purified fibrinogen concentrate (1 dose = 4 g) according to their group assignment.

The amount of fibrinogen in each unit of cryoprecipitate is estimated to be approximately 400 mg [24]. Thus, 4 g of fibrinogen concentrate will be dose-equivalent to 10 units of cryoprecipitate, which is the current recommended dose for fibrinogen supplementation in the setting of acute bleeding [81].

3.3.5 Choice of Comparator

The trial will not include a placebo arm because delaying fibrinogen supplementation in bleeding patients with acquired hypofibrinogenemia would expose them to the negative consequences of excessive blood loss, is not consistent with standard practice [83,84], and would withhold an effective treatment from patients and thus be unethical. Moreover, the question being addressed does not meet any of Freedman's five conditions that would justify the use of a placebo control, which are: 1) no standard treatment exists; 2) standard treatment is not better than placebo; 3) standard treatment is a placebo or no treatment; 4) new evidence has shown uncertainty of the risk-benefit profile of the standard treatment; and 5) effective treatment is not readily available due to cost or supply issues [84,85].

3.3.6 External Validity

This will be a multi-center study performed in up to 12 hospitals with different characteristics. Moreover, patients will be recruited and randomized after the clinical team orders fibrinogen supplementation and the only change to routine practice is the choice of fibrinogen supplementation; thus, patient management in the control arm will reflect current practice and in the intervention arm will reflect how fibrinogen concentrate will be used in practice. For these reasons, the study will have good external validity.

3.3.7 Randomization and Baseline Differences

Given the large size of the study and random patient assignment stratified by center, study groups should be well balanced with respect to important clinical variables. The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial, and neither the individual randomizing nor any of the health care providers will know which treatment will be assigned to the patient when fibrinogen supplementation is ordered.

3.3.8 Recruitment and Informed Consent

This is a pragmatic trial that compares two fibrinogen replacement sources that are currently within the standard-of-care for this procedure and poses no additional risks to patients and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (i.e., bleeding during or after 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 waiver of informed consent before randomization. However, we will obtain consent from patients or their surrogate after surgery. This consent process meets the criteria of the Tri-council policy statement for the ethical conduct for research involving humans, as is outlined in **Section 10.3**.

3.3.9 Blinding of Investigational Medicinal Product (IMP)

Given that the products have quite different physical differences, it is not possible to blind treating clinicians to group assignment. To minimize bias, treating clinicians will be blinded to group assignment until after the product is prepared and released by the blood bank. Moreover, all attempts will be made to blind clinicians outside of the operating room and intensive care unit as well as outcome assessors to group assignment. One method will be to, where possible, use a generic product label in the patient chart and/or the electronic product name (i.e., study fibrinogen product 4 g, rather than specifying type of product used).

3.3.10 Drop-outs and Crossovers

Drop-outs: We anticipate that approximately 10-15% of randomized patients will either not receive the treatment, do not undergo cardiac surgery, or do not agree to remain in the study. The majority will be the former, in whom fibrinogen supplementation will be deemed to be not necessary after it was ordered but before it is administered due to cessation of bleeding or identification of other causes of bleeding. Study sample size has been calculated to compensate for drop-outs.

Product switching: Other than the fibrinogen supplementation order being cancelled, all patients will be treated according to the randomization schedule for the entire treatment period (24 hours after termination of CPB). To ensure minimal product switching, instructions will be entered into the blood bank information system to dictate the randomization product for the 24 hours after randomization and will flag the laboratory technologists if attempts are made to override the instruction. In very rare circumstances (e.g., after catastrophic bleeding during which several doses of fibrinogen supplementation have already been administered), clinicians may opt to switch from one therapy to the other during the treatment period. The reasons for this request will be collected and described. The anticipated number of product switches will be very few (<1%).

3.3.11 Outcome Assessments and Independent Data and Safety Monitoring Committee (IDSMC)

An IDSMC will review accumulating safety, endpoint, and other study data (recruitment, retention and compliance, data quality and timeliness, risk vs. benefit). The function of the IDSMC will be to protect and serve the recruited patients particularly pertaining to patient safety as well as to assist and advise the Sponsor on medical questions and issues of study conduct and continuation. The IDSMC will be independent of the investigating team and the Sponsor in operating and formulating recommendations. The IDSMC full role will be detailed in the IDSMC Charter.

4 STUDY POPULATION

4.1 Population Base

4.1.1 Approximately 1,200 bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be enrolled into the study, with approximately 600 patients assigned to each of the two treatment groups. Patients having other procedures in addition to cardiac surgery will be eligible as long as cardiac surgery with CPB is the index procedure, meaning the heart is the main organ being operated on, with a cardiac surgeon leading the operation. Inclusion Criteria

1. Patients undergoing index cardiac surgery with CPB in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).

4.1.2 Exclusion Criteria

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

1. Receipt of fibrinogen-rich products (fibrinogen concentrate or cryoprecipitate within 24 hours before surgery)
2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate
3. Refusal of ABP, fibrinogen concentrate or cryoprecipitate due to religious or other reasons
4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation)
5. Known pregnancy

4.2 Prior and Concomitant Therapy

Details on medications taken within 1 week before enrolment and any concomitant medications taken during the study must be recorded in the case report form (CRF).

4.2.1 Permitted Concomitant Therapy

Concomitant administration of any therapies required as part of standard patient care is permitted, but must be recorded in the CRFs. We will record all hemostatic drugs or products administered (e.g., heparin and protamine dose, antifibrinolytic drugs, desmopressin, recombinant activated factor VII, prothrombin complex concentrate, idarucizumab, andexanet alpha, or topical hemostatic agents), as well as all procedures that may influence amount of bleeding (e.g., retrograde autologous priming of CPB circuit, cell salvage).

In addition, concomitant medications used to treat SAEs will be reported throughout the duration of follow-up (up to postoperative day 28).

4.2.2 Forbidden Concomitant Therapy

Fibrinogen-rich products within 24 hours before surgery are not allowed. This specifically refers to cryoprecipitate or fibrinogen concentrate, not plasma. Patients undergoing plasmapheresis will be included, but the blood products used as part of the plasmapheresis will not be included in the transfusion outcomes.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients, but only in rare circumstances. Examples include randomization of ineligible patients, adverse events attributed to previous doses of IMP, and specific indication for a specific fibrinogen therapy (either cryoprecipitate or fibrinogen concentrate).

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

4.3.2 Patient Replacement Policy

Patients withdrawn from the study for safety reasons will not be replaced.

4.4 Assignment of Patients to Treatment Groups

Patients will be assigned to treatment with either *Octafibrin* or cryoprecipitate using a permuted-block, stratified (by center) random allocation scheme prepared by a biostatistician not involved in the conduct of the trial. Group allocation will apply to all fibrinogen supplementation orders during the treatment period (up to 24 hours after termination of CPB).

Subjects/patients are not permitted to re-enroll in the study.

4.5 Relevant Protocol Deviations

In the case of any major protocol deviation, the Investigator (Sponsor) will decide on the further participation of the patient in this study.

4.6 Subsequent Therapy

For 24 hours after termination of CPB, patients can receive additional doses of assigned IMP as clinically indicated. Patients requiring additional doses after 24 hours will receive cryoprecipitate.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

5.1 Characterization of Investigational Products

5.1.1 Octafibrin

Octafibrin is a highly purified, lyophilized human plasma fibrinogen concentrate without added albumins. The manufacturing process of *Octafibrin* includes two dedicated virus inactivation/removal steps, i.e., solvent/detergent treatment and nanofiltration.

The solvent/detergent treatment mode of action causes enveloped viruses to be irreversibly destroyed. These include the most transfusion-relevant viruses, such as human immunodeficiency virus types 1 and 2 (human immunodeficiency virus [HIV]-1, HIV-2), hepatitis B virus (HBV) and hepatitis C virus (HCV), and many other adventitious agents, e.g., newly emerging enveloped viruses, such as West Nile virus (WNV).

The Planova 20N filter was specifically developed by Asahi Kasei Pharma Corp. to remove infectious agents from protein solutions on the basis of their size. Thus, this nanofiltration step is in principle effective for removing even very small enveloped and non-enveloped viruses. Nanofiltration may be the only method to date permitting efficient removal of enveloped and non-enveloped viruses under conditions where 90–95% of protein activity is recovered [86].

Composition of Octafibrin

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous (IV) use. Its ingredients are listed in Table 5.

Table 5 Composition of *Octafibrin*

Ingredients	Quantity per mL reconstituted solution, mean values	Standard
Active ingredient		
Fibrinogen as clottable protein	20 mg	Ph. Eur.
Excipients		
Sodium chloride	6 mg	Ph. Eur.
Sodium citrate dehydrate	1.5 mg	Ph. Eur.
Glycine	10 mg	Ph. Eur.
L-arginine hydrochloride	10 mg	Ph. Eur.

Ph. Eur. = Pharmacopoeia Europaea

Octafibrin is a powder for solution for injection supplied in labeled 100 mL vials and provided by Octapharma. *Octafibrin* will be reconstituted with 50 mL sterile water for injections (WFI) produced according to GMP and provided by the clinical site.

The final product will be released by the responsible Octapharma Quality Control Department, according to a defined final product specification.

Conditions for Storage and Use

The IMP has to be stored at room temperature (not more than 25°C) and protected from light. The product must not be frozen. The Investigator/authorized personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

Dose and Dosing Schedule

Patients randomized to *Octafibrin* will receive 4 g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB.

Preparation

Each vial of *Octafibrin* will be reconstituted with 50 mL WFI at room temperature (not more than 25°C). *Octafibrin* dissolves at room temperature to an almost colorless and slightly opalescent solution within 10 minutes. If the solution is cloudy or contains particulates, it should not be used.

Method of Administration

The 4g of *Octafibrin* will be administered immediately after reconstitution over 10 minutes through a free-flowing IV by syringe injection. *Octafibrin* should not be mixed with other medicinal products or crystalloid intravenous solutions.

Packaging and Labelling

Octafibrin will be packaged and labeled for the trial by Octapharma. The label will comply with the Canadian national requirements.

Several batches of IMP may be used throughout the study. The batch numbers will be recorded in the CRFs and reported in the final study report.

5.1.2 Cryoprecipitate

Patients randomized to cryoprecipitate will receive 10 units each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB to 24 hours. Cryoprecipitate will be stored, thawed, and pooled by the blood bank according to current standards. The cryoprecipitate will be infused as per standard hospital protocols at the participating institutions (i.e., infused over 10–30 minutes through standard 170 µm blood infusing set).

5.2 Blinding, Emergency Envelopes, and Breaking the Study Blind

This is a single-blind randomized study, with patients randomized to equivalent doses of cryoprecipitate (1 dose = 10 units) or *Octafibrin* (1 dose = 4 g) (see **Section 5.1**). Given the physical differences in the products, it is not possible to blind clinicians to the IMPs.

The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial (see **Section 9.3**). To minimize bias, neither the individual randomizing nor any of the health care providers will know which treatment will be assigned to a given patient when fibrinogen supplementation is ordered.

Patients and outcome assessors will be blinded by having the compatibility label that will be placed in the patients' paper or electronic chart state "Study fibrinogen product 4g" rather than the actual product used.

5.3 Treatment Compliance

5.3.1 Drug Dispensing and Accountability

A drug dispensing log and the inventory will be kept current by the Investigator, detailing the dates and quantities of fibrinogen concentrate dispensed to each patient. The inventory will be available to the monitor to verify drug accountability during the study. Any unused or partially used fibrinogen concentrate, including unused returned containers, will be accounted for.

Unused fibrinogen concentrate may be destroyed at the study site, however, only after drug accountability has been verified and fully re-conciliated and written approval from the Sponsor has been obtained.

5.3.2 Assessment of Treatment Compliance

Fibrinogen supplementation will be ordered and administered by the clinical team in the hospital and will not be dependent on patient compliance.

6 STUDY CONDUCT

All patients having cardiac surgery with CPB will be the source of potential patients in the study. Patients will be randomized if they bleed after termination of CPB and the clinical team determines that fibrinogen supplementation is required according to current clinical standards for up to 24 hours after termination of CPB. Once the clinical team orders fibrinogen supplementation, the blood bank technologist will confirm patient eligibility and randomize the patient (according to a prepared randomization schedule) to *Octafibrin* or cryoprecipitate and prepare the product.

Patients will be treated according to their group allocation for any subsequent doses for the duration of the treatment period, which is 24 hours after termination of CPB.

Standard coagulation measures, including fibrinogen plasma level, will be obtained before and after the end of each fibrinogen supplementation (ideally within an hour as best practice). Due to the nature of bleeding in these cases, however, IMP doses can be administered before fibrinogen level results are known. Clinical indications for IMP administration are bleeding in the setting of suspected or confirmed low fibrinogen levels (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available, which is the treatment threshold recommended by current guidelines for treatment of bleeding patients) [8,70,71]. In rare cases clinicians may deem it clinically necessary to administer fibrinogen supplementation at levels >2.0 g/L (e.g., uncontrollable bleeding).

All AEs and SAEs occurring after termination of CPB to postoperative day 28 will be recorded. Patients will be followed by research coordinators in each institution. All clinical outcomes will be obtained from patients' medical records and electronic records, history and physical where needed, and via phone contact during the follow-up visits.

The flow chart of assessments by study visit is given on page viii.

6.1 Study Procedure

6.1.1 Prior to Enrolment

First fibrinogen supplementation order from the surgical team received at the blood bank

The blood bank technologist will confirm the following:

- CPB has been terminated
- Inclusion and exclusion criteria are met
- Coagulation measures (coagulation profile) are available or have been collected

The blood bank technologist will then randomize patients to fibrinogen or cryoprecipitate according to the randomization schedule and prepares and releases the product

Subsequent fibrinogen supplementation orders for the next 24 hours

- In addition to repeating the procedures for the first dose, the blood bank technologist will also confirm that fibrinogen plasma level have been re-checked and record value if available.

If no, ask for sample to be sent to the lab prior to and after the end of (within approximately 1 hour) the administration of IMP

Time of IMP infusion in the Operating Room (OR)

The following information will be collected:

- What time was the IMP administration started?
- Time of coagulation analyses (coagulation profile). Samples to be sent to the laboratory before and after the end of IMP infusion (exact sampling time needs to be recorded).

6.1.2 Visit 1: First post-randomization visit (0 to 24 hours after termination of CPB)

For any specified activity that cannot be completed on this visit, additional visits will be made until all study data are obtained..

- Obtain consent from patient or surrogate
- Collect baseline data
 - Demographics
 - Medical history
 - Preoperative concomitant medications
- Collect surgical data
 - Intraoperative concomitant medications
 - CPB time
 - Cross-clamp time
 - Circulatory arrest
 - Vital signs
 - Fluid in- and output monitoring
 - Inotropes and vasopressors
- Collect laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile before and after IMP administration
 - Safety labs (creatinine, liver function tests [AST, ALT], troponin)
- Collect all transfusion and hemostatic agents (number and timing) for the 24 hour period after infusion
- Collect bleeding components using the UDPB criteria
- Collect extubation time
- Collect length of stay in the ICU
- Collect concomitant medications
- Collect AEs and SAEs

6.1.3 Visit 2: Postoperative day 7 (or at discharge if earlier)

- Obtain consent from patient or surrogate (if not already done)

- Collect daily laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile
 - Safety labs (creatinine, liver function tests [AST, ALT], bilirubin, troponin)
- Collect transfusion requirements
- Collect extubation time (if applicable)
- Collect length of stay in the ICU and hospital (if applicable)
- Collect AEs and SAEs

6.1.4 Visit 3: Postoperative day 28 (in person if in hospital or by phone)

- Obtain consent from patient or surrogate (if not already done)
- Collect AEs and SAEs
- Collect extubation time (if applicable)
- Collect length of stay in the ICU (if applicable)
- Collect length of stay in the hospital (if hospital stay is extended)
- Collect concomitant medications

After Visit 3 or on postoperative day 28, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

6.1.5 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply:

Table 6 Time Windows Used in this Study

Time point	Time stated	Tolerance
Interval between visits		
Blood sampling	Before IMP administration	Up to 75 minutes
	After IMP administration	Up to 75 minutes
	Day 7	± 1 day
	Day 28	± 2 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The **duration of the treatment period** is 24 hours from the end of CPB.

The **duration of the study** for an individual patient is 28 days from patient enrollment when patients will be contacted in person or by phone post-discharge.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when 1,200 patients are randomized and have finalized day 28 (or early termination at the time of the interim analysis). It is estimated that the study will take approximately 2 years for recruitment.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor, in consultation with the Independent Data Safety Monitoring Committee (IDSMC), reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Investigators will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and research ethics boards (REBs) will be informed in accordance with national regulations.

Early termination of the study as a whole or by center may apply for the following reasons:

Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.

Early Termination at an Individual Study Center

At any time, the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The a priori determined required recruitment rate is not met.

Should the study be prematurely terminated, all remaining *Octafibrin* will be returned to Octapharma or locally destroyed.

7 ASSESSMENTS AND METHODS

7.1 Baseline Data

The baseline information and medical history will be recorded during Visit 1, i.e., as soon as possible after randomization.

7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are sex, age, height, weight, and Body Mass Index (BMI).

7.1.2 Medical History and Prior/Concomitant Medications

The medical history will be obtained by interviewing the patient or from the medical records.

Prior and concomitant medications will be obtained.

7.2 Study Assessments

7.2.1 Surgical and Surgery-Related Data

The following surgical data will be collected: details of procedure, CPB duration, CPB start-end times, cross-clamp duration, circulatory arrest duration, fluid intake and output, any medications administered, hemodynamic support (e.g., IABP), as well as any blood conservation methods used (e.g., hemoconcentration, retrograde prime, cell salvage).

In addition, extubation time, ICU length of stay, and hospital length of stay will be documented.

7.2.2 Transfusion Data

All blood products and hemostatic agents released from the blood bank and transfused will be collected from the blood bank databases. These include ABPs: RBCs, pooled or apheresis platelets, and plasma. Other hemostatic agents include: DDAVP, prothrombin complex concentrates (PCC), activated recombinant factor VII, idarucizumab, and andexanet alpha.

7.2.3 Bleeding Data

The comparison of ‘major’ bleeding based on the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] (Table 7) will be assessed as a secondary endpoint. The UDPB is a multistage definition for perioperative bleeding based on easily measured clinical end points, including total blood loss from chest tubes within 12 hours, ABPs transfused, surgical re-exploration including cardiac tamponade, delayed sternal closure, and the need for salvage treatment. The following components of the score will not be used for this study: delay in chest closure and use of cryoprecipitate.

Depending on these components, bleeding is graded as insignificant, mild, moderate, severe, or massive. (Table 7) [1].

Table 7 Bleeding categories according to the UDPB in adult cardiac surgery (if different categories indicate mixed definitions of bleeding, the worst definition applies) [1]

Bleeding definition	Postoperative chest tube blood loss within 12 h (mL)	RBC (units)	FFP (units)	PLT (units)	PCCs	rFVIIa	Reexploration /tamponade
Class 0 (in-significant)	<600	0	0	0	No	No	No
Class 1 (mild)	601–800	1	0	0	No	No	No
Class 2 (moderate)	801–1000	2–4	2–4	Yes	Yes	No	No
Class 3 (severe)	1001–2000	5–10	5–10	NA	NA	No	Yes
Class 4 (massive)	>2000	>10	>10	NA	NA	Yes	NA

FFP, fresh frozen plasma; NA, not applicable; PCCs, prothrombin complex concentrates; PLT, platelets; rFVIIa, recombinant activated factor VII; UDPB, universal definition for perioperative bleeding.

7.3 Laboratory Assessments

7.3.1 Test Parameters and Laboratories

Table 8 summarizes all test parameters and the laboratories responsible for analysis.

Table 8 Test parameters and laboratories

Test	Material needed	Responsible laboratory
Coagulation profile		
(PT, PTT, INR, fibrinogen activity via Clauss technique)	Citrated blood	Local
ROTEM FIBTEM A10	Citrated blood	Local, if available
Hematology – standard panel as per local lab	Citrated blood	Local
Clinical chemistry – standard panel as per local lab	Serum	Local
Safety labs		
Troponin	Serum	Local
AST/ALT	Serum	Local
Bilirubin	Serum	Local
Creatinine	Serum	Local

7.3.2 Blood Sampling

All blood sampling will be performed as per standard practice at the local institution.

The *actual* time of blood sampling for fibrinogen will be recorded in the CRF.

7.3.3 Citrated Blood

Citrated blood as required by the local laboratory will be collected and processed in accordance with local requirements.

7.3.4 Serum

For the determination of clinical chemistry and safety labs (alanine aminotransferase, ALT; aspartate aminotransferase, AST; serum creatinine, CREA; troponin), where a serum blood sample has been collected.

7.3.5 Recording of Clinically Significant Abnormal Laboratory Values as AEs/ADRs

Other than abnormal laboratory values due to the underlying condition, the Investigator must assess the clinical significance of abnormal laboratory values outside the specified normal range (see **Section 7.4**). Any clinically significant abnormalities will be documented. All specified clinically significant abnormalities will be documented as AEs/SAEs and investigated.

Additional tests and other evaluations required to establish the significance or etiology of specified abnormalities or to monitor the course of an AE will be obtained if clinically indicated. Follow-up will persist until resolution or up to the Study Completion Visit, whichever occurs first.

7.4 Safety Assessments

7.4.1 Assessments for Safety Endpoints

The following drug safety information will be collected:

- AEs and SAEs temporally associated with the administration of IMP (for definitions and reporting requirements, see **Sections 7.4.2, 7.4.3, 7.4.4** and Appendix 15.1).
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see **Section 7.4.5**).

7.4.2 Adverse Events (AEs)

Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase ‘response to an IMP’ means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Principal Investigator (Sponsor).

Collection of AEs

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as “How have you been since the last visit/during the previous study period?”. In addition, the Investigator will check the patient records for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the CRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the likelihood that they were related to the IMP (causality). The Sponsor will be responsible for assessing the expectedness of each ADR (expected or unexpected).

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

Severity of AEs

The intensity/severity of AEs will be graded as follows:

Mild: an AE, usually transient, which causes discomfort but does not interfere with the patient’s routine activities

Moderate: an AE which is sufficiently discomforting to interfere with the patient’s routine activities

Severe: an AE which is incapacitating and prevents the pursuit of the patient’s routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

Causality of AEs

All AEs will be assessed by a blinded Investigator as to whether they can be explained by the patient’s underlying condition or surgical course. If they are not explainable, then the Investigator will make a determination of the relationship of the AE with the IMP as follows:

Probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient’s clinical state.

Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

Unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.

Not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

Unclassified: reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

Expected: an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.

Unexpected: an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved (by Study Completion visit)
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death will be fully documented and reported.

Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) *IMP-related actions taken in the event of an AE*

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Principal Investigator (Sponsor).

7.4.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is another important medical event.

In this study a number of SAEs are expected because of the nature of the surgery. These events will not be considered as SAEs in this study.

NOTE: The term ‘life-threatening’ refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgement will be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent will be reported as an SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.4.4 SAE Reporting Timelines

All SAEs, suspected to be related to study treatment, will be reported within 24 hours of recognition to the sponsor by telephone, fax, or email:

Keyvan Karkouti MD

Department of Anesthesia
Toronto General Hospital
200 Elizabeth Street, 3EN
Toronto, ON, Canada
M5G 2C4

Phone: 1-416-340-5164
Fax: 1-416-340-3698
Email: keyvan.karkouti@uhn.ca

In addition, all serious adverse events related to Octafibrin will be reported within 1-month of recognition of the event to:

Octapharma's Corporate Drug Safety Unit

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

Fax: +43 1 61032-9949

Email: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

Waivers from the SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.4.5 Other Relevant Safety Information

Pregnancies

Patients who are known to be pregnant will not be included in the study. In patients of reproductive age, pregnancy is ruled out prior to the cardiac surgery as part of standard of care.

Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as an SAE.

a) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

b) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

c) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the electronic CRF (eCRF) must be supported by source data in the patient records, with exceptions listed in **Section 8.1.2**.

The Investigator will permit study-related monitoring, audit(s), REB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (e.g., sub-investigators, clinical research coordinators/assistants, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms (CRF)

After all personal identifiers have been removed, research related data collected will be stored on a secured web-server at ERGOMED, which is a global company specializing on the conduct of clinical trials (headquarters located in England; secured database centre located in Germany). It meets all Canadian and U.S.A. privacy laws.

Study site staff (e.g., blood bank technologist, research coordinator/assistant) will be responsible for completing a CRF for each patient enrolled. All site personnel will be trained on CRF completion. The site is also provided with the approved CRF Completion Guidelines which will assist in data entry and data issues/questions. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or to change CRF data must be listed in the Delegation of Authority Log.

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An Investigator's Brochure (IB) will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of *Octafibrin*.

The IB will be updated at regular intervals by Octapharma and whenever relevant new information concerning the IMP becomes available. This will be delivered by Octapharma to the Principal Investigator who will distribute to the approved study sites.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing CRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

At each study site the Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., cop-

ies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the site investigators will supply the Sponsor or designate, such as the monitors with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Safety Monitoring Committee

An IDSMC will be established by the Sponsor. The IDSMC will be composed of recognized experts in the field of statistics, perioperative medicine, and hematology who are not actively recruiting patients.

The IDSMC will review relevant data periodically (approximately after every 100 patients have been recruited) during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific charter will define in detail the composition, responsibilities, and procedures of the IDSMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external statistician. The principal statistical methodology is described in this section. Further specifics regarding the statistical analysis will be provided in the Statistical Analysis Plan (SAP).

9.1 Determination of Sample Size

The statistical analysis of the primary efficacy variable, i.e., the amount of ABPs, will be based on the mean number of ABP units within the first 24 hours after termination of CPB (μ_F and μ_C).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to the treatment with cryoprecipitate with respect to the mean number of ABP units, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \mu_F / \mu_C \geq (1 + \delta) \quad \text{vs.} \quad H_1: \mu_F / \mu_C < (1 + \delta)$$

will be carried out with a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_C denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term), with treatment group as main effect.

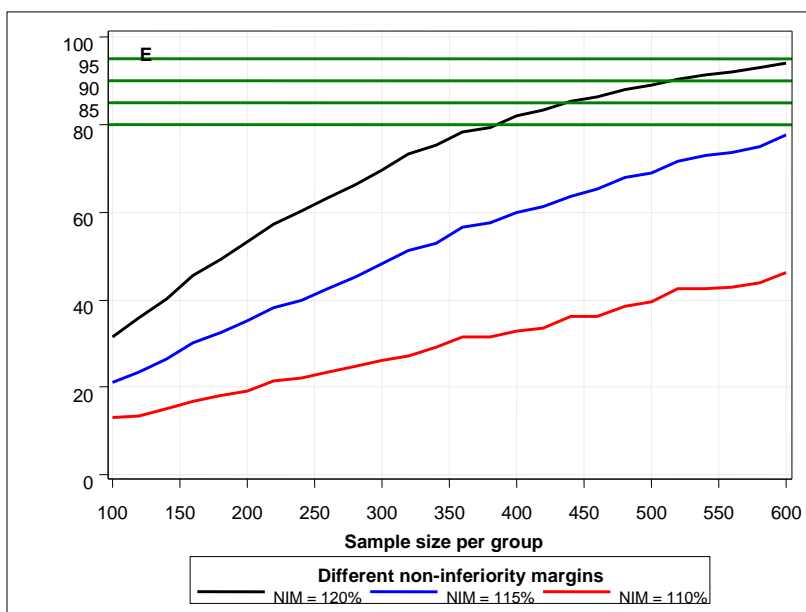
The test of the primary hypothesis in the planned interim and the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_C derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

Based on this method, a one-sided overall type I error probability $\alpha = 0.025$ and a non-inferiority margin of $\delta = 0.20$, simulations have been performed to study the power of the test for different sample sizes.

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units (each dose of apheresis or pooled platelets was counted as 4 units for this analysis to correspond with the number of units in pooled platelets). The empirical distribution function with these sample characteristics was chosen based on results of the TACS study (see **Section 1.1**) with the same endpoint in the same indication and similar treatment.

10,000 studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

The plot below displays the empirical power curves for the test of H_0 vs. H_1 using the Poisson counting regression model analyzed with SAS PROC GENMOD for different sample sizes and values of δ .



As the diagram shows, an empirical power of >90% can be expected with a sample size of at least 550 patients per treatment group if a δ of 0.20 is chosen. For smaller values of δ , no sufficient power can be attained with operationally feasible sample sizes. The choice of the non-inferiority margin $\delta = 0.20$ is also motivated by the large variation of the primary endpoint that is to be expected from previous studies reflecting current clinical practice.

Therefore, it is planned to conduct the study with a maximum sample size of 600 patients in each treatment group and a non-inferiority margin of $\delta = 0.20$.

Assuming that a proportion of about 10% randomized patients will not be treated after randomization or for whom the endpoint cannot be obtained, this would ensure that data on at least 550 patients per treatment group in the mITT population will be available for the statistical analysis as derived from the sample size calculation.

9.2 Statistical Analysis

For the statistical analysis of the efficacy parameters the following analysis populations will be considered:

The primary analysis will be performed on the modified intention to treat (mITT) population, which will include all randomized patients who agree to remain in the study after debriefing. Randomized patients who did not undergo cardiac surgery or received no IMP will be excluded from the analysis. It is anticipated that approximately 10-15% of patients will fall into these categories. In the event that a patient receives treatment that is not in concordance with the randomization schedule, the treatment group will be defined according to the randomization (rather than the actual treatment received).

The per-protocol (PP) population: This analysis population will consist of all patients in the mITT population, excluding patients with major protocol deviations. The following patients will be excluded:

- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 80% of the planned dose
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meeting prior to unblinding for the interim and final analyses. Decisions and outcome will be approved by the Principal Investigator (Sponsor) in consultation with the collaborator (Octapharma).

The mITT analysis population is considered the primary population for analysis of the primary efficacy objective. The evaluation of the primary efficacy endpoint will additionally be performed for the PP population.

9.2.1 Efficacy Analysis Plan

Primary endpoint: total amount of ABP units

The primary efficacy variable is the total number of ABP units (RBCs, pooled and apheresis platelets and plasma) used within 24 hours after termination of CPB. Apheresis units will be counted as their equivalent pooled counterparts (for platelets, 1 apheresis unit = 4 pooled units; for plasma, 1 apheresis unit = 2 pooled units).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses:

$$\begin{aligned} H_0: & \quad \mu_F / \mu_c \geq (1 + \delta) \text{ (inferiority)} \\ \text{vs. } H_1: & \quad \mu_F / \mu_c < (1 + \delta) \text{ (non-inferiority)} \end{aligned}$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect.

The test of the primary hypothesis in the final analysis will be based on the one-sided CI for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the mITT population. A secondary analysis will be performed for the PP population.

Only in case of demonstrated non-inferiority in the mITT and the PP population subsequently the pair of hypotheses:

$$\begin{array}{l} H'_0: \mu_F / \mu_c \geq 1 \\ \text{vs. } H'_1: \mu_F / \mu_c < 1 \end{array}$$

will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary.

Secondary endpoints

The following measurements will be considered exploratory secondary endpoints in the analysis of efficacy of the study treatments:

- Total number of units of ABPs administered from start of cardiac surgery until 7 days after surgery or discharge.
- Distribution of major bleeding type, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery.
- Change in fibrinogen plasma level (measured using the Clauss assay) before and after fibrinogen supplementation for first and subsequent doses.
- Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets, and plasma.
- Primary analysis of secondary endpoints will be based on the mITT population. Additionally, the same analyses will be done on the PP population.
- The total number of ABPs within 7 days/discharge and the different subtypes of ABPs will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.
- Frequency distributions of the major bleeding type according to UDPB will be presented for each treatment group.
- Change in fibrinogen plasma level will be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the *Octafibrin* and cryoprecipitate treatment groups and the corresponding 95% CI will be calculated.

Further exploratory endpoints

Exploratory analyses will include comparisons of length of hospital stay, ICU stay, and ventilation time.

Data collected as part of this study will be used for an economic analysis to be conducted at a later date.

Subgroup analyses for efficacy

The following subgroups will be analyzed: non-elective surgery; complex surgery (procedures other than isolated ACB, single valve, or repair of ASD); and excluding patients who underwent very high-risk procedures. The latter will include all patients who were in critical condition before surgery as well as those determined to be at very high-risk blinded (to the IMP and all outcomes) adjudicators.

9.2.2 Safety Analysis Plan

The safety analysis population (SAF) will include all patients who received at least one dose of the IMP (if no randomization errors occur, this will be the same population as the mITT population). Safety outcomes will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

Grades 3 and 4 SAE (as per the FDA criteria: severe or life-threatening) data will be collected in cases where consent for remaining in the study cannot be obtained. As it relates to this study, typical SAEs of interest will include death, serious thromboembolic events (stroke, myocardial infarction, renal failure, deep vein thrombosis, pulmonary embolism, and hepatic failure). The only data that will be collected other than the SAE type, will be its relation to IMP administration. No data will be collected on patients who refuse consent.

Adverse events, including thromboembolic events

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version as specified in the Data Management Plan. The analysis will focus on treatment emergent adverse events (TEAEs), i.e., AEs that started or worsened after start of infusion with IMP.

All TEAEs, related TEAEs (i.e., AEs probably or possibly related to the IMP), and serious TEAEs will be summarized and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in withdrawal from the study, respectively, will be tabulated using frequency tables if a reasonable number of events of this type are observed.

Analogous frequency tables for thromboembolic events (TEEs, identified using MedDRA SMQs) will be provided.

Patient listings will be provided for patients with SAEs, TEEs, AEs leading to withdrawal from study, and AEs leading to death. These listings will also include patients enrolled but not randomized.

Mortality

The number of patients who died will be summarized. A possible difference between treatment groups will be estimated by a risk ratio with 95% CI. Kaplan-Meier estimates for the time to death distribution will be calculated and graphically presented.

Routine laboratory data

All laboratory values will be classified as normal or abnormal according to the laboratories' normal 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
- Qualitative data based on reference ranges will be described according to the categories (i.e., low, normal, high)

- Shift tables illustrating changes with respect to the laboratories' normal ranges between baseline and a defined scheduled time point
- Number and frequency of patients with clinically significant laboratory values. A separate patient listing will be provided

9.2.3 Handling of Missing Data

In general, missing data will not be imputed. Due to the nature of the study, important variables will have few missing data.

9.3 Randomization, Stratification, and Code Release

Eligible patients will be randomly assigned to receive either *Octafibrin* or cryoprecipitate. Randomization lists using a permuted-block, randomization scheme (stratified by site) will be prepared by the biostatistician and integrated in to the eCRF system. The randomization lists will then be provided to the blood banks of the participating centers who will be in charge of providing the IMP to the OR.

Patients will be identified using a sequential numbering system.

9.4 Interim Analysis

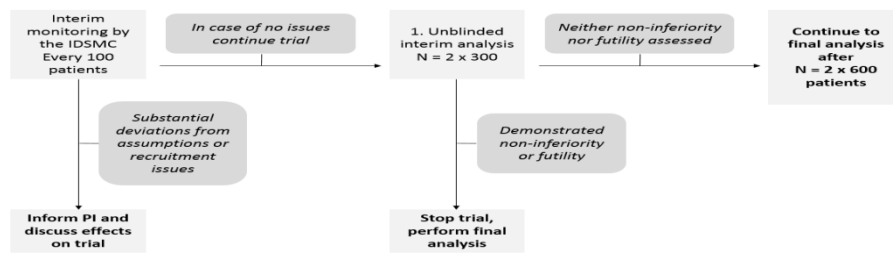
The study employs a group-sequential design that involves one pre-planned interim analysis after 600 patients have been enrolled.

In addition, the IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study. This data monitoring serves the purpose of an ongoing assessment of recruitment problems as well as the compatibility of the accumulating data with the assumptions made at study start. The extent of the information to be reviewed will be defined in the IDSMC charter. The IDSMC will keep all these data monitoring results in strict confidence. Only in case of identified issues during their data monitoring the IDSMC will advise the Principal Investigator (Sponsor) in a non-treatment-disclosing manner on the problems.

The interim analysis will be an unblinded interim analysis with an adjusted type I error rate according to the O'Brien-Fleming method after 600 patients have been enrolled. After this interim analysis, a positive outcome may be claimed and enrolment may be stopped if the test of H_0 vs. H_1 in the mITT population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$ rejects the null hypothesis (efficacy stop). A full final analysis including all study data will be performed and reported if enrolment is stopped after the interim analysis. Also at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

Otherwise, the study will continue until the maximum sample size of $n = 2 \times 600$ patients, is reached. The final analysis will be performed as described above, but with an adjusted one-sided significance level of $\alpha_2 = 0.02242$ to maintain the overall one-sided significance level of $\alpha = 0.025$.

The flow chart below illustrates the decision process underlying the interim analyses. Further details of the interim analyses will be described in the respective sections of the SAP.



10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an REB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO).

10.2 Approval of Study Documents

The study protocol, a sample of the debriefing form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate REB and the Regulatory Authority. The study must be approved by the REB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Consent

This is a pragmatic trial that compares two fibrinogen replacement sources that are currently within the standard-of-care for this procedure, is unlikely to pose additional risks to patients, and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (i.e., bleeding during or after 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. In addition, this complication occurs infrequently and cannot be predicted before surgery. Thus, while it is technically possible to obtain informed consent before all surgeries, it is simply ‘impracticable’ to do so for this specific study, thereby rendering such a study simply unfeasible.

Importantly, the study compares two substitutable therapies that are used as part of routine clinical care, and there is no compelling theoretical basis or any types of data that patients would be placed at risk by participating in the study. The results of this study, on the other hand, would have important societal benefits, as it will help the Canadian Blood Services to determine which of the two products should be supplied in the future. If fibrinogen concentrate is proven to be non-inferior, it will likely be the treatment of choice because it has a lower theoretical risk of viral transmission, improves the efficiency of the blood system (for every unit of cryoprecipitate produced, one unit of platelets, which is often in short supply, is diverted from the blood supply), and allows for more rapid, targeted therapy of bleeding.

The study meets the criteria stated in Article 3.7A of the 2014 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans for identifying situations in which exceptions may be sought for the requirement to seek consent prior to surgery.

Requirements for obtaining informed consent will be determined by the Research Ethics Board of each participating site. Patient or surrogate decision maker will be approached for informed consent within 24-72 hours after surgery. They will be provided as much time as necessary to ask any questions and to make their decision. If initially the patient is not capable of providing consent, consent will be obtained only from the surrogate decision maker. The patient will be re-visited every few days and consent will be obtained from the patient when appropriate. Consent should be obtained within the 28 day duration for each study patient. Any delays in obtaining consent due to extenuating circumstances need to be clearly documented (e.g., when patient dies soon after surgery in which case initiation of consent process from next of kin can be delayed for up to 1-week after death). Study data collection will begin only after informed consent is obtained from the SDM or patient.

Study coordinator or assistant will obtain freely given consent (in person or via telephone) from each patient (or SDM) after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the decision to continue to participate. Consent must be obtained by the patient (or surrogate), before the patient is exposed to any further study-related procedures, namely evaluation and data collection. Should the consent be obtained from the SDM and later declined by the patient, no data will be collected.

Study coordinator or assistant will explain that the patients are completely free to withdraw from the study at any time, without any consequences for their further care and without the need to justify. Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations. In addition to the FIBRES protocol, study hospitals will also follow their institutional guidelines and approvals when consenting and collecting data. Their process will be documented in their SOPs. Again, no data will be collected on patients/SDMs who refuse consent. Please refer to Appendix in 15.2 for the consent and data collection guidelines at Toronto General Hospital.

10.4 Protocol Amendments

Any amendments will be submitted to the competent REB and any authority as required by applicable regulations.

REB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective or design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take when 5 – 15 patients have been randomized at the site. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor or REB and regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been captured.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines) will be prepared by the Sponsor after completion of the study. The Coordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study will be published and may be presented at scientific meetings.

In accordance with standard editorial and ethical practice, the Investigator will publish the multi-center data only in their entirety and not as individual center data. Authorship will be determined by mutual agreement. Any subsequent publications based on subsets of the data will require approval from the Sponsor.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Investigators and or their institutions will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

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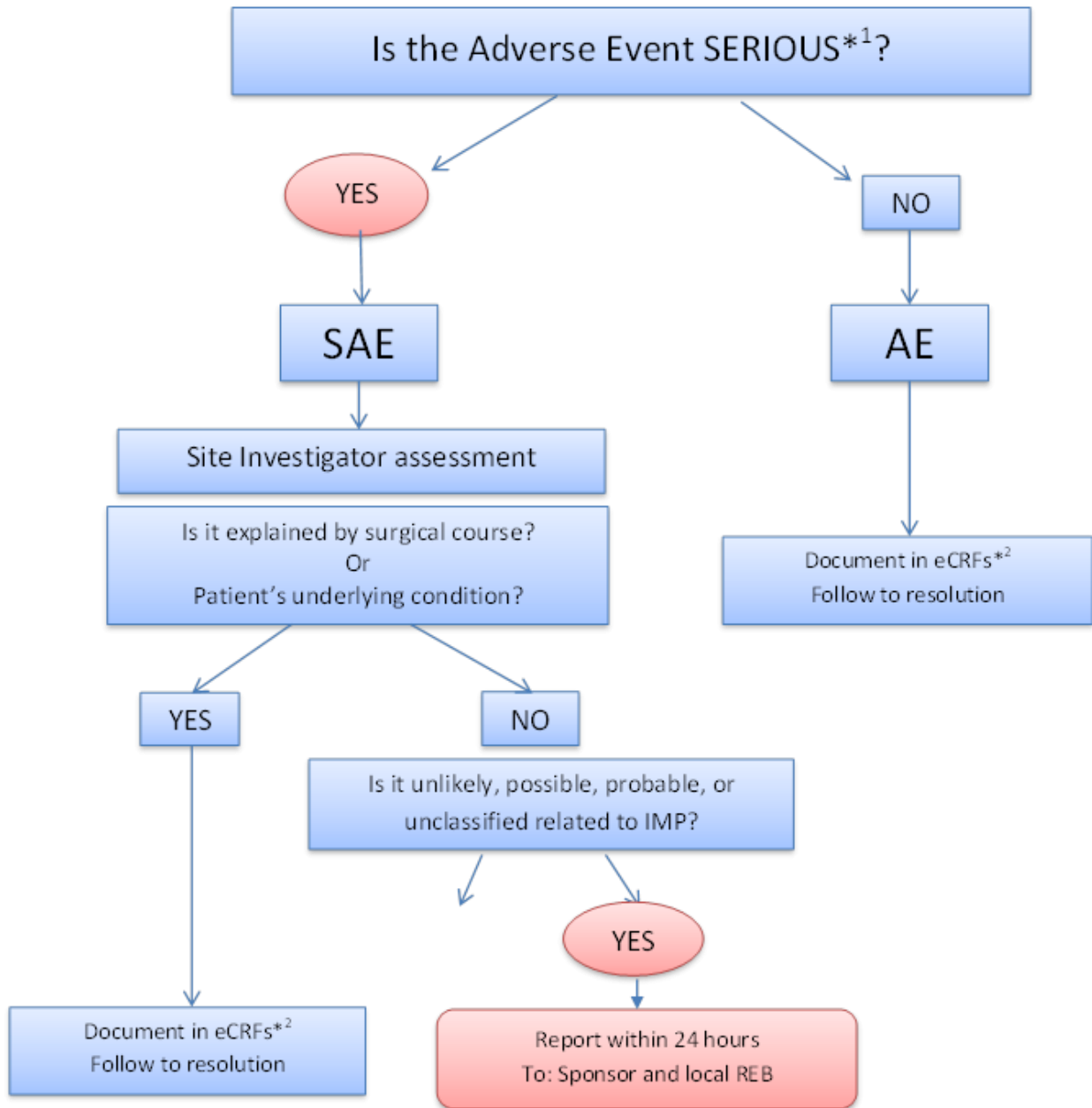
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15 APPENDICES

15.1 Assessment of Adverse Events- Serious Adverse Events: Flow Chart



*1 **Serious AE (SAE)** is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is another important medical event.

*2 **eCRFs** Case Report Forms 09.01 Adverse Events – Serious Adverse Events Report Form and 10.01 Concomitant Medications Form for each adverse event

Red legend refer to the two conditions of expedited reporting (1) the event is serious and (2) unlikely, possible, probable or unclassified related to IMP

Refer to FIBRES SOP- 02 Adverse Events- Data Collection, Assessment, and Reports

15.2 Consent and Data Collection Guidelines at TGH

Scenario	What data can be collected
Written consent obtained from patient or Written/telephone consent obtained from SDM	Data can be collected.
Consent obtained initially (from SDM or patient) and later withdrawn (SDM or patient)	Data can be collected up to the date of withdrawal. No data should be collected after withdrawal, not even SAE data.
Consent obtained from SDM and declined from patient once capable of consenting	No data at all should be collected. Patient's decision overwrites the SDM's.
Consent not obtained due to no SDM or patient incapacity to provide consent	Only type of SAE and relation to the study intervention can be collected, if applicable. No other data should be collected.
Consent declined either by patient/ SDM	Nothing can be collected, not even SAE data.

Guidelines to Obtaining Telephone Consent from Patient/SDM

Patient Consent

The following process must be followed when obtaining telephone consent from patients who have been discharged and have requested more time to review the consent form or to discuss the matter with family/friends.

- Contact the patient a week after discharge (unless they have requested to be contacted at a different time point) and ask whether they are agreeable to participate in the study
- If they agree to participate, then data can be collected. If the patient does not agree, nothing can be collected.
- Attempts for contact with the patient shall be documented and consent shall be obtained in the presence of a witness and documented.

SDM Consent

The following process must be followed when obtaining telephone consent from the SDM:

- The SDM is first contacted to introduce the study and to establish if they are interested in providing consent on behalf of the patient.
- If they are interested, then they are informed that the team will send the consent form to them and will call back within 2-3 days after the ICF is received.
- At the time of the second call, the SDM should be asked whether they agree to participate or not.
- If they agree to participate, then data can be collected. If SDM did not agree, nothing can be collected.
- Attempts for contact with SDM shall be documented and consent shall be obtained in the presence of a witness and documented.

FIBRES Protocol - List of Changes from Version 1.1 to 2.4

Please find below each of the changes made and the reasoning behind them:

1. Clarification of inclusion/exclusion criteria of fibrinogen-containing products

The inclusion criteria was modified for clarification purposes (Section 4.1). We now specify that the cardiac surgery has to be the index surgery to emphasize that it cannot be an ancillary part of the study.

Section 4.2.2 clarifies the exclusion criterion for fibrinogen containing products by specifying that this refers to fibrinogen-rich products (i.e., cryoprecipitate or fibrinogen concentrate).

2. Limiting early withdrawals and ensuring full reporting of serious adverse events

Since this is not a fully blinded study, there is potential for bias if we do not minimize early withdrawals or if we do not obtain information on important outcomes. As a result, we have clarified the conditions for early withdrawal (Section 4.3.1). We have also obtained approval to report on serious adverse events on all patients who receive IMP, even if it is not possible to obtain consent (e.g., due to death) (Section 9.2.2). This would exclude patients who have refused participation.

3. Clarification of subsequent therapy

Section 4.6 has been modified to clarify that the study period is 24 hours and subsequent therapy refers to treatments that are provided after 24 hours.

4. Clarification of fibrinogen levels before and after IMP administration

Since this is a pragmatic trial, IMP administration is based on clinical need and not fibrinogen levels. This is now better clarified in Section 6. We also lifted the requirement the pre- and post- fibrinogen levels be taken **within an hour** of IMP administration from our secondary endpoints (Section 2.2 & 3.1.2), as we have found that, due to the nature of the clinical setting, the laboratory measures may fall outside of the 1 hour time-frame. Even if the pre- and post-IMP fibrinogen levels are outside the one hour period, please continue to record them.

5. Clarification of visits

Timing and purpose of visit 1a was not clear (section 6.1.3). We have removed this visit and have modified visits 1-3 to ensure all required information is collected.

6. Determination of causality of adverse events and reporting

We have now clarified the reporting of adverse events. The new process for Site 1 (Toronto General Hospital) is enclosed in appendix 15.1 and Section 7.4 has been slightly modified to be consistent with this new process.

7. Clarification of the analysis plan

The intention to treat population was clarified. The original protocol specified, but was not clear, that the primary analysis would be conducted on randomized, treated patients who

provided consent. The revised protocol clearly defines this population and labels it as modified intention to treat.

The revised protocol also clearly specifies how apheresis allogeneic blood units will be counted in the analysis plan (Section 9.2.1).

8. New subgroup added to the analysis plan

As per the recommendations of the IDSMC, a new subgroup analysis – excluding critically ill patients – has been added (Section 9.2.1)

9. Consent

This multi-site trial has varying consent procedures determined by each hospital's ethics board. Section 10.3 was modified to reflect the principles all sites have to follow, but to also allow leeway to include the varying requirements set at each site. In the instances where patient consent cannot be obtained (i.e. patient does not regain the capacity to give consent), all SAEs will be recorded for the purpose of patient safety. In the instances where a patient requires more time to review the study, or substitute decision maker (SDM) is not coming to the hospital telephone consent can be obtained. The two scripts (one each per patient and SDM) outline the process and script to be followed. Since recruitment is complete, we would still like to submit the telephone consents to assist site in contacting and obtaining consent from patients/SDMs who are not returning to the hospital.

CLINICAL STUDY PROTOCOL

FIBRES

FIBrinogen REplenishment in Surgery

Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients

Investigational Product:	<i>Octafibrin</i>
Indication:	Acquired fibrinogen deficiency
Study Design:	Prospective, multi-center, randomized, active-control, single-blinded non-inferiority study
Sponsor:	Keyvan Karkouti
Study Number:	FIBRES (FORMA-06)
EudraCT and/or IND Number: Clinicaltrials.gov Registration	FEF NCT03037424
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 4 2016
Planned Clinical End:	Quarter 4 2018
Date of Original Protocol:	24-Nov-2016 <u>V1.1</u>
Version: Date of Amendment:	1-103- July-2018 <u>V2.4</u>
Coordinating Investigator:	Keyvan Karkouti MD Department of Anesthesia Toronto General Hospital 200 Elizabeth Street, 3EN Toronto, ON M5G 2C4 Canada

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FIBRES Protocol 2.4_TrackChanges from Version 1.1_03-July-2018 ~~DOC ID 2444~~

STUDY OUTLINE

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
Name of Investigational Product: <i>Octafibrin</i>	Protocol Identification Code: (FORMA-06)
Name of Active Ingredient: Human fibrinogen	Date of Final Protocol: 24-Nov-2016 03-July-2018 V2.4

Title of Study: Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients
Indication: Acquired fibrinogen deficiency
Number of Study Centre(s): Up to 12 Canadian hospitals
Objectives: Primary Objective: The primary objective of this study is to demonstrate that the fibrinogen concentrate <i>Octafibrin</i> is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products (ABPs) administered during the first 24 hours after termination of cardiopulmonary bypass (CPB). Secondary Objectives: The secondary objectives include: <ul style="list-style-type: none">• Comparison of efficacy as measured by the total and individual number of ABPs transfused from the beginning of surgery up to postoperative day 7• Comparison of the amount of bleeding during the first 24 hours after termination of CPB• Comparison of the effect on fibrinogen levels observed within 1 hour before and 1 hour after <u>the first dose of</u> fibrinogen supplementation

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
Name of Investigational Product: <i>Octafibrin</i>	Protocol Identification Code: (FORMA-06)
Name of Active Ingredient: Human fibrinogen	Date of Final Protocol: 24-Nov-2016 03-July-2018 V2.4

- Comparison of safety as measured by adverse events (AE) and serious adverse events (SAEs) during the first 28 days after termination of CPB
- Comparison of other secondary safety endpoints including, duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalization.

Study Design:

This is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require up to 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank receives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB). No other aspects of care will be modified.

The primary efficacy outcome will be the number of ABPs (red blood cells [RBCs], pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB. Safety outcomes will be measured for the first 28 days after surgery, which is the duration of participation of each patient in the trial. Comparisons will be by modified intention-to-treat (~~ITT~~mITT) (primary) and per-protocol (PP) analysis. One interim analysis will be conducted after 600 patients have been ~~treated~~enrolled to determine whether the study should be terminated for safety reasons, demonstrated non-inferiority or futility reasons.

Name of Sponsor: Keyvan Karkouti, Toronto General Hospital	
Name of Investigational Product: <i>Octafibrin</i>	Protocol Identification Code: (FORMA-06)
Name of Active Ingredient: Human fibrinogen	Date of Final Protocol: 24-Nov-2016 03-July-2018 V2.4

Number of Patients: Total = 1200; randomized to two arms.
Patient Selection Criteria: Inclusion Criteria: 1. Patients undergoing <u>index</u> cardiac surgery with CPB in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia). Exclusion Criteria: Patients who meet any of the following criteria are <i>not</i> eligible for the study: <ol style="list-style-type: none">1. Receipt of fibrinogen-containing<u>rich</u> products, including (fibrinogen concentrate or cryoprecipitate) within 24 hours before surgery (to exclude patients with significant blood loss before surgery)2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate3. Refusal of <u>ABPs</u> fibrinogen concentrate or cryoprecipitate due to religious or other reasons4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation, which is the upper limit of the normal range)5. Known pregnancy
Test Product, Dose, and Mode of Administration: <i>Octafibrin</i> and cryoprecipitate will be administered intravenously. Patients randomized to <i>Octafibrin</i> will receive 4 g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB. Patients randomized to cryoprecipitate will receive 10 units each time fibrinogen supplementation is ordered during the first 24 hours after the termination of CPB.
Duration of Treatment: The first 24 hours after termination of CPB.

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint

The primary endpoint, which is of efficacy, is the comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.

Secondary efficacy endpoints

- Comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.
- Comparison of major bleeding, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] during the first 24 hours after termination of CPB.
- Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) ~~within 1 hour~~ before and ~~1 hour~~ after the first dose of fibrinogen supplementation.

Secondary safety endpoints:

- Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, will be compared between the groups up to postoperative day 28.
- Other secondary safety endpoints that will also be compared between groups are:
 - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
 - Duration of intensive care unit (ICU) stay up to postoperative day 28
 - Duration of hospitalization up to postoperative day 28

Study Procedures:

First fibrinogen supplementation order from the surgical team received at the blood bank

The blood bank technologist confirms eligibility with the clinical team and will then randomize patients to fibrinogen or cryoprecipitate according to the randomization schedule and prepares and releases the product

Visit 1: First post-randomization visit (0 to 24 hours after termination of CPB)

Obtain consent from patient or surrogate
Collect baseline and surgical data
Collect laboratory, transfusion and bleeding data
Collect extubation time and LOS in the ICU
Collect concomitant medications
Collect AEs and SAEs

~~Visit 1a: 0-36 hours if any subsequent doses of IMP are given~~

~~Coagulation analyses
Collect laboratory, transfusion and bleeding data
Collect extubation time and LOS in the ICU
Collect concomitant medications
Collect AEs and SAEs~~

Visit 2: Postoperative day 7 (or at discharge if earlier)

Obtain consent from patient or surrogate (if not already done)
Collect laboratory and transfusion data
Collect extubation time, LOS in the ICU and hospital (if applicable)
Collect AEs and SAEs

Visit 3: Postoperative day 28 (in person if in hospital or by phone)

Obtain consent from patient or surrogate (if not already done)
Collect AEs and SAEs
Collect extubation time, LOS in the ICU, LOS in the hospital

Statistical Analysis Plan:

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses: $H_0: \mu_F / \mu_c \geq (1 + \delta)$ (inferiority) vs. $H_1: \mu_F / \mu_c < (1 + \delta)$ (non-inferiority) will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$ (μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively). Testing of the hypothesis in the final analysis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect. The test of the primary hypothesis in the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the ~~ITT~~modified intention to treat (mITT) population~~-, which will include all randomized patients who agree to remain in the study after debriefing. Randomized patients who did~~

not undergo cardiac surgery or received no IMP will be excluded from the analysis.

A secondary analysis will be performed for the PP population, which will exclude all patients with major deviations. Only in case of demonstrated non-inferiority in the ~~ITT~~mITT and the PP population subsequently the pair of hypotheses: $H_0: \mu_F / \mu_c \geq 1$ vs. $H_1: \mu_F / \mu_c < 1$ will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary.

The safety analysis population (SAF) will include all patients who ~~receive~~opted to remain in the study and received at least one dose of the IMP ~~(if no randomization errors occur, this will be the same population as the ITT population).~~. Safety outcomes will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

FLOW CHART OF ASSESSMENTS

Table 1 Flow Chart of Assessments Performed Throughout the Study

Procedures	Prior to enrolment	Visit 1 Post-randomization (0 to 24 h) ^a	Visit 1a-0-36-h any additional IMP	Visit 2 POD7/DC	Visit 3 POD28
Blood bank receives fibrinogen order ^a	x	(x) ^d			
Inclusion and exclusion criteria	x				
Randomization	x				
IMP administration ^b		x			
Patient (surrogate) debriefing and consent		x		(x)	(x)
Baseline data					
Demographics		x			
Medical history		x			
Preoperative medications		x			
Surgical data					
Intraoperative medications		x			
CPB time		x			
Cross-clamp time		x			
Circulatory arrest		x			
Vital signs		x			
Fluid in- and output monitoring		x			
Inotropes and vasopressors		x		*	
Laboratory assessments					
Chemistry ^f		x		x	*
Hematology ^f		x ^c		x	*
Coagulation profile ^f		x ^c		x	*
Safety labs ^f		x		x	*
Transfusion requirements^g					
RBCs		x		x	*
Pooled and apheresis platelets		x		x	*
Plasma		x		x	*
Other hemostatic products		x		x	*
Blood loss determination using UDPB		x		x	*
Extubation time		x		(x)	(x)
ICU length of stay		x		(x)	(x)
Hospital length of stay				x	(x)
AEs and SAEs		x		x	x
Concomitant medications		x		x	x
Physical examination		x		*	*

Deleted Cells

Deleted Cells

^aFor any activities not completed during this visit, additional visits will be undertaken to complete activities

^a After the start of surgery and during or after CPB.

^b IMP will first can be administered after start/termination of surgery/CPB based on the physician's judgement. The first IMP dose can be administered before and/or fibrinogen levels are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5-2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM-A10 of <12 mm, if available).

^cPrior to Before and 60 minutes after IMP administration.

^d Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

^e 24 hours after IMP administration

^f As per standard practice

() If needed

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol,
Good Clinical Practice and applicable regulatory requirements.

Keyvan Karkouti MD

Coordinating Investigator and Sponsor	Signature	Date
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LIST OF ABBREVIATIONS

Abbreviation	Description
ABP	Allogeneic Blood Product
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CREA	Serum Creatinine
CRF	Case Report Form
CRO	Contract Research Organisation
DDAVP	Desmopressin
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IABP	Intra-Aortic Balloon Pump
IB	Investigator's Brochure
ICU	Intensive Care Unit
IDSMC	Independent Data Safety Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT mITT	Intention-To-Treat Modified Intention-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating Room
PCC	Prothrombin Complex Concentrate
POD	Postoperative Day
POD7/DC	Postoperative Day 7 or at Discharge
PP	Per-Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
REB	Research Ethics Board

SAE	Serious Adverse Event
SAF	Safety Analysis Population
<u>SDM</u>	<u>Substitute Decision Maker</u>
SDV	Source Data Verification
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Event
UDPB	Universal Definition of Perioperative Bleeding
WFI	Water for Injections
WNV	West Nile Virus

1 INTRODUCTION

1.1 Background

Human fibrinogen

Human fibrinogen is a plasma glycoprotein synthesized in the liver, and it circulates in the plasma at a concentration of 2.9–4.5 g/L. In healthy human adults, about 2–5 g of fibrinogen is synthesized daily, and the same amount is catabolized [2,3]. Fibrinogen is essential for primary and secondary hemostasis, wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen into fibrin, and often the interaction of fibrinogen with various proteins and cells. The plasma half-life of fibrinogen, under normal physiological conditions, has been estimated to be 3–5 days [4,5].

Acquired hypofibrinogenemia in cardiac surgery

Coagulopathy leading to excessive bleeding is a serious complication of cardiac surgery requiring cardiopulmonary bypass (CPB). Occurring in more than 10% of cases, it frequently necessitates the transfusion of large amounts of allogeneic blood products (ABPs) and is associated with an increased risk of adverse outcomes, such as multi-organ failure and death [6,7]. While the causes of coagulopathy are usually multifactorial, acute acquired hypofibrinogenemia – defined as an acute drop in fibrinogen plasma level – is believed to be the primary factor [8].

Fibrinogen is a critical component of the coagulation cascade as it is both a precursor for fibrin and a cofactor that enhances platelet aggregation [8,9,10,11]. Unlike other coagulation factors that have a large reserve margin [12], a modest drop in fibrinogen levels to <1.5–2.0 g/L impairs coagulation and increases bleeding complications [13,14,15,16,17,18,19,20,21].

Several factors predispose cardiac surgical patients to developing acquired hypofibrinogenemia. These include loss of fibrinogen due to surgical bleeding, dilution due to administration of fluids and CPB prime, and consumption due to activation of the coagulation cascade during CPB (despite anticoagulation with heparin) [21]. As a result, fibrinogen plasma level drops by an average of 40–50% during cardiac surgery [21], and the critical level of <1.5–2.0 g/L is reached in approximately 5% of patients [22]. It is in this group of patients that fibrinogen supplementation is crucial (and current standard of care) to prevent excessive hemorrhage, large-volume transfusion, and associated adverse outcomes [8,23].

Options available for fibrinogen supplementation

There are two primary options available for fibrinogen supplementation: cryoprecipitate and purified human-derived fibrinogen concentrate [8]. Cryoprecipitate is an ABP that is prepared by thawing fresh frozen plasma at 2 to 4° C, harvesting the resultant precipitate by centrifugation, and then re-freezing it at –20 °C.

Cryoprecipitate is currently the mainstay of therapy in North America, but it has several important limitations.

First, the amount of fibrinogen in each unit of cryoprecipitate is highly variable, ranging from 120 to 796 mg per unit [24], and the transfused fibrinogen is only about 50% recoverable [25,26]. As a result, the response

to cryoprecipitate is limited and variable, ranging from an increase of 0.05–0.1 g/L in fibrinogen levels per unit transfused [24]. To achieve adequate fibrinogen plasma level for hemostasis, therefore, cryoprecipitate is typically administered in 10 unit pools, which exposes patients to the risks of multiple allogeneic units.

Second, thawing, reconstituting in plasma, and pooling of cryoprecipitate is time consuming and labor intensive, which precludes rapid therapy.

Third, cryoprecipitate is not a purified product and contains large amounts of contaminants such as fibronectin and platelet microparticles [24]. These contaminants are not benign and may cause adverse outcomes such as microvascular thrombosis and organ dysfunction [24,27]. In one observational study, cryoprecipitate was independently associated with a two-fold increase in the risk of death, which was larger than the risk associated with any other blood products [28].

Since cryoprecipitate is not purified, it also contains other pro-hemostatic factors in addition to fibrinogen, including coagulation factor VIII, von Willebrand factor, and coagulation factor XIII, which may be beneficial if the cause of bleeding is multifactorial and not solely due to fibrinogen deficiency [8,24]. This theoretical benefit, however, is not supported by existing data, which is not surprising given that these factors do not usually drop below critical levels during cardiac surgery unless there is massive bleeding, in which case patients would receive plasma transfusions that would contain these factors [21,29,30].

The second option for fibrinogen supplementation is to administer **purified human-derived fibrinogen concentrate**, which is currently the mainstay of therapy for acquired hypofibrinogenemia in much of Europe. In North America, however, this therapy is only approved for the treatment of *congenital* hypofibrinogenemia, and its use for acquired hypofibrinogenemia is currently off-label and therefore not widespread.

The fibrinogen concentrate that will be used for this study, *Octafibrin*, is similar to cryoprecipitate in that it is derived from human plasma, but it has several important advantages [31].

First, it undergoes several virus removal and inactivation steps (nanofiltration [20 nm filter] and solvent detergent treatment), which remove contaminants and inactivate viruses. Thus, it is likely to have a lower risk of transmission of infectious agents. Indeed, a Canadian consensus statement from 2008 recommends adoption of pathogen inactivation strategies once they become available to reduce the risk of transfusion transmissible diseases [32].

Second, it is a highly purified concentrate, containing a consistent amount of fibrinogen (approximately 1 g per vial), and the response to therapy is potentially more predictable and more robust than for cryoprecipitate [33,34,35,36].

Third, since (unlike cryoprecipitate) the product can be administered immediately after it is reconstituted with sterile water, it allows for rapid fibrinogen supplementation.

Review of the literature

The use of cryoprecipitate and fibrinogen concentrate in congenital hypofibrinogenemia is supported by several small, non-controlled studies [37,38,39]. Both therapies have also been shown to successfully increase fibrinogen levels and improve clot formation in various in vitro and in vivo models of fibrinogen deficiency [11,40,41,42,43,44,45]. There are also several observational studies showing improved outcomes when fibrinogen supplementation is used in bleeding patients with acquired hypofibrinogenemia, but the bulk of these studies only examined fibrinogen concentrate [46,47,48,49,50,51,52,53,54,55].

There are several studies that have explored the efficacy of fibrinogen concentrate as a ‘universal’ hemostatic agent i.e., not targeted specifically for patients with acquired hypofibrinogenemia – in cardiac and other types of surgery. While several early-stage trials were mostly positive [56,57,58,59,60,61,62,63], a

Cochrane review found that they were inconclusive [64,65]. In a recently completed randomized multi-centered trial, fibrinogen supplementation as first-line therapy in bleeding adult cardiac surgical patients was not efficacious, but this study had multiple limitations. It used fibrinogen supplementation as part of a rigid treatment algorithm that was not consistent with current best-practice, used fibrinogen concentrate as a universal hemostatic agent irrespective of other coagulation defects, and had several design flaws with very high post-randomization drop-outs and transfusion protocol violations [66].

Overall, therefore, the well-established practice of fibrinogen supplementation in bleeding patients with acquired hypofibrinogenemia is primarily based on mechanistic principles rather than high-grade clinical evidence. Yet, this practice is so entrenched that it is uniformly endorsed by existing guidelines [25,67,68,69,70,71,72,73,74], and most would agree that it is neither clinically nor ethically appropriate to withhold fibrinogen supplementation from bleeding patients with confirmed or presumed (in cases of severe bleeding) acquired hypofibrinogenemia [75], thus precluding the conduct of placebo-controlled trials.

To determine the most appropriate fibrinogen supplementation therapy, comparative randomized trials between cryoprecipitate and fibrinogen concentrate are needed, but there is a dearth of such trials. One experimental study found that cryoprecipitate and fibrinogen concentrate have similar abilities in correcting clot firmness in an in vitro model of hemodilution [40]. Two small retrospective observational studies found that fibrinogen concentrate results in a generally more robust fibrinogen response than cryoprecipitate in various groups of patients with acquired hypofibrinogenemia, but these studies were not equipped to compare the safety and effectiveness of the two therapies [33,34]. One randomized comparative clinical trial that included 63 children (<7 years old) who were bleeding after cardiac surgery and had a fibrinogen level of <1.0 g/L found no differences between fibrinogen concentrate and cryoprecipitate in terms of efficacy and safety, but this study was in a pediatric population and was underpowered to prove non-inferiority [76].

Propensity-score matching and TACS study

As background work for the proposed trial, a retrospective comparison of fibrinogen concentrate versus cryoprecipitate was performed at Toronto General Hospital after a point-of-care-based transfusion algorithm for guiding coagulation management in bleeding cardiac surgical patients had been instituted in January 2013 [77].

For the treatment of acquired hypofibrinogenemia, cryoprecipitate was used during the first 11 months after the algorithm was introduced (n=51), and fibrinogen concentrate was used thereafter (n=99), resulting in a homogeneous cohort of patients allowing comparison of the two therapies using propensity-score matching. Despite the low power of the study, the results do suggest that the two therapies have similar risk-benefit profiles. These results have helped inform the appropriate outcome and the required sample size for the randomized trial presented in this protocol (

Field Code Changed

Table 2 and Table 3).

Table 2 Transfusion data in propensity-score matched patients

Variables	Cryoprecipitate (n=43)	Fibrinogen concentrate (n=43)	p value
RBC transfusion			
n (%)	39 (91%)	34 (79%)	0.2
Units	6 (2–12)	4 (1–12)	0.2
Plasma transfusion			
n (%)	36 (84%)	30 (70%)	0.2
Units	4 (2–8)	4 (0–8)	0.2
Platelet transfusion			
n (%)	42 (98%)	35 (81%)	0.03
Pools	3 (1–5)	2 (1–4)	0.04
Total allogeneic units*	12 (7–27)	10 (4–21)	0.15
Severe/Massive bleeding**	30 (70%)	27 (63%)	0.5

*Number of transfused units of red blood cells (RBCs) + units of plasma + pools of platelets

**According to the universal definition of perioperative bleeding in cardiac surgery (occurrence of any of the following: 24-hour chest tube drainage >1L; RBC transfusion ≥5 units; plasma transfusion ≥5 units; rescue therapy with recombinant activated factor VII; or surgical re-exploration) [1]

Table 3 Adverse outcome data in propensity-score matched patients

Variables	Cryo- precipitate	Fibrinogen concentrate	p value
Acute kidney injury*	13 (30%)	10 (23%)	0.6
Hepatic dysfunction**	9 (21%)	5 (12%)	0.4
Stroke	3 (7%)	1 (2%)	0.6
Deep vein thrombosis and pulmonary embolism	0	0	–
Myocardial infarction	3 (7%)	1 (2%)	0.6
Death	9 (21%)	7 (16%)	0.8
Composite***	19 (44%)	12 (28%)	0.17

*>40% drop in estimated glomerular rate within one week of surgery [78]

**Alanine aminotransferase >150 U/L within one week of surgery [79]

***One or more of the listed complications

Further preliminary data was obtained from a recently completed multi-center trial (funded by the Canadian Institutes of Health Research) that assessed the effectiveness of a point-of-care coagulation management algorithm at 12 Canadian hospitals and included 7404 patients (TACS study; Circulation; In Press; Clinical-Trials.gov ID NCT02200419). During the 7-month trial, 447 (6%) patients received cryoprecipitate (n=394) or fibrinogen concentrate (n=61). Transfusion rates and adverse outcomes in these patients (

Table 4) were similar to those in the propensity-matched single-center study described above.

Table 4 Outcomes of TACS study patients who received cryoprecipitate (n=394) or fibrinogen concentrate (n=61)

Variables	Received cryoprecipitate or fibrinogen concentrate (n=447/7404)
RBC transfusion	382 (85%)
Plasma transfusion	368 (82%)
Platelet transfusion	388 (87%)
Total allogeneic units	13 (7–23)
Severe/Massive bleeding	344 (77%)
Adverse outcome data	
Acute kidney injury	113 (26%)
Stroke	23 (5%)
Myocardial infarction	5 (1%)
Death	54 (12%)
Composite*	145 (32%)

*One or more of the listed complications

1.2 Rationale for Conducting the Study

The purpose of this study is to determine whether the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate with respect to efficacy when used to treat bleeding in cardiac surgical patients with acquired hypofibrinogenemia. Hemostatic management in bleeding surgical patients is evolving from empirical therapy with non-purified ABPs to targeted therapy with purified products [80]. The proposed study, by comparing two currently available but distinctly different therapies for treating acute acquired hypofibrinogenemia in bleeding surgical patients, non-purified cryoprecipitate versus purified human-derived fibrinogen concentrate, is well aligned with this change. Given the practical and theoretical advantages of purified fibrinogen concentrate over cryoprecipitate detailed above (improved safety, ease of administration, predictable and robust effect on fibrinogen plasma levels), we believe that a finding of non-inferiority will lead to the use of purified fibrinogen concentrate in place of cryoprecipitate in clinical practice.

This study uses a pragmatic approach for data collection leaving the surgical team to maintain the standard of care accepted by their institution. This is important since other multi-center studies that have included a very strict design so far have failed when studied in later phase trials because of the inability of the sites to accurately follow the specified design, which itself has been criticized for not being consistent with usual clinical practice.

1.3 Benefit-Risk Statement

Substituting either fibrinogen concentrate or cryoprecipitate for the other is not expected to pose any material risks to the participants. Patients will only be included in the trial when their clinicians have ordered fibrinogen supplementation for treatment of bleeding that is thought to be due to acquired hypofibrinogenemia. Thus, no patient will receive fibrinogen supplementation solely for the purposes of this study.

Octafibrin, the fibrinogen concentrate to be used in this study, is under development for the treatment of congenital afibrinogenemia and hypofibrinogenemia. *Octafibrin* has been shown to have comparable (and in some instances superior) pharmacokinetics, hemostatic effects, and safety profile to *Riastap* (CSL Behring), which is an approved (by Health Canada and FDA) purified human-derived fibrinogen concentrate. Ongoing studies looking at the treatment of bleeding and surgery in patients with congenital fibrinogen deficiency, have shown excellent efficacy and safety profile so far. *Octafibrin* has been submitted to EU, USA, and Canada for licensing approval in the indication named above.

The experience to date with this concentrate has shown an excellent safety profile that is in all likelihood superior to that of cryoprecipitate [8,75]. As discussed, fibrinogen concentrate is pathogen inactivated and can be administered in predictable doses, making its administration likely to be both safer than, and at least as efficacious as, cryoprecipitate.

1.4 Principal Investigator ~~(and Sponsor)~~

The Sponsor and Coordinating Investigator of this study is Keyvan Karkouti MD at the Department of Anesthesia, Toronto General Hospital, 200 Elizabeth Street, 3EN, Toronto, ON, Canada.

Octapharma AG will support the conduct of this study by awarding an unrestricted grant for study conduct ~~and~~ supporting data management, statistical services, and supplying the fibrinogen concentrate.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate that the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of ABPs administered during the first 24 hours after termination of CPB.

2.2 Secondary Objectives

The secondary objectives include:

- Comparison of efficacy as measured by the total and individual number of ABPs transfused from the beginning of surgery up to postoperative day 7
- Comparison of the amount of bleeding during the first 24 hours after termination of CPB
- Comparison of the effect on fibrinogen levels observed ~~within 1 hour~~ before and ~~1 hour~~ after the first dose of fibrinogen supplementation
- Comparison of safety as measured by adverse events (AEs) and serious adverse events (SAEs) during the first 28 days after termination of CPB
- Comparison of other secondary safety endpoints including, duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalization.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary endpoint, which is of efficacy, is the comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.

3.1.2 Secondary Endpoints

Secondary efficacy endpoints

- Comparison of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.
- Comparison of major bleeding, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] (**Section 7.2.3**) during the first 24 hours after termination of CPB.
- Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) ~~within 1 hour~~ before and ~~1 hour~~ after the end of the first dose of fibrinogen supplementation.

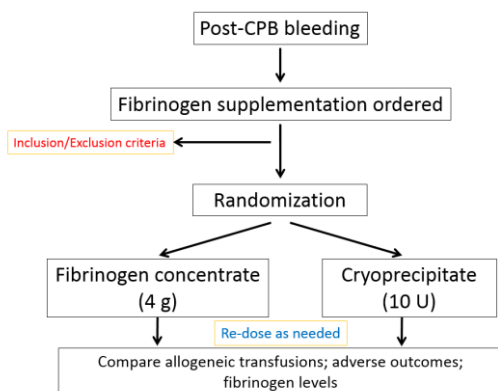
Secondary safety endpoints

- Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, will be compared between the groups up to postoperative day 28.
- Other secondary safety endpoints that will also be compared between groups are:
 - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
 - Duration of intensive care unit (ICU) stay up to postoperative day 28
 - Duration of hospitalization up to postoperative day 28

3.2 Overall Study Design and Plan

This is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require approximately 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank re-



ceives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB) [see flowchart below].

The primary efficacy outcome will be the number of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB, with the primary comparisons being by modified intention-to-treat (ITT-mITT; see Section 9.2).

Safety outcomes will be measured for the first 28 days, which is the duration of participation of each patient in the trial. One interim analysis will be conducted after 600 patients have been treated/enrolled to determine whether the study should be terminated for safety, demonstrated non-inferiority or futility reasons.

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Non-inferiority Design

A non-inferiority rather than superiority design was selected because both products are used to supplement fibrinogen in acquired hypofibrinogenemia. However, purified fibrinogen concentrate has important advantages over cryoprecipitate (it is faster to prepare, easier to administer, has a more predictable response and a better safety profile) that would make it the preferred option if it was found to be non-inferior to cryoprecipitate [81].

3.3.2 Choice of Primary Endpoint

The primary efficacy endpoint is the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the 24 hours after termination of CPB. This is a clinically relevant outcome that has been used in previous randomized fibrinogen trials [57]. Moreover, it is a primary outcome that has been accepted by the European Medicines Agency (EMA) for a major multi-center clinical study (ClinicalTrials.gov Identifier: NCT01475669).

3.3.3 Major Bleeding as Secondary Endpoint

Major bleeding after the index surgery ~~according to~~ based on the UDPB in cardiac surgery is a secondary outcome [1]. This is a validated, prognostically important clinical outcome in cardiac surgery [1,82]. Kinnunen et al. found that patients with major bleeding according to this definition had a greater than four-fold increase in the risk-adjusted odds of death compared with all other patients [82]. In our preliminary data, major bleeding as per the UDPB definition was associated with a 31-fold increase in the risk-adjusted odds of death compared to those with insignificant bleeding. In terms of prognostic value, major bleeding was the second most prognostically important variable (superseded only by renal failure) in a model that included all SAEs.

3.3.4 Dose Rationale

Each time fibrinogen supplementation is ordered, patients will receive either cryoprecipitate (1 dose = 10 units = approximately 4 g) or purified fibrinogen concentrate (1 dose = 4 g) according to their group assignment.

The amount of fibrinogen in each unit of cryoprecipitate is estimated to be approximately 400 mg [24]. Thus, 4 g of fibrinogen concentrate will be dose-equivalent to 10 units of cryoprecipitate, which is the current recommended dose for fibrinogen supplementation in the setting of acute bleeding [81].

3.3.5 Choice of Comparator

The trial will not include a placebo arm because delaying fibrinogen supplementation in bleeding patients with acquired hypofibrinogenemia would expose them to the negative consequences of excessive blood loss, is not consistent with standard practice [83,84], and would withhold an effective treatment from patients and thus be unethical. Moreover, the question being addressed does not meet any of Freedman's five conditions that would justify the use of a placebo control, which are: 1) no standard treatment exists; 2) standard treatment is not better than placebo; 3) standard treatment is a placebo or no treatment; 4) new evidence has shown uncertainty of the risk-benefit profile of the standard treatment; and 5) effective treatment is not readily available due to cost or supply issues [84,85].

3.3.6 External Validity

This will be a multi-center study performed in up to 12 hospitals with different characteristics. Moreover, patients will be recruited and randomized after the clinical team orders fibrinogen supplementation and the only change to routine practice is the choice of fibrinogen supplementation; thus, patient management in the control arm will reflect current practice and in the intervention arm will reflect how fibrinogen concentrate will be used in practice. For these reasons, the study will have good external validity.

3.3.7 Randomization and Baseline Differences

Given the large size of the study and random patient assignment stratified by center, study groups should be well balanced with respect to important clinical variables. The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial, and neither the individual randomizing nor any of the health care providers will know which treatment will be assigned to the patient when fibrinogen supplementation is ordered.

3.3.8 Recruitment and Informed Consent

This is a pragmatic trial that compares two fibrinogen replacement sources that are currently within the standard-of-care for this procedure and poses no additional risks to patients and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (i.e., bleeding during or after 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 ~~qualified~~ qualifies for waiver of informed consent ~~followed by a postoperative debriefing to before randomization. However, we will obtain consent from patients (or their surrogate decision-maker), providing them the opportunity to withdraw from the study. The waiver of consent request after surgery. This consent process~~ meets the criteria of the Tri-council policy statement for the ethical conduct for research involving humans, as is outlined in **Section 10.3.**

3.3.9 Blinding of Investigational Medicinal Product (IMP)

Given that the products have quite different physical differences, it is not possible to blind treating clinicians to group assignment. To minimize bias, treating clinicians will be blinded to group assignment until after the product is prepared and released by the blood bank. Moreover, all attempts will be made to blind clinicians outside of the operating room and intensive care unit as well as outcome assessors ~~will remain blinded by using to group assignment. One method will be to, where possible, use~~ a generic product label in the patient chart and/or the electronic product name (i.e., study fibrinogen product 4 g, rather than specifying type of product used).

3.3.10 Drop-outs and Crossovers

Drop-outs: We anticipate that ~~the intervention will not be administered in~~ <5 ~~approximately 10-15%~~ of randomized patients ~~for will either not receive the treatment, do not undergo cardiac surgery, or do not agree to remain in the study. The majority will be the former, in whom fibrinogen supplementation will be deemed to be not necessary after it was ordered. This but before it is usually administered~~ due to cessation of bleeding or identification of other causes of bleeding ~~after the product is ordered but before it is administered. Patients may also drop out after having received the therapy if they (or their decision-makers) do not provide consent for the study. These patients will be included in the analysis if they provide permission for the use of their data. Based on past experience, however, we do not anticipate a significant number of post-therapy drop-outs.~~ Study sample size has been calculated to compensate for drop-outs.

Product switching: Other than the fibrinogen supplementation order being cancelled, all patients will be treated according to the randomization schedule for the entire treatment period (24 hours after termination of CPB). To ensure minimal product switching, instructions will be entered into the blood bank information system to dictate the randomization product for the 24 hours after randomization and will flag the laboratory

technologists if attempts are made to override the instruction. In very rare circumstances (e.g., after catastrophic bleeding during which several doses of fibrinogen supplementation have already been administered), clinicians may opt to switch from one therapy to the other during the treatment period. The reasons for this request will be collected and described. The anticipated number of product switches will be very few (<1%).

3.3.11 Outcome Assessments and Independent Data and Safety Monitoring Committee (IDSMC)

An IDSMC will review accumulating safety, endpoint, and other study data (recruitment, retention and compliance, data quality and timeliness, risk vs. benefit). The function of the IDSMC will be to protect and serve the recruited patients particularly pertaining to patient safety as well as to assist and advise the Sponsor on medical questions and issues of study conduct and continuation. The IDSMC will be independent of the investigating team and the Sponsor in operating and formulating recommendations. The IDSMC full role will be detailed in the IDSMC Charter.

4 STUDY POPULATION

4.1 Population Base

4.1.1 Approximately 1,200 bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenemia after CPB will be enrolled into the study, with approximately 600 patients assigned to each of the two treatment groups. Patients having other procedures in addition to cardiac surgery will be eligible as long as cardiac surgery with CPB is the index procedure, meaning the heart is the main organ being operated on, with a cardiac surgeon leading the operation. Inclusion Criteria

~~4.1.2~~ Inclusion Criteria

1. Patients undergoing index cardiac surgery with CPB in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).

~~2.~~

~~4.1.3~~ 4.1.2 Exclusion Criteria

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

1. Receipt of fibrinogen-~~containing~~rich products, ~~including (fibrinogen~~ concentrate or cryoprecipitate within 24 hours before surgery ~~(to exclude patients with significant blood loss before surgery)~~
2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate
3. Refusal of ABP, fibrinogen concentrate or cryoprecipitate due to religious or other reasons
4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation, ~~which is the upper limit of the normal range~~)
5. Known pregnancy

4.2 Prior and Concomitant Therapy

Details on medications taken within 1 week before enrolment and any concomitant medications taken during the study must be recorded in the case report form (CRF).

4.2.1 Permitted Concomitant Therapy

Concomitant administration of any therapies required as part of standard patient care is permitted, but must be recorded in the CRFs. We will record all hemostatic drugs or products administered (e.g., heparin and protamine dose, antifibrinolytic drugs, desmopressin, recombinant activated factor VII, prothrombin complex concentrate, idarucizumab, andexanet alpha, or topical hemostatic agents), as well as all procedures that may influence amount of bleeding (e.g., retrograde autologous priming of CPB circuit, cell salvage).

In addition, concomitant medications used to treat SAEs will be reported throughout the duration of follow-up (up to postoperative day 28).

4.2.2 Forbidden Concomitant Therapy

Fibrinogen-~~containing~~rich products within 24 hours before surgery are not allowed. This specifically refers to cryoprecipitate or fibrinogen concentrate, not plasma. Patients undergoing plasmapheresis will be included, but the blood products used as part of the plasmapheresis will not be included in the transfusion outcomes.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients ~~in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study non-interpretable, unnecessary withdrawal of patients will be avoided, but only in rare circumstances. Examples include randomization of ineligible patients, adverse events attributed to previous doses of IMP, and specific indication for a specific fibrinogen therapy (either cryoprecipitate or fibrinogen concentrate).~~

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

4.3.2 Patient Replacement Policy

Patients withdrawn from the study for safety reasons will not be replaced.

4.4 Assignment of Patients to Treatment Groups

Patients will be assigned to treatment with either *Octafibrin* or cryoprecipitate using a permuted-block, stratified (by center) random allocation scheme prepared by a biostatistician not involved in the conduct of the trial. Group allocation will apply to all fibrinogen supplementation orders during the treatment period (up to 24 hours after termination of CPB).

Subjects/patients are not permitted to re-enroll in the study.

4.5 Relevant Protocol Deviations

In the case of any major protocol deviation, the Investigator (Sponsor) will decide on the further participation of the patient in this study.

4.6 Subsequent Therapy

~~During the first 36~~For 24 hours after termination of CPB, ~~the patient will be treated as per the standard of care at the participating institution.~~

~~Additional infusions of the randomized IMP patients can be given if felt necessary by the clinical team. All information on subsequent dosing should be captured and the reason for these~~receive additional infusions.

~~should be documented in the patient record.~~ doses of assigned IMP as clinically indicated. Patients requiring additional doses after 24 hours will receive cryoprecipitate.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

5.1 Characterization of Investigational Products

5.1.1 Octafibrin

Octafibrin is a highly purified, lyophilized human plasma fibrinogen concentrate without added albumins. The manufacturing process of *Octafibrin* includes two dedicated virus inactivation/removal steps, i.e., solvent/detergent treatment and nanofiltration.

The solvent/detergent treatment mode of action causes enveloped viruses to be irreversibly destroyed. These include the most transfusion-relevant viruses, such as human immunodeficiency virus types 1 and 2 (human immunodeficiency virus [HIV]-1, HIV-2), hepatitis B virus (HBV) and hepatitis C virus (HCV), and many other adventitious agents, e.g., newly emerging enveloped viruses, such as West Nile virus (WNV).

The Planova 20N filter was specifically developed by Asahi Kasei Pharma Corp. to remove infectious agents from protein solutions on the basis of their size. Thus, this nanofiltration step is in principle effective for removing even very small enveloped and non-enveloped viruses. Nanofiltration may be the only method to date permitting efficient removal of enveloped and non-enveloped viruses under conditions where 90–95% of protein activity is recovered [86].

Composition of Octafibrin

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous (IV) use. Its ingredients are listed in Table 5.

Table 5 Composition of *Octafibrin*

Ingredients	Quantity per mL reconstituted solution, mean values	Standard
Active ingredient		
Fibrinogen as clottable protein	20 mg	Ph. Eur.
Excipients		
Sodium chloride	6 mg	Ph. Eur.
Sodium citrate dehydrate	1.5 mg	Ph. Eur.
Glycine	10 mg	Ph. Eur.
L-arginine hydrochloride	10 mg	Ph. Eur.

Ph. Eur. = Pharmacopoeia Europaea

Octafibrin is a powder for solution for injection supplied in labeled 100 mL vials and provided by Octapharma. *Octafibrin* will be reconstituted with 50 mL sterile water for injections (WFI) produced according to GMP and provided by the clinical site.

The final product will be released by the responsible Octapharma Quality Control Department, according to a defined final product specification.

Conditions for Storage and Use

The IMP has to be stored at room temperature (not more than 25°C) and protected from light. The product must not be frozen. The Investigator/authorized personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

Dose and Dosing Schedule

Patients randomized to *Octafibrin* will receive 4 g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB.

Preparation

Each vial of *Octafibrin* will be reconstituted with 50 mL WFI at room temperature (not more than 25°C). *Octafibrin* dissolves at room temperature to an almost colorless and slightly opalescent solution within 10 minutes. If the solution is cloudy or contains particulates, it should not be used.

Method of Administration

The 4g of *Octafibrin* will be administered immediately after reconstitution over 10 minutes through a free-flowing IV by syringe injection. *Octafibrin* should not be mixed with other medicinal products or crystalloid intravenous solutions.

Packaging and Labelling

Octafibrin will be packaged and labeled for the trial by Octapharma. The label will comply with the Canadian national requirements.

Several batches of IMP may be used throughout the study. The batch numbers will be recorded in the CRFs and reported in the final study report.

5.1.2 Cryoprecipitate

Patients randomized to cryoprecipitate will receive 10 units each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB to 24 hours. Cryoprecipitate will be stored, thawed, and pooled by the blood bank according to current standards. The cryoprecipitate will be infused as per standard hospital protocols at the participating institutions (i.e., infused over 10–30 minutes through standard 170 µm blood infusing set).

5.2 Blinding, Emergency Envelopes, and Breaking the Study Blind

This is a single-blind randomized study, with patients randomized to equivalent doses of cryoprecipitate (1 dose = 10 units) or *Octafibrin* (1 dose = 4 g) (see **Section 5.1**). Given the physical differences in the products, it is not possible to blind clinicians to the IMPs.

The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial (see **Section 9.3**). To minimize bias, neither the individual randomizing nor any of the health care providers will know which treatment will be assigned to a given patient when fibrinogen supplementation is ordered.

Patients and outcome assessors will be blinded by having the compatibility label that will be placed in the patients' paper or electronic chart state "Study fibrinogen product 4g" rather than the actual product used.

5.3 Treatment Compliance

5.3.1 Drug Dispensing and Accountability

A drug dispensing log and the inventory will be kept current by the Investigator, detailing the dates and quantities of fibrinogen concentrate dispensed to each patient. The inventory will be available to the monitor to verify drug accountability during the study. Any unused or partially used fibrinogen concentrate, including ~~empty~~unused returned containers, will be accounted for.

Unused fibrinogen concentrate may be destroyed at the study site, however, only after drug accountability has been verified and fully re-conciliated and written approval from the Sponsor has been obtained.

5.3.2 Assessment of Treatment Compliance

Fibrinogen supplementation will be ordered and administered by the clinical team in the hospital and will not be dependent on patient compliance.

6 STUDY CONDUCT

All patients having cardiac surgery with CPB will be the source of potential patients in the study. Patients will be randomized if they bleed after termination of CPB and the clinical team determines that fibrinogen supplementation is required according to current clinical standards for up to 24 hours after termination of CPB. Once the clinical team orders fibrinogen supplementation, the blood bank technologist will confirm patient eligibility and randomize the patient (according to a prepared randomization schedule) to *Octafibrin* or cryoprecipitate and prepare the product.

Patients will be treated according to their group allocation for any subsequent doses for the duration of the treatment period, which is 24 hours after termination of CPB.

Standard coagulation measures, including fibrinogen plasma level, will be obtained ~~within one hour before and one hour after the end of each fibrinogen supplementation, (ideally within an hour as per standard best practice. The first). Due to the nature of bleeding in these cases, however, IMP doses~~ can be administered before fibrinogen level ~~results are known in bleeding patients, but all subsequent doses must have confirmation of.~~ Clinical indications for IMP administration are bleeding in the setting of suspected or confirmed low fibrinogen ~~level~~ levels (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available, which is the treatment threshold recommended by current guidelines for treatment of bleeding patients) [8,70,71]. ~~In rare cases clinicians may deem it clinically necessary to administer fibrinogen supplementation at levels >2.0 g/L (e.g., uncontrollable bleeding).~~

All AEs and SAEs occurring after termination of CPB to postoperative day 28 will be recorded. Patients will be followed by research coordinators in each institution. All clinical outcomes will be obtained from patients' medical records and electronic records, history and physical where needed, and via phone contact during the follow-up visits.

The flow chart of assessments by study visit is given on page x.

6.1 Study Procedure

6.1.1 Prior to Enrolment

First fibrinogen supplementation order from the surgical team received at the blood bank

The blood bank technologist will confirm the following:

- CPB has been terminated
- Inclusion and exclusion criteria are met
- Coagulation measures (coagulation profile) are available or have been collected

The blood bank technologist will then randomize patients to fibrinogen or cryoprecipitate according to the randomization schedule and prepares and releases the product

Subsequent fibrinogen supplementation orders for the next 24 hours

- In addition to repeating the procedures for the first dose, the blood bank technologist will also confirm that fibrinogen plasma level have been re-checked. ~~If yes, and~~ record value ~~and confirm~~ < 2.0 g/L (by the Clauss method), ~~in addition to equivalent point of care alternatives e.g., ROTEM assay FIBTEM A10 of < 12 mm, if available.~~

If no, ask for sample to be sent to the lab prior to ~~and after the end of~~ (within approximately 1 hour) the administration of IMP

- ~~[Study drug should not be released at this point by the blood bank without lab confirmation]~~

Time of IMP infusion in the Operating Room (OR)

~~Nurse or coordinator will collect the~~ The following ~~information will be collected:~~

- What time was the IMP administration started?
- Time of coagulation analyses (coagulation profile). Samples to be sent to the laboratory ~~prior to IMP infusion before~~ and ~~at 60 min~~ after ~~the end of~~ IMP infusion (exact sampling time needs to be recorded).

6.1.2 Visit 1: First post-randomization visit (0 to 24 hours after termination of CPB)

For any specified activity that cannot be completed on this visit, additional visits will be made until all study data are obtained.

- Obtain consent from patient or surrogate
- Collect baseline data
 - Demographics
 - Medical history
 - Preoperative concomitant medications
- Collect surgical data
 - Intraoperative concomitant medications
 - CPB time
 - Cross-clamp time
 - Circulatory arrest
 - Vital signs
 - Fluid in- and output monitoring
 - Inotropes and vasopressors
- Collect laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile before and after IMP administration
 - Safety labs (creatinine, liver function tests [AST, ALT], troponin)

- Collect all transfusion requirements and hemostatic agents (number and timing) for the 24 hour period after infusion
 - ~~RBCs~~
 - ~~Pooled or apheresis platelets~~
 - ~~Plasma~~
- ~~Collect bleeding components using the UDPB criteria~~
- ~~Collect extubation time~~
- ~~Collect length of stay in the ICU~~
- ~~Collect concomitant medications~~
- ~~Collect AEs and SAEs~~

~~6.1.3~~ Visit 1a: 0-36 hours if any subsequent doses of IMP are given

- ~~Coagulation analyses (including coagulation profile). Samples to be sent to the laboratory prior to IMP infusion and at 60 min after IMP infusion (exact sampling time needs to be recorded).~~
- ~~Collect laboratory assessments where available as part of routine care~~
 - ~~Chemistry (sodium, potassium, chloride, bicarbonate, pH)~~
 - ~~Hematology (complete blood count)~~
 - ~~Coagulation profile before and after IMP administration~~
 - ~~Safety labs (creatinine, liver function tests [AST, ALT], troponin)~~
- ~~Collect transfusion requirements (number and timing) for the 24 hour period after infusion~~
 - ~~RBCs~~
 - ~~Pooled or apheresis platelets~~
 - ~~Plasma~~
- Collect bleeding components using the UDPB criteria
- Collect extubation time
- Collect length of stay in the ICU
- Collect concomitant medications
- Collect AEs and SAEs

6.1.46.1.3 Visit 2: Postoperative day 7 (or at discharge if earlier)

- Obtain consent from patient or surrogate (if not already done)
- Collect daily laboratory assessments where available as part of routine care
 - Chemistry (sodium, potassium, chloride, bicarbonate, pH)
 - Hematology (complete blood count)
 - Coagulation profile
 - Safety labs (creatinine, liver function tests [AST, ALT], bilirubin, troponin)
- Collect transfusion requirements

- Collect extubation time (if applicable)
- Collect length of stay in the ICU and hospital (if applicable)
- Collect AEs and SAEs

~~6.1.56.1.4~~ **Visit 3: Postoperative day 28 (in person if in hospital or by phone)**

- Obtain consent from patient or surrogate (if not already done)
- Collect AEs and SAEs
- Collect extubation time (if applicable)
- Collect length of stay in the ICU (if applicable)
- Collect length of stay in the hospital (if hospital stay is extended)
- Collect concomitant medications

After Visit 3 or on postoperative day 28, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

~~6.1.66.1.5~~ **Time Windows Used in this Study, including Tolerances**

In this study, the following time windows and tolerances apply:

Table 6 Time Windows Used in this Study

Time point	Time stated	Tolerance
Interval between visits		
Blood sampling	before Before IMP administration	≤ 30 Up to 75 minutes
	60 minutes after After IMP administration	± 45 Up to 75 minutes
	Day 7	± 1 day
	Day 28	± 2 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The **duration of the treatment period** is 24 hours from the end of CPB.

The **duration of the study** for an individual patient is 28 days from patient enrollment when patients will be contacted in person or by phone post-discharge.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when 1,200 patients are randomized and have finalized day 28 (or early termination at the time of the interim analysis). It is estimated that the study will take approximately 2 years for recruitment.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor, in consultation with the Independent Data Safety Monitoring Committee (IDSMC), reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Investigators will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and research ethics boards (REBs) will be informed in accordance with national regulations.

Early termination of the study as a whole or by center may apply for the following reasons:

Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk assessment.

Early Termination at an Individual Study Center

At any time, the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The a priori determined required recruitment rate is not met.

Should the study be prematurely terminated, all remaining *Octafibrin* will be returned to Octapharma or locally destroyed.

7 ASSESSMENTS AND METHODS

7.1 Baseline Data

The baseline information and medical history will be recorded during Visit 1, i.e., as soon as possible after randomization.

7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are sex, age, height, weight, and Body Mass Index (BMI).

7.1.2 Medical History and Prior/Concomitant Medications

The medical history will be obtained by interviewing the patient or from the medical records.

Prior and concomitant medications will be obtained.

7.2 Study Assessments

7.2.1 Surgical and Surgery-Related Data

The following surgical data will be collected: details of procedure, CPB duration, CPB start-end times, cross-clamp duration, circulatory arrest duration, fluid intake and output, any medications administered, hemodynamic support (e.g., IABP), as well as any blood conservation methods used (e.g., hemoconcentration, retrograde prime, cell salvage).

In addition, extubation time, ICU length of stay, and hospital length of stay will be documented.

7.2.2 Transfusion Data

All blood products and hemostatic agents released from the blood bank and transfused will be collected from the blood bank databases. These include ABPs: RBCs, pooled or apheresis platelets, and plasma. Other hemostatic agents include: DDAVP, prothrombin complex concentrates (PCC), activated recombinant factor VII, idarucizumab, and andexanet alpha. ~~For the purposes of the study, a unit will refer to 1 unit of RBCs, 1 dose of pooled or apheresis platelets, or 1 unit of plasma.~~

7.2.3 Bleeding Data

The comparison of ‘major’ bleeding based on the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery [1] (Table 7) will be assessed as a secondary endpoint. The UDPB is a multistage definition for perioperative bleeding based on easily measured clinical end points, including total blood loss from chest tubes within 12 hours, ABPs transfused, surgical re-exploration including cardiac tamponade, delayed sternal closure, and the need for salvage treatment. The following components of the score will not be used for this study: delay in chest closure and use of cryoprecipitate.

Depending on these components, bleeding is graded as insignificant, mild, moderate, severe, or massive. (Table 7) [1].

Table 7 Bleeding categories according to the UDPB in adult cardiac surgery (if different categories indicate mixed definitions of bleeding, the worst definition applies) [1]

Bleeding definition	Postoperative chest tube blood loss within 12 h (mL)	RBC (units)	FFP (units)	PLT (units)	Cryoprecipitate	PCCs	rFVIIa	Reexploration /tamponade
Class 0 (insignificant)	<600	0 [*]	0	0		No	No	No No
Class 1 (mild)	601–800	1	0	0		No	No	No No
Class 2 (moderate)	801–1000	2–4	2–4	Yes		Yes Yes	No	No
Class 3 (severe)	1001–2000	5–10	5–10	NA		NA NA	No	Yes
Class 4 (massive)	>2000	>10	>10	NA		NA NA	Yes	NA

FFP, fresh frozen plasma; NA, not applicable; PCCs, prothrombin complex concentrates; PLT, platelets; rFVIIa, recombinant activated factor VII; UDPB, universal definition for perioperative bleeding.

~~*Correction of preoperative anemia or hemodilution only; the number of RBCs used should only be considered in the UDPB when accompanied by other signs of perioperative bleeding.~~

7.3 Laboratory Assessments

7.3.1 Test Parameters and Laboratories

Table 8 summarizes all test parameters and the laboratories responsible for analysis.

Table 8 Test parameters and laboratories

Test	Material needed	Responsible laboratory
Coagulation profile		
(PT, PTT, INR, fibrinogen activity via Clauss technique)	Citrated blood	Local
ROTEM FIBTEM A10	Citrated blood	Local, if available
Hematology – standard panel as per local lab	Citrated blood	Local
Clinical chemistry – standard panel as per local lab	Serum	Local
Safety labs		
Troponin	Serum	Local
AST/ALT	Serum	Local
Bilirubin	Serum	Local
Creatinine	Serum	Local

7.3.2 Blood Sampling

All blood sampling will be performed as per standard practice at the local institution.

The *actual* time of blood sampling for fibrinogen will be recorded in the CRF.

7.3.3 Citrated Blood

Citrated blood as required by the local laboratory will be collected and processed in accordance with local requirements.

7.3.4 Serum

For the determination of clinical chemistry and safety labs (alanine aminotransferase, ALT; aspartate aminotransferase, AST; serum creatinine, CREA; troponin), where a serum blood sample has been collected.

7.3.5 Recording of Clinically Significant Abnormal Laboratory Values as AEs/ADRs

Other than abnormal laboratory values due to the underlying condition, the Investigator must assess the clinical significance of abnormal laboratory values outside the specified normal range (see **Section 7.4**). Any clinically significant abnormalities will be documented. All specified clinically significant abnormalities will be documented as AEs/SAEs and investigated.

Additional tests and other evaluations required to establish the significance or etiology of specified abnormalities or to monitor the course of an AE will be obtained if clinically indicated. Follow-up will persist until resolution or up to the Study Completion Visit, whichever occurs first.

7.4 Safety Assessments

7.4.1 Assessments for Safety Endpoints

The following drug safety information will be collected:

- AEs and SAEs temporally associated with the administration of IMP (for definitions and reporting requirements, see **Sections 7.4.2, 7.4.3, and 7.4.4**); and [Appendix 15.1](#)).
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see **Section 7.4.5**).

7.4.2 Adverse Events (AEs)

Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Principal Investigator (Sponsor).

Collection of AEs

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as “How have you been since the last visit/during the previous study period?”. In addition, the Investigator will check the patient records for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the CRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the likelihood that they were related to the IMP (causality). The Sponsor will be responsible for assessing the expectedness of each ADR (expected or unexpected).

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

Severity of AEs

The intensity/severity of AEs will be graded as follows:

Mild: an AE, usually transient, which causes discomfort but does not interfere with the patient’s routine activities

Moderate: an AE which is sufficiently discomforting to interfere with the patient’s routine activities

Severe: an AE which is incapacitating and prevents the pursuit of the patient’s routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

Causality of AEs

~~The relationship of AEs to the administered IMP will be assessed by the Investigator:~~

All AEs will be assessed by a blinded Investigator as to whether they can be explained by the patient’s underlying condition or surgical course. If they are not explainable, then the Investigator will make a determination of the relationship of the AE with the IMP as follows:

Probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response

pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.

Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

Unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.

Not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

Unclassified: reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

Expected: an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.

Unexpected: an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved (by Study Completion visit)
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death will be fully documented and reported.

Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started

- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Principal Investigator (Sponsor).

7.4.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is another important medical event.

In this study a number of SAEs are expected because of the nature of the surgery. These events will not be considered as SAEs in this study.

NOTE: The term ‘life-threatening’ refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgement ~~should~~will be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent ~~should~~will be reported as an SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.4.4 SAE Reporting Timelines

All SAEs, ~~whether or not they are~~ suspected to be related to study treatment, ~~are to~~will be reported ~~immediately~~within 24 hours of recognition to the sponsor by telephone, fax, or email ~~to the Sponsor~~.

Keyvan Karkouti MD

Department of Anesthesia
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~~Canada~~

Phone: 1-416-340-5164

Fax: 1-416-340-3698

Email: keyvan.karkouti@uhn.ca

In addition, all serious adverse events related to Octafibrin will be reported within 24 hours after 1-month of recognition of the event, a Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

Fax: +43 1 61032-9949

Email: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

Waivers from the SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.4.5 Other Relevant Safety Information

Pregnancies

Patients who are known to be pregnant will not be included in the study. In patients of reproductive age, pregnancy is ruled out prior to the cardiac surgery as part of standard of care.

Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as an SAE.

a) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

b) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

c) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the electronic CRF (eCRF) must be supported by source data in the patient records, with exceptions listed in **Section 8.1.2**.

The Investigator will permit study-related monitoring, audit(s), REB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (e.g., sub-investigators, clinical research coordinators/assistants, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms (CRF)

After all personal identifiers have been removed, research related data collected will be stored on a secured web-server at ERGOMED, which is a global company specializing on the conduct of clinical trials (headquarters located in England; secured database centre located in Germany). It meets all Canadian and U.S.A. privacy laws.

Study site staff (e.g., blood bank technologist, research coordinator/assistant) will be responsible for completing a CRF for each patient enrolled. All site personnel will be trained on CRF completion. The site is also provided with the approved CRF Completion Guidelines which will assist in data entry and data issues/questions. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or to change CRF data must be listed in the Delegation of Authority Log.

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and ‘manual’ queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query’s response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)’ designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An Investigator’s Brochure (IB) will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor’s possession necessary for the Investigator to be fully and accurately informed about the safety of *Octafibrin*.

The IB will be updated at regular intervals by Octapharma and whenever relevant new information concerning the IMP becomes available. This will be delivered by Octapharma to the Principal Investigator who will distribute to the approved study sites.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing CRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

At each study site the Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) are authorized to perform tasks relating to the study.

8.4 Investigator’s Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., cop-

ies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the site investigators will supply the Sponsor or designate, such as the monitors with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Safety Monitoring Committee

An IDSMC will be established by the Sponsor. The IDSMC will be composed of recognized experts in the field of statistics, perioperative medicine, and hematology who are not actively recruiting patients.

The IDSMC will review relevant data periodically (approximately after every 100 patients have been recruited) during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific charter will define in detail the composition, responsibilities, and procedures of the IDSMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external statistician. The principal statistical methodology is described in this section. Further specifics regarding the statistical analysis will be provided in the Statistical Analysis Plan (SAP).

9.1 Determination of Sample Size

The statistical analysis of the primary efficacy variable, i.e., the amount of ABPs, will be based on the mean number of ABP units within the first 24 hours after termination of CPB (μ_F and μ_C).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to the treatment with cryoprecipitate with respect to the mean number of ABP units, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \mu_F / \mu_C \geq (1 + \delta) \quad \text{vs.} \quad H_1: \mu_F / \mu_C < (1 + \delta)$$

will be carried out with a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_C denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term), with treatment group as main effect.

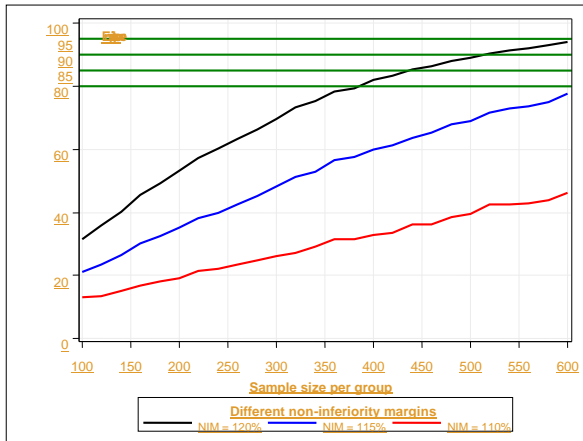
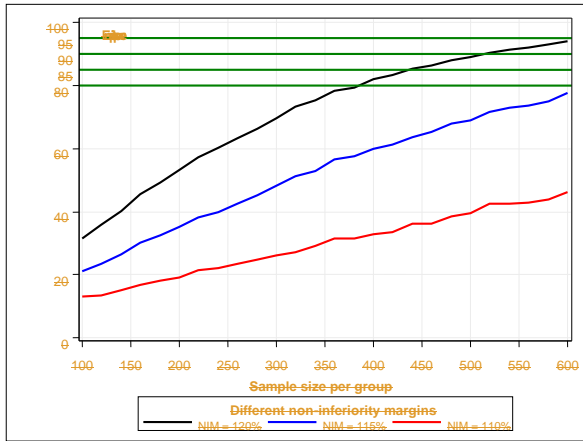
The test of the primary hypothesis in the planned interim and the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_C derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

Based on this method, a one-sided overall type I error probability $\alpha = 0.025$ and a non-inferiority margin of $\delta = 0.20$, simulations have been performed to study the power of the test for different sample sizes.

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units- [\(each dose of apheresis or pooled platelets was counted as 4 units for this analysis to correspond with the number of units in pooled platelets\)](#). The empirical distribution function with these sample characteristics was chosen based on results of the TACS study (see **Section 1.1**) with the same endpoint in the same indication and similar treatment.

10,000 studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

The plot below displays the empirical power curves for the test of H_0 vs. H_1 using the Poisson counting regression model analyzed with SAS PROC GENMOD for different sample sizes and values of δ .



As the diagram shows, an empirical power of >90% can be expected with a sample size of at least 550 patients per treatment group if a δ of 0.20 is chosen. For smaller values of δ , no sufficient power can be attained with operationally feasible sample sizes. The choice of the non-inferiority margin $\delta = 0.20$ is also motivated by the large variation of the primary endpoint that is to be expected from previous studies reflecting current clinical practice.

Therefore, it is planned to conduct the study with a maximum sample size of 600 patients in each treatment group and a non-inferiority margin of $\delta = 0.20$.

Assuming that a proportion of about 10% randomized patients will not be treated after randomization or for whom the endpoint cannot be obtained, this would ensure that data on at least 550 patients per treatment group in the ~~ITT~~mITT population will be available for the statistical analysis as derived from the sample size calculation.

9.2 Statistical Analysis

For the statistical analysis of the efficacy parameters the following analysis populations will be considered:

The ~~ITT~~primary analysis will be performed on the modified intention to treat (mITT) population~~-All, which will include all~~ randomized patients who agree to remain in the study after debriefing. Randomized patients who did not undergo cardiac surgery or received no IMP will be excluded from the analysis. It is anticipated that approximately 10-15% of patients will fall into these categories. In the event that a patient receives treatment that is not in concordance with the randomization schedule, the treatment group will be defined according to the randomization (rather than the actual treatment received).

~~If no randomization errors are observed the ITT population will be identical to the safety analysis population (SAF), which will be all randomized patients who opted to remain in the study and who received at least one dose of IMP.~~

The per-protocol (PP) population: This analysis population will consist of all patients in the ~~ITT~~mITT population, excluding patients with major protocol deviations. The following patients will be excluded:

- ~~Patients who do not receive an IMP after randomization~~
- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 80% of the planned dose
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meeting prior to unblinding for the interim and final analyses. Decisions and outcome will be approved by the Principal Investigator (Sponsor) in consultation with the collaborator (Octapharma).

The ~~ITT~~mITT analysis population is considered the primary population for analysis of the primary efficacy objective. The evaluation of the primary efficacy endpoint will additionally be performed for the PP population.

9.2.1 Efficacy Analysis Plan

Primary endpoint: total amount of ABP units

The primary efficacy variable is the total number of ABP units (RBCs, pooled and apheresis platelets and plasma) used within 24 hours after termination of CPB. Apheresis units will be counted as their equivalent

pooled counterparts (for platelets, 1 apheresis unit = 4 pooled units; for plasma, 1 apheresis unit = 2 pooled units).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses:

$$\begin{aligned} H_0: & \mu_F / \mu_c \geq (1 + \delta) \text{ (inferiority)} \\ \text{vs. } H_1: & \mu_F / \mu_c < (1 + \delta) \text{ (non-inferiority)} \end{aligned}$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect.

The test of the primary hypothesis in the final analysis will be based on the one-sided CI for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the ITT population. A secondary analysis will be performed for the PP population.

Only in case of demonstrated non-inferiority in the ~~ITT~~ and the PP population subsequently the pair of hypotheses:

$$\begin{aligned} H'_0: & \mu_F / \mu_c \geq 1 \\ \text{vs. } H'_1: & \mu_F / \mu_c < 1 \end{aligned}$$

will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary.

Secondary endpoints

The following measurements will be considered exploratory secondary endpoints in the analysis of efficacy of the study treatments:

- Total number of units of ABPs administered from start of cardiac surgery until 7 days after surgery or discharge.
- Distribution of major bleeding type, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery.
- Change in fibrinogen plasma level (measured using the Clauss assay) ~~within 1 hour before and 1 hour~~ after fibrinogen supplementation for first and subsequent doses.
- Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets, and plasma.
- Primary analysis of secondary endpoints will be based on the ~~ITT~~ population. Additionally, the same analyses will be done on the PP population.
- The total number of ABPs within 7 days/discharge and the different subtypes of ABPs will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.
- Frequency distributions of the major bleeding type according to UDPB will be presented for each treatment group.
- Change in fibrinogen plasma level will be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the *Octafibrin* and cryoprecipitate treatment groups and the corresponding 95% CI will be calculated.

Further exploratory endpoints

Exploratory analyses will include comparisons of length of hospital stay, ICU stay, and ventilation time.

Data collected as part of this study will be used for an economic analysis to be conducted at a later date.

Subgroup analyses for efficacy

The following subgroups will be analyzed: non-elective surgery; complex surgery (procedures other than isolated ACB, single valve, or repair of ASD); ~~and excluding patients who underwent very high-risk procedures. The latter will include all patients who were in critical condition before surgery as well as those determined to be at very high-risk blinded (to the IMP and all outcomes) adjudicators.~~

9.2.2 Safety Analysis Plan

The safety analysis population (SAF) will include all patients who ~~receivereceived~~ at least one dose of the IMP (if no randomization errors occur, this will be the same population as the ~~ITT~~ population). Safety outcomes will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

Grades 3 and 4 SAE (as per the FDA criteria: severe or life-threatening) data will be collected in cases where consent for remaining in the study cannot be obtained. As it relates to this study, typical SAEs of interest will include death, serious thromboembolic events (stroke, myocardial infarction, renal failure, deep vein thrombosis, pulmonary embolism, and hepatic failure). The only data that will be collected other than the SAE type, will be its relation to IMP administration. No data will be collected on patients who refuse consent.

Adverse events, including thromboembolic events

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version as specified in the Data Management Plan. The analysis will focus on treatment emergent adverse events (TEAEs), i.e., AEs that started or worsened after start of infusion with IMP.

All TEAEs, related TEAEs (i.e., AEs probably or possibly related to the IMP), and serious TEAEs will be summarized and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in withdrawal from the study, respectively, will be tabulated using frequency tables if a reasonable number of events of this type are observed.

Analogous frequency tables for thromboembolic events (TEEs, identified using MedDRA SMQs) will be provided.

Patient listings will be provided for patients with SAEs, TEEs, AEs leading to withdrawal from study, and AEs leading to death. These listings will also include patients enrolled but not randomized.

Mortality

The number of patients who died will be summarized. A possible difference between treatment groups will be estimated by a risk ratio with 95% CI. Kaplan-Meier estimates for the time to death distribution will be calculated and graphically presented.

Routine laboratory data

All laboratory values will be classified as normal or abnormal according to the laboratories' normal 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
- Qualitative data based on reference ranges will be described according to the categories (i.e., low, normal, high)

- Shift tables illustrating changes with respect to the laboratories' normal ranges between baseline and a defined scheduled time point
- Number and frequency of patients with clinically significant laboratory values. A separate patient listing will be provided

9.2.3 Handling of Missing Data

In general, missing data will not be imputed. Due to the nature of the study, important variables will have few missing data.

9.3 Randomization, Stratification, and Code Release

Eligible patients will be randomly assigned to receive either *Octafibrin* or cryoprecipitate. Randomization lists using a permuted-block, randomization scheme (stratified by site) will be prepared by the biostatistician and integrated in to the eCRF system. The randomization lists will then be provided to the blood banks of the participating centers who will be in charge of providing the IMP to the OR.

Patients will be identified using a sequential numbering system.

9.4 Interim Analysis

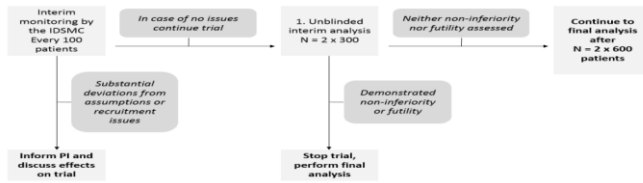
The study employs a group-sequential design that involves one pre-planned interim analysis after 600 patients have ~~completed the study-been enrolled~~.

In addition, the IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study. This data monitoring serves the purpose of an ongoing assessment of recruitment problems as well as the compatibility of the accumulating data with the assumptions made at study start. The extent of the information to be reviewed will be defined in the IDSMC charter. The IDSMC will keep all these data monitoring results in strict confidence. Only in case of identified issues during their data monitoring the IDSMC will advise the Principal Investigator (Sponsor) in a non-treatment-disclosing manner on the problems.

The interim analysis will be an unblinded interim analysis with an adjusted type I error rate according to the O'Brien-Fleming method after 600 patients have been enrolled. After this interim analysis, a positive outcome may be claimed and enrolment may be stopped if the test of H_0 vs. H_1 in the ~~FF-mITT~~ population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$ rejects the null hypothesis (efficacy stop). A full final analysis including all study data will be performed and reported if enrolment is stopped after the interim analysis. Also at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

Otherwise, the study will continue until the maximum sample size of $n = 2 \times 600$ patients, is reached. The final analysis will be performed as described above, but with an adjusted one-sided significance level of $\alpha_2 = 0.02242$ to maintain the overall one-sided significance level of $\alpha = 0.025$.

The flow chart below illustrates the decision process underlying the interim analyses. Further details of the interim analyses will be described in the respective sections of the SAP.



10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an REB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO).

10.2 Approval of Study Documents

The study protocol, a sample of the debriefing form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate REB and the Regulatory Authority. The study must be approved by the REB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 ~~Waiver of~~ Consent

This is a pragmatic trial that compares two fibrinogen replacement sources that are currently within the standard-of-care for this procedure, is unlikely to pose additional risks to patients, and entails no additional interventions outside of normal clinical care. Moreover, due to the emergency nature of the condition being studied (i.e., bleeding during or after 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. In addition, this complication occurs infrequently and cannot be predicted before surgery. Thus, while it is technically possible to obtain informed consent before all surgeries, it is simply 'impracticable' to do so for this specific study, thereby rendering such a study simply unfeasible.

Importantly, the study compares two substitutable therapies that are used as part of routine clinical care, and there is no compelling theoretical basis or any types of data that patients would be placed at risk by participating in the study. The results of this study, on the other hand, would have important societal benefits, as it will help the Canadian Blood Services to determine which of the two products should be supplied in the future. If fibrinogen concentrate is proven to be non-inferior, it will likely be the treatment of choice because it has a lower theoretical risk of viral transmission, improves the efficiency of the blood system (for every unit of cryoprecipitate produced, one unit of platelets, which is often in short supply, is diverted from the blood supply), and allows for more rapid, targeted therapy of bleeding.

The study meets the criteria stated in Article 3.7A of the 2014 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans for identifying situations in which exceptions may be sought for the requirement to seek ~~prior~~ consent prior to surgery.

~~We will obtain consent from the patient or a surrogate decision maker as soon as possible after randomization for collection and analysis of patient data. The Investigator (or delegate as appropriate) will obtain freely given written consent from each patient (or surrogate) Requirements for obtaining informed consent will be determined by the Research Ethics Board of each participating site. Patient or surrogate decision maker will be approached for informed consent within 24-72 hours after surgery. They will be provided as much time as necessary to ask any questions and to make their decision. If initially the patient is not capable of providing consent, consent will be obtained only from the surrogate decision maker. The patient will be re-visited every few days and consent will be obtained from the patient when appropriate. Consent should be obtained within the 28 day duration for each study patient. Any delays in obtaining consent due to extenuating circumstances need to be clearly documented (e.g., when patient dies soon after surgery in which case initiation of consent process from next of kin can be delayed for up to 1-week after death). Study data collection will begin only after informed consent is obtained from the SDM or patient.~~

~~Study coordinator or assistant will obtain freely given consent (in person or via telephone) from each patient (or SDM) after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the decision to continue to participate. The informed consent form must be signed, with name and date and time noted Consent must be obtained by the patient (or surrogate), before the patient is exposed to any further study-related procedures, namely evaluation and data collection. Should the consent be obtained from the SDM and later declined by the patient, no data will be collected.~~

~~The Investigator (or delegate) Study coordinator or assistant will explain that the patients are completely free to withdraw from the study at any time, without any consequences for their further care and without the need to justify. Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations. In addition to the FIBRES protocol, study hospitals will also follow their institutional guidelines and approvals when consenting and collecting data. Their process will be documented in their SOPs. Again, no data will be collected on patients/SDMs who refuse consent. Please refer to Appendix in 15.2 for the consent and data collection guidelines at Toronto General Hospital.~~

10.4 Protocol Amendments

Any amendments will be submitted to the competent REB and any authority as required by applicable regulations.

REB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective or design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifi-

er. Documents not intended for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take ~~place shortly after the inclusion of the first patient~~, when 5 – 15 patients have been randomized at the site. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor or REB and regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been captured.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines) will be prepared by the Sponsor after completion of the study. The Coordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study will be published and may be presented at scientific meetings.

In accordance with standard editorial and ethical practice, the Investigator will publish the multi-center data ~~only~~only in their entirety and not as individual center data. Authorship will be determined by mutual agreement. Any subsequent publications based on subsets of the data will require approval from the Sponsor.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Investigators and or their institutions will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

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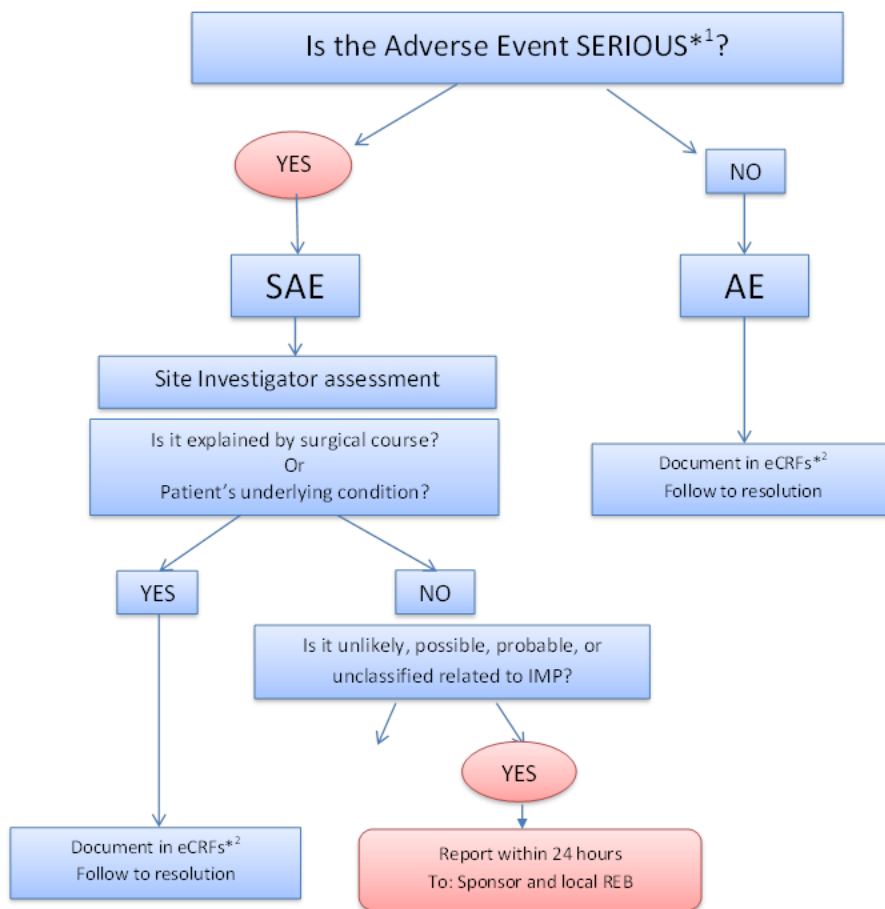
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15 APPENDICES

Not applicable.

15.1 Assessment of Adverse Events- Serious Adverse Events: Flow Chart



*1 Serious AE (SAE) is any untoward medical occurrence that at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is another important medical event.

*2 eCRFs Case Report Forms 09/01 Adverse Events – Serious Adverse Events Report Form and 10/01 Concomitant Medications Form for each adverse event

Red legend refer to the two conditions of expedited reporting (1) the event is serious and (2) unlikely, possible, probable or unclassified related to IMP.

Refer to FIBRES SOP- 02 Adverse Events- Data Collection, Assessment, and Reports.

15.2 Consent and Data Collection Guidelines at TGH

<u>Scenario</u>	<u>What data can be collected</u>
<u>Written consent obtained from patient or Written/telephone consent obtained from SDM</u>	<u>Data can be collected.</u>
<u>Consent obtained initially (from SDM or patient) and later withdrawn (SDM or patient)</u>	<u>Data can be collected up to the date of withdrawal. No data should be collected after withdrawal, not even SAE data.</u>
<u>Consent obtained from SDM and declined from patient once capable of consenting</u>	<u>No data at all should be collected. Patient's decision overwrites the SDM's.</u>
<u>Consent not obtained due to no SDM or patient incapacity to provide consent</u>	<u>Only type of SAE and relation to the study intervention can be collected, if applicable. No other data should be collected.</u>
<u>Consent declined either by patient/ SDM</u>	<u>Nothing can be collected, not even SAE data.</u>

Guidelines to Obtaining Telephone Consent from Patient/SDM

Patient Consent

The following process must be followed when obtaining telephone consent from patients who have been discharged and have requested more time to review the consent form or to discuss the matter with family/friends.

- Contact the patient a week after discharge (unless they have requested to be contacted at a different time point) and ask whether they are agreeable to participate in the study
- If they agree to participate, then data can be collected. If the patient does not agree, nothing can be collected.
- Attempts for contact with the patient shall be documented and consent shall be obtained in the presence of a witness and documented.

SDM Consent

The following process must be followed when obtaining telephone consent from the SDM:

- The SDM is first contacted to introduce the study and to establish if they are interested in providing consent on behalf of the patient.
- If they are interested, then they are informed that the team will send the consent form to them and will call back within 2-3 days after the ICF is received.
- At the time of the second call, the SDM should be asked whether they agree to participate or not.
- If they agree to participate, then data can be collected. If SDM did not agree, nothing can be collected.
- Attempts for contact with SDM shall be documented and consent shall be obtained in the presence of a witness and documented.



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Principal Investigator:	Keyvan Karkouti, MD
Sponsor:	Keyvan Karkouti; Toronto General Hospital
Title of Protocol:	Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenaemia in bleeding adult cardiac surgical patients
Protocol Version/Date:	TBD
CRF Version:	TBD
Supersedes SAP Version:	N/A (initial version)

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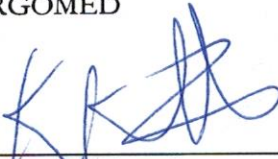
Document authorization



Hans P. Hucke
Trial Statistician
ERGOMED

27. Sep. 2016

Signature
Date (dd-mmm-yyyy)



Keyvan Karkouti
Principal Investigator
Toronto General Hospital

27 - Sep - 2016

Signature
Date (dd-mmm-yyyy)

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Consistency check with the Protocol (one option to be selected)

- This is to confirm that as part of the SAP finalization consistency check with the current protocol / protocol amendment was performed by the trial statistician, and no changes to the protocol (statistical section) are required
- Changes to the analysis principles were required, and the responsible team has confirmed commitment to update the study protocol
- Changes to the analysis principles were required (as outlined in revision history section of this SAP).

Hans-Peter Hucke

Trial Statistician

ERGOMED

Signature

Date (dd-mmm-yyyy)

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Change control

Date	Author	Reason	Version
2016-09-27	Hans P. Hucke	First version	1.0



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LIST OF ABBREVIATIONS

Abbreviation	Description
ABP	Allogenic Blood Product
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
AUC	Area Under the Concentration-Time Curve
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CRO	Contract Research Organization
DMP	Data Management Plan
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
IDSMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
SAE	Serious Adverse Event
SAF	Safety Analysis Set
TLFs	Tables, listings, figures

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1 STUDY MATERIAL

The following material was considered for this SAP:

Document	Version, Date
Protocol, incl. last amendment	Version 1.0, 2016-09-22
CRF	TBD
DMP	TBD
DVP	TBD

2 STUDY INFORMATION

2.1 Primary objective

The primary objective of this study is to demonstrate that the fibrinogen concentrate *Oc-tafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products (ABPs) administered during the first 24 hours after termination of CPB.

2.2 Secondary objective

The secondary objectives include:

- Comparison of efficacy as measured by the total and individual number of allogeneic blood products transfused from the beginning of surgery up to postoperative day 7
- Comparison of the amount of bleeding during the first 24 hours after termination of CPB
- Comparison of the effect on fibrinogen levels observed within 1 hour before and 1 hour after fibrinogen supplementation

2.3 Study design

The study is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require up to 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenaemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (Oc-



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tafibrin) or cryoprecipitate when the blood bank receives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB).

Details on the study procedures, measurements and their timing can be found in the study protocol and the trial flow chart below:

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Trial flow chart

Procedures	Prior to enrolment	Visit 1 Post-randomization (0 to 24 Hr)	Visit 2 24–36 h post IMP	Visit 2a 24–36 h post additional IMP	Visit 3 POD7/DC	Visit 4 POD28
Blood bank receives fibrinogen order^a	x	(x) ^d				
Inclusion and exclusion criteria	x					
Randomization	x					
IMP administration		x				
Confirm integrated consent	x					
Obtain delayed consent		x	(x)	(x)	(x)	
Baseline data						
Demographics		x				
Medical history		x				
Preoperative medications		x				
Surgical data						
Intraoperative medications		x				
CPB time		x				
X-clamp time		x				
Circulatory arrest		x				
Vital signs		x				
Fluid in- and output monitoring		x				
Inotropes and vasopressors		x	x	x		
Laboratory assessments						
Chemistry ^f		x	x	x	x	
Hematology ^f		x ^c	x	x	x	
Coagulation profile ^f		x ^c	x	x	x	
Safety labs ^f		x	x	x	x	
Transfusion requirements^e						
Allogeneic red blood cells		x	x	x	x	
Pooled platelets		x	x	x	x	
Plasma		x	x	x	x	
Other hemostatic products		x	x	x	x	
Blood loss determination using UDPB		x	x	x	x	
Extubation time		x	x	(x)	(x)	(x)
ICU length of stay		x	x	(x)	(x)	(x)
Hospital length of stay					x	(x)
AEs and SAEs		x	x	x	x	x
Concomitant medications		x	x	x	x	x
Physical examination		x	x	x	x	x

^a After the start of surgery and during or after CPB.

^b IMP will first be administered after start of surgery based on the physician's judgement. The first IMP dose can be administered before fibrinogen levels are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available).

^c Prior to and 60 minutes after IMP administration.

^d Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

^e 24 hours after IMP administration, ^f As per standard practice, () If needed

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2.4 Planned sample size

The estimation of the sample size for the trial took into account the primary objective of the trial (demonstrating non-inferiority), the statistical analysis method (Poisson regression for count data) and the results of a comparable previous study conducted by the principal investigator in the same indication using the ABP endpoint during the years 2014/2015.

The statistical analysis of the primary efficacy variable, i.e., the amount of ABPs, will be based on the mean number of ABP units within the first 24 hours following CPB (μ_F and μ_C).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to the treatment with cryoprecipitate with respect to the mean number of ABP units, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \mu_F / \mu_C \geq (1 + \delta) \quad \text{vs.} \quad H_1: \mu_F / \mu_C < (1 + \delta)$$

will be carried out with a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of δ . Here, μ_F and μ_C denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term), with treatment group as main effect.

The test of the primary hypothesis in the planned interim and the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_C derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

Based on this method and a one-sided overall type I error probability $\alpha = 0.025$, simulations have been performed to study the power of the test for different sample sizes and values of the non-inferiority margin δ .

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units. The empirical distribution function with these sample characteristics was chosen based on results of the TACS study [3] with the same endpoint in the same indication and similar treatment.

10,000 studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

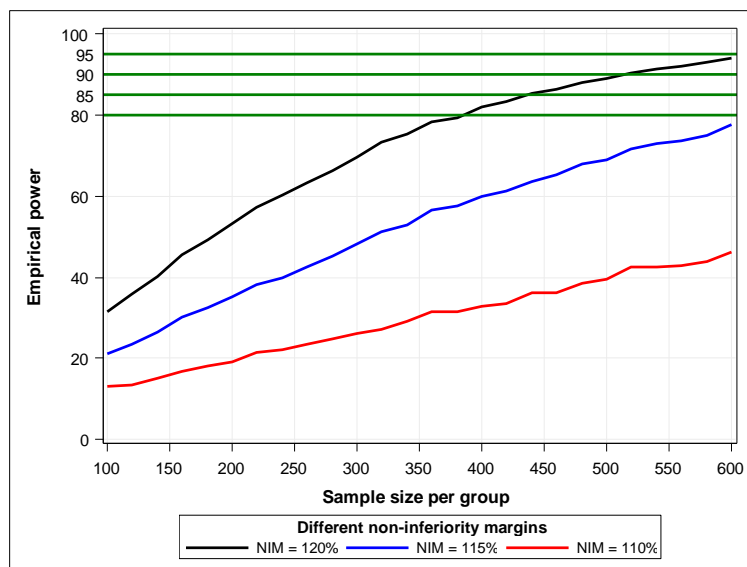
The plot below displays the empirical power curves for the test of H_0 vs. H_1 using the Poisson counting regression model analyzed with SAS PROC GENMOD for sample sizes up to 600 patients per group and three values of the non-inferiority margin (NIM).

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As the diagram shows, an empirical power of >90% can be expected with a sample size of at least 550 patients per treatment group if a δ of 0.20 is chosen. For smaller values of δ , no sufficient power can be attained with operationally feasible sample sizes. The choice of the non-inferiority margin $\delta = 0.20$ is also due to the substantial intrinsic variation in the primary endpoint that has to be expected from previous studies reflecting current clinical practice. Therefore it is planned to conduct the study with a maximum sample size of 600 patients in each treatment group and a non-inferiority margin of $\delta = 0.20$.

Assuming that a proportion of about 10% randomized patients will not be treated after randomization or for whom the endpoint cannot reliably be obtained, this would ensure that data on at least 550 patients per treatment group in the ITT population will be available for the statistical analysis as derived from the sample size calculation.

3 GENERAL INFORMATION

3.1 Deviations from the trial protocol with regard to statistical analyses

There are no deviations from the statistical methods described in the trial protocol.

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3.2 Individual protocol deviations

Any deviation from protocol will be discussed case by case before database lock or unblinding whether the deviation has to be regarded as minor or as major (and therefore lead to exclusion from particular analysis populations).

The assessment of individual protocol deviations will be made in a blinded data review meeting. A complete listing of protocol deviations and the judgment for assessment of subject disposition will be signed before database lock. All deviations along with the disposition of each subject will be recorded in a separate database member that will become part of the study database. A description of all major protocol violations will be included in the table part of the clinical trial report.

Criteria for major protocol violations will include:

- Patients who do not receive an IMP after randomization
- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 75 of the planned dose
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

4 ANALYSIS POPULATIONS

The disposition of subjects will be displayed according to the following analysis populations:

- Screening failures,
- Safety (SAF) population,
- Intention-to-Treat (ITT) population,
- Per-Protocol (PP) population.

4.1 Screening Failures

Screening failures are patients who did not receive IMP or did not provide delayed informed consent. Only baseline demographic and anamnestic data on screening failures will be listed.

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4.2 Safety population

The safety (SAF) population will include all randomized patients with delayed informed consent who received at least one dose of IMP.

4.3 Intention-to-treat population

The intention-to-treat (ITT) population includes all randomized patients receiving at least one dose of IMP who provided delayed informed consent. In the event that a patient receives the wrong treatment for infusion, the treatment group will be defined according to the randomization (rather than the actual treatment received).

If no randomization errors are observed the ITT population will be identical to the safety analysis population (SAF).

4.4 Per-protocol population

The per-protocol (PP) population is a subset of the ITT population excluding patients with major protocol deviations. The following patients will be excluded:

- Patients who do not receive an IMP after randomization
- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 75% of the planned dose
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meeting prior to unblinding for the interim and final analyses. Decisions and outcome will be approved by the Principal Investigator (Sponsor) in consultation with the Trial Statistician).

The ITT analysis population is considered the primary population for analysis of the primary efficacy objective. However, the evaluation of all efficacy endpoints will additionally be performed for the PP population.



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4.5 Subgroup analyses

Subgroup analyses of the primary and secondary efficacy are planned for the following subgroups:

- non-elective surgery,
- complex surgery (procedures other than isolated ACB, single valve, or repair of ASD).

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5 STATISTICAL ANALYSES

All statistical analyses will be performed using SAS® for Windows (Version 9.3 or higher).

Descriptive statistics will always be given by treatment group. For baseline and basic variables, they will also be given for the entire population.

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

Descriptive statistics for continuous data

Number of subjects (N), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum will be presented. Usually mean, standard deviation and quartiles will have 1 decimal more than the original values (as given with min, max); N has no decimals. These descriptive statistics will be determined for measured values and for differences to baseline.

Descriptive statistics for categorical data

Absolute frequencies (N) and relative frequencies (%) will be presented with 0 or 1 decimal, respectively. For changes from baseline, shift tables may be generated.

Inferential statistics

If not stated otherwise, all statistical tests will be performed two-sided and at a type I error probability of $\alpha=0.05$. The p-values of the test statistics will be printed consistently with 4 decimals (p<0.0001 will be displayed, if the p-values are less than 0.0001).

If not stated otherwise, all confidence intervals (CI) will be two-sided and at a coverage probability of $1-\alpha = 0.95$.

Listings

All subject data will be listed by subject sorted by treatment group. Identification variables will be center number, subject number and treatment. Any derived data listed will also be stored permanently and will be calculated as outlined in section 8.1 of this SAP.

5.1 Conventions

5.1.1 Baseline definition

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

5.1.2 Missing data

No imputation of missing values is planned.

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5.1.3 Pooling of centers

No pooling of centers will be performed.

5.2 Demographic and other background data

The disposition of subjects (cf. Section 4) will be tabulated by treatment and for the entire population. Details on protocol deviations will be listed.

Discontinued patients will be described by frequency distributions including the reasons and in individual listings.

Demographic data (sex, age, height, weight, and Body Mass Index (BMI)) will be summarized in tables and presented for the ITT and PP population. Homogeneity tests between treatment groups and centers will be performed for the demographic data at an alpha level of 10%.

The following surgical-related data will only be listed:

- Details of procedure,
- CPB duration,
- CPB start-end times,
- Cross-clamp duration,
- Circulatory arrest duration,
- Vital signs,
- Fluid intake and output,
- Medications administered,
- Hemodynamic support (e.g., IABP),
- Blood conservation methods used.

5.3 IMP exposure, compliance

All IMP treatment details will be listed. Patient compliance (amount of IMP received / planned amount of IMP) will be calculated for each patient and summary statistics be presented by treatment group.

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5.4 Medical history, physical examination

Data on medical history and physical examination will be listed. Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Codes will be reviewed by a designated Medical Expert and approved by the Principal Investigator before data base lock.

5.5 Prior and concomitant medication

Any relevant medication taken at time of enrolment will be listed as prior medication. All new medications taken during the study period are defined as 'Concomitant'. Any changes of medications during the study period will also be recorded.

All details of prior and concomitant medications will be listed including, the route, dose, frequency, start and stop date and indication.

Medications will be coded using the WHO DD thesaurus in the version current at the time of enrollment of the first patient. Coding will be performed by the CRO and agreed upon with the Principal Investigator before data base lock. (cf. data management plan (DMP)). For concomitant medications tables will show the frequencies of patients by WHO DD preferred term. Prior medication will only be listed.

5.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

5.7 Efficacy

5.7.1 Primary efficacy endpoint

The primary efficacy variable is the total number of ABP units (sum of RBCs, pooled and apheresis platelets and FFP) used within 24 hours after termination of CPB.

In a first analysis step, descriptive statistics on the total number of ABP units within 24 hours of CPB will be provided by treatment group. These statistics will be provided for the ITT and the PP population.

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the pair of hypotheses:

$$\begin{aligned} H_0: & \mu_F / \mu_c \geq (1 + \delta) \text{ (inferiority)} \\ \text{vs. } H_1: & \mu_F / \mu_c < (1 + \delta) \text{ (non-inferiority)} \end{aligned}$$

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will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect.

The test of the primary hypothesis in the final analysis will be based on the one-sided CI for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the ITT population. A secondary analysis will be performed for the PP population to study the robustness of the results.

Only in case of demonstrated non-inferiority in the ITT and the PP population subsequently the pair of hypotheses:

$$H'_0: \mu_F / \mu_c \geq 1$$

vs. $H'_1: \mu_F / \mu_c < 1$

will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary and therefore the test will be done at the same type I error level as the test of non-inferiority.

5.7.2 Secondary efficacy endpoints

The secondary endpoints listed below will be analyzed in an exploratory manner only, presenting summary tables (frequency tables or sampling statistics according to data type) along with the presentation of 95 % confidence intervals and p-values for exploratory tests of treatment group differences. Results will be presented for the ITT and the PP population.

- Total number of units of ABPs administered from start of cardiac surgery until 7 days after surgery or discharge.
- Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets and plasma.
- Distribution of major bleeding type, using the validated universal definition of peri-operative bleeding (UDPB) in cardiac surgery.
- Change in fibrinogen plasma level (measured using the Clauss assay) within 1 hour before and 1 hour after fibrinogen supplementation for first and subsequent doses.

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The total number of ABPs within 7 days/discharge and the different subtypes of ABPs will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

Frequency distributions of the major bleeding type according to UDPB will be presented for each treatment group.

Change in fibrinogen plasma level will be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the *Octafibrin* and cryoprecipitate treatment groups and the corresponding 95% CI will be calculated.

5.8 Pharmacokinetics / Pharmacodynamics

Not applicable.

5.9 Safety

All analyses will be performed for the SAF population.

5.9.1 Adverse events

Adverse events (AEs) will be coded by the CRO according to the MedDRA thesaurus. Coding will be agreed upon with the Principal Investigator before database lock (cf. DMP).

Treatment-emergent adverse events (TEAE) will be analyzed, i.e. all new and worsening pre-existing adverse events occurring after first IMP administration up to postoperative day 28. 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 analyzed like different phases of the same AE.

A descriptive analysis will be performed. Global incidences of primary system organ classes (SOC) and preferred terms (PT) will be calculated for

- All TEAE irrespective of the causality assessment
- TEAE by relationship (likely and possible related)
- TEAEs by worst severity
- Serious TEAEs

This analysis comprises the following set of tables separated by treatment group:

- Global incidence

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

Multiple counts within a PT 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 subject identification, age, sex, AE descriptors, start and end of treatment will be prepared for the following types of TAEs:

- Serious adverse events (SAE)
- Adverse events which led to discontinuation
- Myocardial infraction
- Stroke
- Acute liver injury
- Acute kidney injury
- Thromboembolic events

The number of patients who died will be summarized. 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.

All adverse events recorded since enrollment will be listed in the data part of the report. Only TEAEs will be summarized in the tables.

5.9.2 Laboratory variables

In case of derived items in the database (i.e. after substitution of invalid values by missings, after transformation to standard units etc., see DMP), only the derived items will be analyzed. Results of all individual lab tests will be listed in original and standard units in appendix 16.2 to the clinical trial report.

All laboratory values will be classified as normal or abnormal according to the laboratories' normal 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. On addition mean concentration vs. time profiles (including standard deviations) will be plotted by treatment to illustrate any time trends.

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- Qualitative data based on reference ranges will be described according to the categories (i.e., low, normal, high).
- Shift tables illustrating changes with respect to the laboratories' normal ranges between baseline and a defined scheduled time point.
- Number and frequency of patients with clinically significant laboratory values (e.g. > 3 x ULN).
- Patient listings will be provided showing individual lab abnormalities.

5.10 Other safety variables

The following additional safety variables will be summarized in tables separated by treatment group:

- Duration of mechanical ventilation up to postoperative day 28
- Duration of intensive care unit (ICU) stay up to postoperative day 28
- Duration of hospitalization up to postoperative day 28

5.11 Interim analyses

The study employs a group-sequential design that involves one pre-planned interim analysis after 600 patients have completed the study.

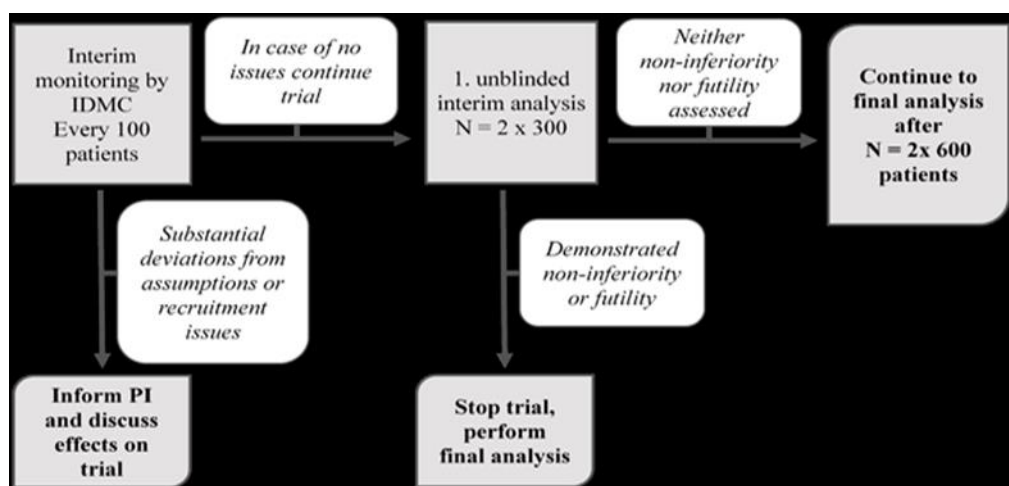
In addition, IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study. This data monitoring serves the purpose of an ongoing assessment of recruitment problems as well as the compatibility of the accumulating data with the assumptions made at study start. The extent of the information to be reviewed will be defined in the IDSMC charter. The IDSMC will keep all these data monitoring results in strict confidence. Only in case of identified issues during their data monitoring the IDSMC will advise the Principal Investigator in a non-treatment-disclosing manner on the problems.

The interim analysis will be an unblinded interim analysis with an adjusted type I error rate according to the O'Brien-Fleming method after 600 patients have been enrolled. After this interim analysis, a positive outcome may be claimed and enrolment may be stopped if the test of H_0 vs. H_1 in the ITT population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$ rejects the null hypothesis (efficacy stop). A full final analysis including all study data will be performed and reported if enrolment is stopped after the interim analysis. Also at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

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Otherwise, the study will continue until the maximum sample size of $n = 2 \times 600$ patients, is reached. The final analysis will be performed as described above, but with an adjusted significance level of $\alpha_2 = 0.02242$ to maintain the overall one-sided significance level of $\alpha = 0.025$

The flow chart below illustrates the decision process underlying the interim analyses.



6 QUALITY CONTROL

The SAP will be signed off only when approval by the Principal Investigator is received.

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 SAS programmer.

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

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Date of Issue: 2016-09-27	

7 REFERENCES

- [1] Cameron, A. C.; P. K. Trivedi (1998). Regression Analysis of Count Data, New York: Cambridge University Press
- [2] Hilbe, J. M. (2008). Negative Binomial Regression, New York: Cambridge University Press
- [3] Karkouti K, Callum J, Wijeyesundera DN et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. Circulation 2016;pii: CIRCULATIONAHA.116.023956. [Epub ahead of print]

8 APPENDICES

8.1 Formulas for derived variables

Variable	Description
<i>A detailed list of all derivations will be compiled upon protocol approval by Health Canada</i>	

8.2 List of Tables, Listings, Figures

A complete lists 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 both the Principal Investigator, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced. Therefore, this list will be approved by both parties before commencing the statistical programming.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have 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.

All statistical output will identify the underlying analysis populations and indicate the number of patients/events in this population (N) and the number of patient/events actually contributing to the particular output (n). All statistical output will be presented per treatment group and in total (if applicable).

All patient listings will contain additionally to the patient identification the analysis population and the treatment group.

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8.3 Additional details on statistical methods

As the total number of allogenic blood products and similarly the number of RBCs, platelets and FFP transfused represent integer count data the use of statistical methods for count data is indicated for their analysis (see e.g. [1] and [2]).

Such methods are typically employed in the context of a generalized linear model (GLM) using the Poisson or Negative Binomial distributions as error terms.

As these models typically employ a logarithmic link function as a constituent part, it appears natural to state the null and alternative hypotheses in terms of the ratio of the treatment means. After such a logarithmic transformation these hypotheses take the form of a linear difference in the model parameters.

This allows the direct application of the GLM and their associated inferences (test and confidence intervals). The numerical analyses will be performed with the GENMOD procedure of the SAS system. During the analysis with PROC GENMOD the model assumptions (e.g. assumptions about the deviance) will be checked and all details of the analyses be reported in the appendix 16.1.9 to the clinical trial report.

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Principal Investigator:	Keyvan Karkouti, MD
Sponsor:	Keyvan Karkouti; Toronto General Hospital
Title of Protocol:	Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenaemia in bleeding adult cardiac surgical patients
Protocol Version/Date:	Version 2.4 / 2018-07-03
CRF Version:	Version 3.0 / 2018-04-21
Supersedes SAP Version:	N/A (initial version)

Confidential

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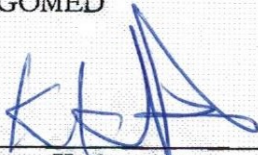
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Document authorization

Hans P. Hucke
Trial Statistician
ERGOMED

2018-10-15

Signature
Date (dd-mmm-yyyy)



Keyvan Karkouti
Principal Investigator
Toronto General Hospital

2018-10-15

Signature
Date (dd-mmm-yyyy)

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Consistency check with the Protocol

- This is to confirm that as part of the SAP finalization consistency check with the current protocol / protocol amendment was performed by the trial statistician, and no changes to the protocol (statistical section) are required
- Changes to the analysis principles were required, and the responsible team has confirmed commitment to update the study protocol
- Changes to the analysis principles were required (as outlined in revision history section of this SAP).

**Hans-Peter Hucke**

Trial Statistician

ERGOMED



Signature

Date (dd-mmm-yyyy)

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Change control

Date	Author	Reason	Version
2016-09-27	Hans P. Hucke	First version	1.0
2018-10-08	Hans P. Hucke	Changes due to amended protocol	2.00
2018-10-15	Hans P. Hucke	Minor Changes due to sponsor comments	2.10

<p>STATISTICAL ANALYSIS PLAN Protocol No: FIBRES (FORMA-06)</p>	
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LIST OF ABBREVIATIONS

Abbreviation	Description
ABP	Allogenic Blood Product
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
AUC	Area Under the Concentration-Time Curve
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CRO	Contract Research Organization
DMP	Data Management Plan
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
IDSMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
REB	Research Ethics Board
SAE	Serious Adverse Event
SAF	Safety Analysis Set
TLFs	Tables, listings, figures

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1 STUDY MATERIAL

The following material was considered for this SAP:

Document	Version, Date
Protocol, incl. last amendment	Version 2.4 / 2018-07-03
CRF	Version 3.0 / 2018-04-21
DMP	Version 1.0 / 2017-10-05
DVP	Version 1.0 / 2018-04-25

2 STUDY INFORMATION

2.1 Primary objective

The primary objective of this study is to demonstrate that the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products (ABPs) administered during the first 24 hours after termination of CPB.

2.2 Secondary objective

The secondary objectives include:

Comparison of efficacy as measured by the total and individual number of allogeneic blood products transfused from the beginning of surgery up to postoperative day 7

Comparison of the amount of bleeding during the first 24 hours after termination of CPB

Comparison of the effect on fibrinogen levels observed within 1 hour before and 1 hour after fibrinogen supplementation

2.3 Study design

The study is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require up to 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenaemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (Octafibrin) or cryoprecipitate when the blood bank receives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB).

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Details on the study procedures, measurements and their timing can be found in the study protocol and the trial flow chart below:

Procedures	Prior to enrollment	Visit 1 Post-randomization (0 to 24 Hr)	Visit 2 24–36 h post IMP	Visit 2a 24–36 h post additional IMP	Visit 3 POD7/DC	Visit 4 POD28
Blood bank receives fibrinogen order ^a	x	(x) ^d				
Inclusion and exclusion criteria	x					
Randomization	x					
IMP administration		x				
Confirm integrated consent	x					
Obtain delayed consent		x	(x)	(x)	(x)	
Baseline data						
Demographics		x				
Medical history		x				
Preoperative medications		x				
Surgical data						
Intraoperative medications		x				
CPB time		x				
X-clamp time		x				
Circulatory arrest		x				
Vital signs		x				
Fluid in- and output monitoring		x				
Inotropes and vasopressors		x	x	x		
Laboratory assessments						
Chemistry ^f		x	x	x	x	
Hematology ^f		x ^c	x	x	x	
Coagulation profile ^f		x ^c	x	x	x	
Safety labs ^f		x	x	x	x	
Transfusion requirements^e						
Allogeneic red blood cells		x	x	x	x	
Pooled platelets		x	x	x	x	
Plasma		x	x	x	x	
Other hemostatic products		x	x	x	x	
Blood loss determination using UDPB		x	x	x	x	
Extubation time		x	x	(x)	(x)	(x)
ICU length of stay		x	x	(x)	(x)	(x)
Hospital length of stay					x	(x)
AEs and SAEs		x	x	x	x	x
Concomitant medications		x	x	x	x	x
Physical examination		x	x	x	x	x

^a After the start of surgery and during or after CPB.

^b IMP will first be administered after start of surgery based on the physician's judgement. The first IMP dose can be administered before fibrinogen levels are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g., ROTEM assay FIBTEM A10 of <12 mm, if available).

^c Prior to and 60 minutes after IMP administration.

^d Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

^e 24 hours after IMP administration, ^f As per standard practice, () If needed

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2.4 Planned sample size

The estimation of the sample size for the trial took into account the primary objective of the trial (demonstrating non-inferiority), the statistical analysis method (Poisson regression for count data) and the results of a comparable previous study conducted by the principal investigator in the same indication using the ABP endpoint during the years 2014/2015.

The statistical analysis of the primary efficacy variable, i.e., the amount of ABPs, will be based on the mean number of ABP units within the first 24 hours following CPB (μ_F and μ_c).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to the treatment with cryoprecipitate with respect to the mean number of ABP units, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \mu_F / \mu_c \geq (1 + \delta) \quad \text{vs.} \quad H_1: \mu_F / \mu_c < (1 + \delta)$$

will be carried out with a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of δ . Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term), with treatment group as main effect.

The test of the primary hypothesis in the planned interim and the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

Based on this method and a one-sided overall type I error probability $\alpha = 0.025$, simulations have been performed to study the power of the test for different sample sizes and values of the non-inferiority margin δ .

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units. The empirical distribution function with these sample characteristics was chosen based on results of the TACS study [3] with the same endpoint in the same indication and similar treatment.

10,000 studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

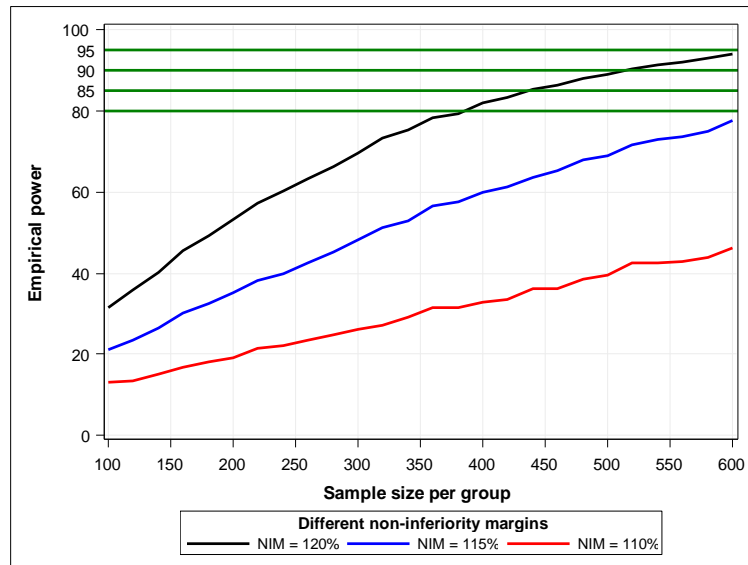
The plot below displays the empirical power curves for the test of H_0 vs. H_1 using the Poisson counting regression model analyzed with SAS PROC GENMOD for sample sizes up to 600 patients per group and three values of the non-inferiority margin (NIM) .

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As the diagram shows, an empirical power of >90% can be expected with a sample size of at least 550 patients per treatment group if a δ of 0.20 is chosen. For smaller values of δ , no sufficient power can be attained with operationally feasible sample sizes. The choice of the non-inferiority margin $\delta = 0.20$ is also due to the substantial intrinsic variation in the primary endpoint that has to be expected from previous studies reflecting current clinical practice.

Therefore it is planned to conduct the study with a maximum sample size of 600 patients in each treatment group and a non-inferiority margin of $\delta = 0.20$.

Assuming that a proportion of about 10% randomized patients will not be treated after randomization or for whom the endpoint cannot reliably be obtained, this would ensure that data on at least 550 patients per treatment group in the mITT population will be available for the statistical analysis as derived from the sample size calculation.

3 GENERAL INFORMATION

3.1 Deviations from the trial protocol with regard to statistical analyses

There are no deviations from the statistical methods described in the trial protocol.

3.2 Individual protocol deviations

Any deviation from protocol will be discussed case by case before database lock or unblinding whether the deviation has to be regarded as minor or as major (and therefore lead to exclusion from particular analysis populations).

The assessment of individual protocol deviations will be made in a blinded data review meeting. A complete listing of protocol deviations and the judgment for assessment of subject disposition will

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be signed before database lock. All deviations along with the disposition of each subject will be recorded in a separate database member that will become part of the study database. A description of all major protocol violations will be included in the table part of the clinical trial report.

Criteria for major protocol violations will include:

- Patients who do not receive an IMP after randomization
- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 80% of the planned dose for their initial dosing
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

4 ANALYSIS POPULATIONS

The disposition of subjects will be displayed according to the following analysis populations:

- Non-Treated
- Non-Qualified,
- modified Intention To Treat (mITT) population
- Safety (SAF) population
- Per-Protocol (PP) population.

4.1 Non - Treated

This population consists of all patients who were enrolled, but did not receive any IMP.

4.2 Non - Qualified

This population consists of all patients who were enrolled and received at least one dose of IMP, but did not meet any of the following criteria:

- Unrestricted consent available by patient, SDM or REB,
- Performed procedure was cardiac surgery.

Only information on the treatment administered will be listed.

4.3 modified Intention To Treat (mITT) population

The modified Intention To Treat (mITT) population will include all randomized patients who received at least one dose of IMP and who met both of the following criteria:

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- Unrestricted consent available by patient, SDM or REB, and
- Performed procedure was cardiac surgery.

4.4 Safety population

The safety population (SAF) will consist of all patients of the mITT population and in addition all those patients of the Non-Qualified population for whom restricted REB approval is available to use recorded SAE data only.

The SAF population will only be utilized in summaries and listings of SAEs and their relation to IMP. No other data on this population will be analyzed or reported within this trial.

4.5 Per-protocol population

The per-protocol (PP) population is a subset of the mITT population excluding patients with important protocol deviations. Patients showing any of the following criteria will be considered for exclusion:

- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 80% of the planned dose (first dose only)
- Patients who significantly violate inclusion/exclusion criteria
- Patients without recording of the primary efficacy endpoint

A final decision about the classification of protocol deviations as important and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meeting prior to unblinding for the interim and final analyses. Decisions and outcome will be approved by the Principal Investigator (Sponsor) in consultation with the collaborator (Octapharma).

The mITT analysis population is considered the most relevant population for analysis of the primary efficacy objective. However, the evaluation of all efficacy endpoints will additionally be presented for the PP population.

4.6 Subgroup analyses

Subgroup analyses of the primary and secondary efficacy are planned for the following subgroups:

- Non-elective surgery patients,
- Complex surgery patients (procedures other than isolated ACB, single valve, or repair of ASD),
- High-risk surgery patients, i.e. those that meet any of the following criteria according to adjudicators:
 - In critical condition before surgery,

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5 STATISTICAL ANALYSES

All statistical analyses will be performed using SAS[®] for Windows (Version 9.4 or higher).

Descriptive statistics will always be given by treatment group. For baseline and basic variables, they will also be given for the entire population.

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

Descriptive statistics for continuous data

Number of subjects (N), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum will be presented. Usually mean, standard deviation and quartiles will have 1 decimal more than the original values (as given with min, max); N has no decimals. These descriptive statistics will be determined for measured values and for differences to baseline.

Descriptive statistics for categorical data

Absolute frequencies (N) and relative frequencies (%) will be presented with 0 or 1 decimal, respectively. For changes from baseline, shift tables may be generated.

Inferential statistics

If not stated otherwise, all statistical tests will be performed two-sided and at a type I error probability of $\alpha=0.05$. The p-values of the test statistics will be printed consistently with 4 decimals ($p<0.0001$ will be displayed, if the p-values are less than 0.0001).

If not stated otherwise, all confidence intervals (CI) will be two-sided and at a coverage probability of $1-\alpha = 0.95$.

Listings

All subject data will be listed by subject sorted by treatment group. Identification variables will be center number, subject number and treatment. Any derived data listed will also be stored permanently and will be calculated as outlined in section 8.1 of this SAP.

5.1 Conventions

5.1.1 Baseline definition

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

5.1.2 Missing data

No imputation of missing values is planned.

5.1.3 Pooling of centers

No pooling of centers will be performed.

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5.2 Demographic and other background data

The disposition of subjects (cf. Section 4) will be tabulated by treatment and for the entire population. Details on protocol deviations will be listed.

Discontinued patients will be described by frequency distributions including the reasons and in individual listings.

Demographic data (sex, age, height, weight, and Body Mass Index (BMI)) will be summarized in tables and presented for the mITT and PP population. Homogeneity tests between treatment groups and centers will be performed for the demographic data at an alpha level of 10%.

The following surgical-related data will only be listed:

- Details of procedure,
- CPB duration,
- CPB start-end times,
- Cross-clamp duration,
- Circulatory arrest duration,
- Vital signs,
- Fluid intake and output,
- Medications administered,
- Hemodynamic support (e.g., IABP),
- Blood conservation methods used.

5.3 IMP exposure, compliance

All IMP treatment details will be listed. Patient compliance (amount of IMP received / planned amount of IMP) will be calculated for each patient and summary statistics be presented by treatment group.

5.4 Medical history, physical examination

Data on medical history and physical examination will be listed. Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Codes will be reviewed by a designated Medical Expert and approved by the Principal Investigator before data base lock.

5.5 Prior and concomitant medication

Any relevant medication taken at time of enrolment will be listed as prior medication. All new medications taken during the study period are defined as 'Concomitant'. Any changes of medications during the study period will also be recorded.

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All details of prior and concomitant medications will be listed including, the route, dose, frequency, start and stop date and indication.

Medications will be coded using the WHO DD thesaurus in the version current at the time of enrollment of the first patient. Coding will be performed by the CRO and agreed upon with the Principal Investigator before data base lock. (cf. data management plan (DMP)). For concomitant medications tables will show the frequencies of patients by WHO DD preferred term. Prior medication will only be listed.

5.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

5.7 Efficacy

5.7.1 Primary efficacy endpoint

The primary efficacy variable is the total number of ABP units (sum of RBCs, pooled and apheresis platelets and FFP) used within 24 hours after termination of CPB.

In a first analysis step, descriptive statistics on the total number of ABP units within 24 hours of CPB will be provided by treatment group. These statistics will be provided for the mITT and the PP population.

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the hypotheses:

$$H_0: \mu_F / \mu_c \geq (1 + \delta) \text{ (inferiority)}$$

vs. $H_1: \mu_F / \mu_c < (1 + \delta) \text{ (non-inferiority)}$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect.

The test of the primary hypothesis in the final analysis will be based on the one-sided CI for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the mITT population. A secondary analysis will be performed for the PP population to study the robustness of the results.

Only in case of demonstrated non-inferiority in the mITT and the PP population subsequently the hypotheses:

$$H'_0: \mu_F / \mu_c \geq 1$$

vs. $H'_1: \mu_F / \mu_c < 1$

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will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary and therefore the test will be done at the same type I error level as the test of non-inferiority.

5.7.2 Secondary efficacy endpoints

The secondary endpoints listed below will be analyzed in an exploratory manner only, presenting summary tables (frequency tables or sampling statistics according to data type) along with the presentation of 95 % confidence intervals and p-values for exploratory tests of treatment group differences. Results will be presented for the mITT and the PP population.

- Total number of units of ABPs administered from start of cardiac surgery until 7 days after surgery or discharge.
- Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets and plasma.
- Distribution of major bleeding type, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery.
- Change in fibrinogen plasma level (measured using the Clauss assay) within 1 hour before and 1 hour after fibrinogen supplementation for first and subsequent doses.

The total number of ABPs within 7 days/discharge and the different subtypes of ABPs will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

Frequency distributions of the major bleeding type according to UDPB will be presented for each treatment group.

Change in fibrinogen plasma level will be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the *Octafibrin* and cryoprecipitate treatment groups and the corresponding 95% CI will be calculated.

5.8 Pharmacokinetics / Pharmacodynamics

Not applicable.

5.9 Safety

All analyses will be performed for the mITT population. Only for analysis of SAEs the SAF population will be used additionally.

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5.9.1 Adverse events

Adverse events (AEs) will be coded by the CRO according to the MedDRA thesaurus. Coding will be agreed upon with the Principal Investigator before database lock (cf. DMP).

Treatment-emergent adverse events (TEAE) will be analyzed, i.e. all new and worsening pre-existing adverse events occurring after first IMP administration up to postoperative day 28. 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 analyzed like different phases of the same AE.

A descriptive analysis will be performed. Global incidences of primary system organ classes (SOC) and preferred terms (PT) will be calculated for

- All TEAE irrespective of the causality assessment
- TEAE by relationship (likely and possible related)
- TEAEs by worst severity
- Serious TEAEs

This analysis comprises the following set of tables separated by treatment group:

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

Multiple counts within a PT 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 subject identification, age, sex, AE descriptors, start and end of treatment will be prepared for the following types of TAEs:

- Serious adverse events (SAE)
- Adverse events which led to discontinuation
- Myocardial infraction
- Stroke
- Acute liver injury
- Acute kidney injury
- Thromboembolic events

The number of patients who died will be summarized. 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.

All adverse events recorded since enrollment will be listed in the data part of the report. Only TEAEs will be summarized in the tables.

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5.9.2 Laboratory variables

In case of derived items in the database (i.e. after substitution of invalid values by missings, after transformation to standard units etc., see DMP), only the derived items will be analyzed. Results of all individual lab tests will be listed in original and standard units in appendix 16.2 to the clinical trial report.

All laboratory values will be classified as normal or abnormal according to the laboratories' normal 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 illustrating changes with respect to the laboratories' normal ranges between baseline and a defined scheduled time point.
- Number and frequency of patients with clinically significant laboratory values (e.g. $> 3 \times \text{ULN}$).
- Patient listings will be provided showing individual lab abnormalities.

5.10 Other safety variables

The following additional safety variables will be summarized in tables separated by treatment group:

- Duration of mechanical ventilation up to postoperative day 28
- Duration of intensive care unit (ICU) stay up to postoperative day 28
- Duration of hospitalization up to postoperative day 28

5.11 Interim analyses

The study employs a group-sequential design that involves one pre-planned interim analysis after 600 patients have been enrolled

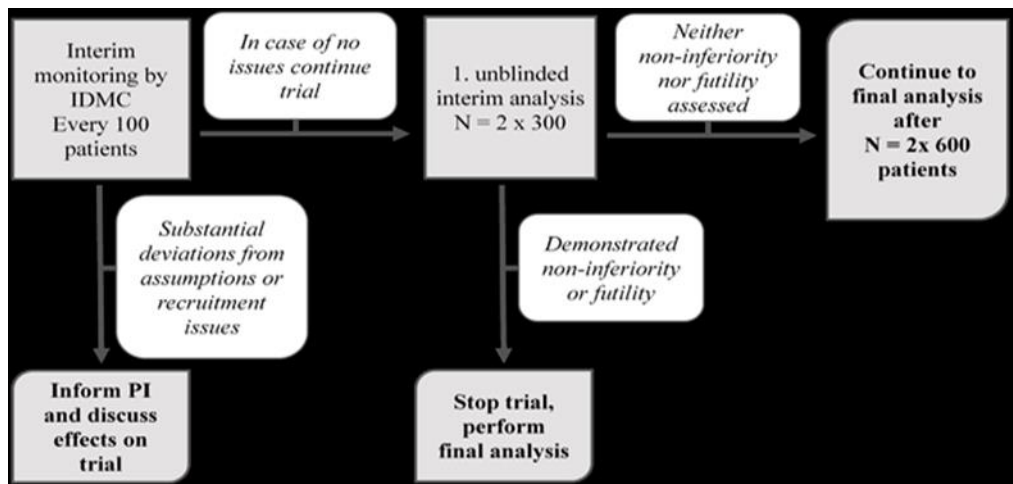
In addition, IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study. This data monitoring serves the purpose of an ongoing assessment of recruitment problems as well as the compatibility of the accumulating data with the assumptions made at study start. The extent of the information to be reviewed will be defined in the IDSMC charter. The IDSMC will keep all these data monitoring results in strict confidence. Only in case of identified issues during their data monitoring the IDSMC will advise the Principal Investigator in a non-treatment-disclosing manner on the problems.

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The interim analysis will be an unblinded interim analysis with an adjusted type I error rate according to the O'Brien-Fleming method after 600 patients have been enrolled. After this interim analysis, a positive outcome may be claimed and enrolment may be stopped if the test of H_0 vs. H_1 in the mITT population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$ rejects the null hypothesis (efficacy stop). A full final analysis including all study data will be performed and reported if enrolment is stopped after the interim analysis. Also at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

Otherwise, the study will continue until the maximum sample size of $n = 2 \times 600$ patients, is reached. The final analysis will be performed as described above, but with an adjusted significance level of $\alpha_2 = 0.02242$ to maintain the overall one-sided significance level of $\alpha = 0.025$

The flow chart below illustrates the decision process underlying the interim analyses.



6 QUALITY CONTROL

The SAP will be signed off only when approval by the Principal Investigator is received.

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 SAS programmer.

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

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7 REFERENCES

- [1] Cameron, A. C.; P. K. Trivedi (2014). Regression Analysis of Count Data, 2nd ed., New York: Cambridge University Press
- [2] Hilbe, J. M. (2008). Negative Binomial Regression, New York: Cambridge University Press
- [3] Karkouti K, Callum J, Wijeyesundera DN et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. Circulation 2016;pii: CIRCULATIONAHA.116.023956. [Epub ahead of print]

8 APPENDICES

8.1 Formulas for derived variables

Variable	Description
ABP _{24h}	Total units of Allogenic Blood Products administered within 24 hours of surgery, defined as: #RBCs + #FFPs + 4*#Platelets transfused in this time period
ABP _{7D}	Total units of Allogenic Blood Products administered within 7 days of surgery, defined as: #RBCs + #FFPs + 4*#Platelets transfused in this time period
Duration of mechanical ventilation	# of days on ventilation until postoperative day 28

8.2 List of Tables, Listings, Figures

A complete lists 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 both the Principal Investigator, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced. Therefore, this list will be approved by both parties before commencing the statistical programming.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have 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.

All statistical output will identify the underlying analysis populations and indicate the number of patients/events in this population (N) and the number of patient/events actually contributing to the particular output (n). All statistical output will be presented per treatment group and in total (if applicable).

All patient listings will contain additionally to the patient identification the analysis population and the treatment group.

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8.3 Additional details on statistical methods

As the total number of allogenic blood products and similarly the number of RBCs, platelets and FFP transfused represent integer count data the use of statistical methods for count data is indicated for their analysis (see e.g. [1] and [2]).

Such methods are typically employed in the context of a generalized linear model (GLM) using the Poisson or Negative Binomial distributions as error terms.

As these models typically employ a logarithmic link function as a constituent part, it appears natural to state the null and alternative hypotheses in terms of the ratio of the treatment means. After such a logarithmic transformation these hypotheses take the form of a linear difference in the model parameters.

This allows the direct application of the GLM and their associated inferences (test and confidence intervals). The numerical analyses will be performed with the GENMOD procedure of the SAS system. During the analysis with PROC GENMOD the model assumptions (e.g. assumptions about the deviance) will be checked and all details of the analyses be reported in the appendix 16.1.9 to the clinical trial report.

FIBRES Statistical Analysis Plan- List of Changes from Version 1.0 to 2.1

Below are the changes made to the Statistical Analysis Plan (SAP). These changes were made to reflect the updated FIBRES study protocol:

1. Correction of Listed Protocol Deviations

Sections 3.2 and 4.5 of the SAP were corrected to state a deviation had occurred when a patient received less than 80% (not 75%) of their initial dosing.

2. Population Analysis

In section 4, the intention to treat population was clarified. The original protocol specified, but was not clear, that the primary analysis would be conducted on randomized, treated patients who provided consent. The revised protocol clearly defines this population and labels it as modified intention to treat.

The high-risk (or critically ill) subgroup, which was added to the amended protocol, was also added to the SAP.

3. Safety

It was clarified that all analyses would be performed for the mITT population (Section 5.9). Only for analysis of SAEs, the Safety Analysis Set (SAF) population would be used additionally.

4. Interim Analyses

It was clarified the interim analysis would be initiated after 600 patients had been enrolled (i.e., randomized and treated).

5. Appendices

A table was added in the appendices to specify how apheresis allogeneic blood units would be counted in the SAP (Section 8.1).



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Principal Investigator:	Keyvan Karkouti, MD
Sponsor:	Keyvan Karkouti; Toronto General Hospital
Title of Protocol:	Prospective, multi-center, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenaemia in bleeding adult cardiac surgical patients
Protocol Version/Date:	FIB Version 2.4 / 2018-07-03
CRF Version:	FIB Version 3.0 / 2018-04-21
Supersedes SAP Version:	N/A (initial version)

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Document authorization

Hans P. Hucke
Trial Statistician
ERGOMED

Signature
Date (dd-mmm-yyyy)

Keyvan Karkouti
Principal Investigator
Toronto General Hospital

Signature
Date (dd-mmm-yyyy)

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Consistency check with the Protocol (~~one option to be selected~~)

- This is to confirm that as part of the SAP finalization consistency check with the current protocol / protocol amendment was performed by the trial statistician, and no changes to the protocol (statistical section) are required
- Changes to the analysis principles were required, and the responsible team has confirmed commitment to update the study protocol
- Changes to the analysis principles were required (as outlined in revision history section of this SAP).

Hans-Peter Hucke
Trial Statistician
ERGOMED

Signature
Date (dd-mmm-yyyy)

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Change control

Date	Author	Reason	Version
2016-09-27	Hans P. Hucke	First version	1.0
<u>2018-10-08</u>	<u>Hans P. Hucke</u>	<u>Changes due to amended protocol</u>	<u>2.00</u>
<u>2018-10-15</u>	<u>Hans P. Hucke</u>	<u>Minor Changes due to sponsor comments</u>	<u>2.10</u>

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABP	Allogenic Blood Product
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
AUC	Area Under the Concentration-Time Curve
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CRO	Contract Research Organization
DMP	Data Management Plan
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
IDSMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous

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MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
<u>REB</u>	<u>Research Ethics Board</u>
SAE	Serious Adverse Event
SAF	Safety Analysis Set
TLFs	Tables, listings, figures

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1 STUDY MATERIAL

The following material was considered for this SAP:

Document	Version, Date
Protocol, incl. last amendment	Version 1.0, 2016-09-22 2.4 / 2018-07-03
CRF	TBD Version 3.0 / 2018-04-21
DMP	TBD Version 1.0 / 2017-10-05
DVP	TBD Version 1.0 / 2018-04-25

2 STUDY INFORMATION

2.1 Primary objective

The primary objective of this study is to demonstrate that the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. Efficacy will be measured by the total number of allogeneic blood products (ABPs) administered during the first 24 hours after termination of CPB.

2.2 Secondary objective

The secondary objectives include:

Comparison of efficacy as measured by the total and individual number of allogeneic blood products transfused from the beginning of surgery up to postoperative day 7

Comparison of the amount of bleeding during the first 24 hours after termination of CPB

Comparison of the effect on fibrinogen levels observed within 1 hour before and 1 hour after fibrinogen supplementation

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2.3 Study design

The study is a pragmatic, prospective, multi-center, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. Up to 12 Canadian hospitals will participate, and the trial will require up to 2 years for patient recruitment.

Approximately twelve-hundred bleeding adult cardiac surgical patients who require fibrinogen supplementation due to acquired hypofibrinogenaemia after CPB will be included. Patients will be randomized to receive equivalent doses of either fibrinogen concentrate (Octafibrin) or cryoprecipitate when the blood bank receives the first order for fibrinogen supplementation and deems it to be in accordance with accepted clinical standards. Thereafter, patients will be treated according to their assigned group each time fibrinogen supplementation is ordered during the treatment period (24 hours after termination of CPB).

Details on the study procedures, measurements and their timing can be found in the study protocol and the trial flow chart below:

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Trial flow chart

Procedures	Prior to enrollment	Visit 1 Post-randomization (0 to 24 Hr)	Visit 2 24–36 h post IMP	Visit 2a 24–36 h post additional IMP	Visit 3 POD7/DC	Visit 4 POD28
Blood bank receives fibrinogen order ^a	x	(x) ^d				
Inclusion and exclusion criteria	x					
Randomization	x					
IMP administration		x				
Confirm integrated consent	x					
Obtain delayed consent		x	(x)	(x)	(x)	
Baseline data						
Demographics		x				
Medical history		x				
Preoperative medications		x				
Surgical data						
Intraoperative medications		x				
CPB time		x				
X-clamp time		x				
Circulatory arrest		x				
Vital signs		x				
Fluid in- and output monitoring		x				
Inotropes and vasopressors		x	x	x		
Laboratory assessments						
Chemistry ^f		x	x	x	x	
Hematology ^f		x ^c	x	x	x	
Coagulation profile ^f		x ^c	x	x	x	
Safety labs ^f		x	x	x	x	
Transfusion requirements^e						
Allogenic red blood cells		x	x	x	x	
Pooled platelets		x	x	x	x	
Plasma		x	x	x	x	
Other hemostatic products		x	x	x	x	
Blood loss determination using UDPB		x	x	x	x	
Extubation time		x	x	(x)	(x)	(x)
ICU length of stay		x	x	(x)	(x)	(x)
Hospital length of stay					x	(x)

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AEs and SAEs		x	x	x	x	x
Concomitant medications		x	x	x	x	x
Physical examination		x	x	x	x	x

^a After the start of surgery and during or after CPB.

^b IMP will first be administered after start of surgery based on the physician's judgement. The first IMP dose can be administered before fibrinogen levels are known in bleeding patients, but all subsequent doses must have confirmation of low fibrinogen level (<1.5–2.0 g/L by the Clauss method in addition to equivalent point-of-care alternatives e.g, ROTEM assay FIBTEM A10 of <12 mm, if available).

^c Prior to and 60 minutes after IMP administration.

^d Patients will be treated according to their group allocation for any subsequent doses needed during the treatment period.

^e 24 hours after IMP administration, ^f As per standard practice, ^g If needed

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2.4 Planned sample size

The estimation of the sample size for the trial took into account the primary objective of the trial (demonstrating non-inferiority), the statistical analysis method (Poisson regression for count data) and the results of a comparable previous study conducted by the principal investigator in the same indication using the ABP endpoint during the years 2014/2015.

The statistical analysis of the primary efficacy variable, i.e., the amount of ABPs, will be based on the mean number of ABP units within the first 24 hours following CPB (μ_F and μ_c).

To demonstrate that treatment with *Octafibrin* is clinically not inferior to the treatment with cryoprecipitate with respect to the mean number of ABP units, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \mu_F / \mu_c \geq (1 + \delta) \quad \text{vs.} \quad H_1: \mu_F / \mu_c < (1 + \delta)$$

will be carried out with a type I error probability of $\alpha = 0.025$ and a clinical non-inferiority margin of δ . Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term), with treatment group as main effect.

The test of the primary hypothesis in the planned interim and the final analysis will be based on the one-sided confidence interval (CI) for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

Based on this method and a one-sided overall type I error probability $\alpha = 0.025$, simulations have been performed to study the power of the test for different sample sizes and values of the non-inferiority margin δ .

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units. The empirical distribution function with these sample characteristics was chosen based on results of the TACS study [3] with the same endpoint in the same indication and similar treatment.

10,000 studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

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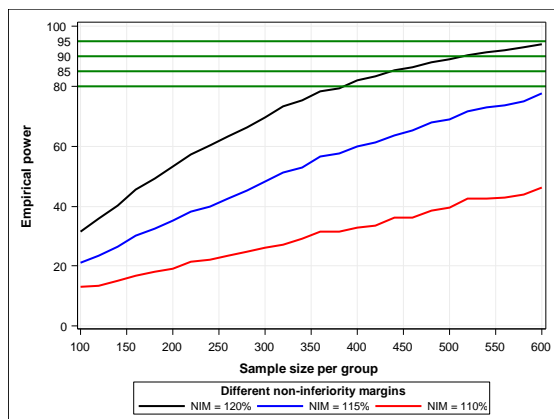
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The plot below displays the empirical power curves for the test of H_0 vs. H_1 using the Poisson counting regression model analyzed with SAS PROC GENMOD for sample sizes up to 600 patients per group and three values of the non-inferiority margin (NIM).



As the diagram shows, an empirical power of >90% can be expected with a sample size of at least 550 patients per treatment group if a δ of 0.20 is chosen. For smaller values of δ , no sufficient power can be attained with operationally feasible sample sizes. The choice of the non-inferiority margin $\delta = 0.20$ is also due to the substantial intrinsic variation in the primary endpoint that has to be expected from previous studies reflecting current clinical practice.

Therefore it is planned to conduct the study with a maximum sample size of 600 patients in each treatment group and a non-inferiority margin of $\delta = 0.20$.

Assuming that a proportion of about 10% randomized patients will not be treated after randomization or for whom the endpoint cannot reliably be obtained, this would ensure that data on at least 550 patients per treatment group in the FFmTT population will be available for the statistical analysis as derived from the sample size calculation.



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3 GENERAL INFORMATION

3.1 Deviations from the trial protocol with regard to statistical analyses

There are no deviations from the statistical methods described in the trial protocol.

3.2 Individual protocol deviations

Any deviation from protocol will be discussed case by case before database lock or unblinding whether the deviation has to be regarded as minor or as major (and therefore lead to exclusion from particular analysis populations).

The assessment of individual protocol deviations will be made in a blinded data review meeting. A complete listing of protocol deviations and the judgment for assessment of subject disposition will be signed before database lock. All deviations along with the disposition of each subject will be recorded in a separate database member that will become part of the study database. A description of all major protocol violations will be included in the table part of the clinical trial report.

Criteria for major protocol violations will include:

- Patients who do not receive an IMP after randomization
- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than ~~75~~80% of the planned dose for their initial dosing
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

4 ANALYSIS POPULATIONS

The disposition of subjects will be displayed according to the following analysis populations:

- ~~Screening failures,~~

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- Non-Treated
- Non-Qualified,
- modified Intention To Treat (mITT) population
- Safety (SAF) population;
- ~~Intention to Treat (ITT) population;~~
- Per-Protocol (PP) population.

4.1 Screening Failures

4.1 Screening failures are Non - Treated

This population consists of all patients who were enrolled, but did not receive any IMP or,

4.2 Non - Qualified

This population consists of all patients who were enrolled and received at least one dose of IMP, but did not provide delayed informed consent or meet any of the following criteria:

- Unrestricted consent- available by patient, SDM or REB,
- Performed procedure was cardiac surgery.

Only baseline demographic and anamnestic data information on screening failures the treatment administered will be listed.

4.3 modified Intention To Treat (mITT) population

The modified Intention To Treat (mITT) population will include all randomized patients who received at least one dose of IMP and who met both of the following criteria:

- Unrestricted consent available by patient, SDM or REB, and

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- ~~Performed procedure was cardiac surgery.~~

4.24.4 Safety population

The safety (SAF) population (SAF) will ~~include~~ consist of all randomized patients with delayed informed consent who received at least one dose of IMP.

4.3 ~~Intention to treat of the mITT~~ population

The intention to treat (ITT) population includes and in addition all randomized those patients receiving at least one dose of IMP who provided delayed informed consent. In the event that a patient receives of the wrong treatment Non-Qualified population for infusion, the treatment group will be defined according to the randomization (rather than the actual treatment received), whom restricted REB approval is available to use recorded SAE data only.

If no randomization errors are observed the ITT The SAF population will only be identical utilized in summaries and listings of SAEs and their relation to the safety analysis IMP. No other data on this population (SAF) will be analyzed or reported within this trial.

4.44.5 Per-protocol population

The per-protocol (PP) population is a subset of the ~~ITT~~ mITT population excluding patients with major important protocol deviations. The Patients showing any of the following patients criteria will be excluded ~~considered~~ for exclusion:

- ~~Patients who do not receive an IMP after randomization~~
- ~~Patients who receive an IMP different to the IMP assigned by randomization~~
- ~~Patients who receive less than 75~~80% of the planned dose (first dose only)
- ~~Patients who significantly violate inclusion/exclusion criteria~~
- ~~Patients with missing without recording of the primary efficacy assessment endpoint~~

A final decision about the classification of protocol deviations as major important and minor and their consequences regarding assignment of patients to analysis populations will be made during the

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blinded data review meeting prior to unblinding for the interim and final analyses. Decisions and outcome will be approved by the Principal Investigator (Sponsor) in consultation with the ~~Trial Statistician~~ collaborator (Octapharma).

The ~~ITT~~ analysis population is considered the ~~primary~~ most relevant population for analysis of the primary efficacy objective. However, the evaluation of all efficacy endpoints will additionally be ~~performed~~ presented for the PP population.

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4.54.6 Subgroup analyses

Subgroup analyses of the primary and secondary efficacy are planned for the following subgroups:

- ~~non~~Non-elective surgery patients,
- ~~complex~~Complex surgery patients (procedures other than isolated ACB, single valve, or repair of ASD).

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- High-risk surgery patients, i.e. those that meet any of the following criteria according to adjudicators:
 - In critical condition before surgery.

5 STATISTICAL ANALYSES

All statistical analyses will be performed using SAS® for Windows (Version 9.34 or higher).

Descriptive statistics will always be given by treatment group. For baseline and basic variables, they will also be given for the entire population.

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

Descriptive statistics for continuous data

Number of subjects (N), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum will be presented. Usually mean, standard deviation and quartiles will have 1 decimal more than the original values (as given with min, max); N has no decimals. These descriptive statistics will be determined for measured values and for differences to baseline.

Descriptive statistics for categorical data

Absolute frequencies (N) and relative frequencies (%) will be presented with 0 or 1 decimal, respectively. For changes from baseline, shift tables may be generated.

Inferential statistics

If not stated otherwise, all statistical tests will be performed two-sided and at a type I error probability of $\alpha=0.05$. The p-values of the test statistics will be printed consistently with 4 decimals (p<0.0001 will be displayed, if the p-values are less than 0.0001).

If not stated otherwise, all confidence intervals (CI) will be two-sided and at a coverage probability of $1-\alpha = 0.95$.

Listings

All subject data will be listed by subject sorted by treatment group. Identification variables will be center number, subject number and treatment. Any derived data listed will also be stored permanently and will be calculated as outlined in section 8.1 of this SAP.

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5.1 Conventions

5.1.1 Baseline definition

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

5.1.2 Missing data

No imputation of missing values is planned.

5.1.3 Pooling of centers

No pooling of centers will be performed.

5.2 Demographic and other background data

The disposition of subjects (cf. Section 4) will be tabulated by treatment and for the entire population. Details on protocol deviations will be listed.

Discontinued patients will be described by frequency distributions including the reasons and in individual listings.

Demographic data (sex, age, height, weight, and Body Mass Index (BMI)) will be summarized in tables and presented for the ~~FFmIII~~ and PP population. Homogeneity tests between treatment groups and centers will be performed for the demographic data at an alpha level of 10%.

The following surgical-related data will only be listed:

- Details of procedure,
- CPB duration,
- CPB start-end times,
- Cross-clamp duration,
- Circulatory arrest duration,
- Vital signs,

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- Fluid intake and output,
- Medications administered,
- Hemodynamic support (e.g., IABP),
- Blood conservation methods used.

5.3 IMP exposure, compliance

All IMP treatment details will be listed. Patient compliance (amount of IMP received / planned amount of IMP) will be calculated for each patient and summary statistics be presented by treatment group.

5.4 Medical history, physical examination

Data on medical history and physical examination will be listed. Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Codes will be reviewed by a designated Medical Expert and approved by the Principal Investigator before data base lock.

5.5 Prior and concomitant medication

Any relevant medication taken at time of enrolment will be listed as prior medication. All new medications taken during the study period are defined as 'Concomitant'. Any changes of medications during the study period will also be recorded.

All details of prior and concomitant medications will be listed including, the route, dose, frequency, start and stop date and indication.

Medications will be coded using the WHO DD thesaurus in the version current at the time of enrollment of the first patient. Coding will be performed by the CRO and agreed upon with the Principal Investigator before data base lock. (cf. data management plan (DMP)). For concomitant medications tables will show the frequencies of patients by WHO DD preferred term. Prior medication will only be listed.

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5.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

5.7 Efficacy

5.7.1 Primary efficacy endpoint

The primary efficacy variable is the total number of ABP units (sum of RBCs, pooled and apheresis platelets and FFP) used within 24 hours after termination of CPB.

In a first analysis step, descriptive statistics on the total number of ABP units within 24 hours of CPB will be provided by treatment group. These statistics will be provided for the ~~FFPmITT~~ and the PP population.

To demonstrate that treatment with *Octafibrin* is clinically not inferior to treatment with cryoprecipitate with respect to total number of ABPs, a two-sample, one-sided test of the ~~pair of~~ hypotheses:

$$H_0: \mu_F / \mu_c \geq (1 + \delta) \text{ (inferiority)}$$

$$\text{vs. } H_1: \mu_F / \mu_c < (1 + \delta) \text{ (non-inferiority)}$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.20$. Here, μ_F and μ_c denote the mean number of ABPs in the *Octafibrin* and cryoprecipitate treatment groups, respectively.

Testing of the hypothesis will be performed in the context of a Poisson regression model (generalized linear model for count data with log-link function and a Poisson error term) with treatment group as main effect.

The test of the primary hypothesis in the final analysis will be based on the one-sided CI for the ratio μ_F / μ_c derived from the estimated least square means (LSmeans) of this model. Non-inferiority will be concluded if the upper limit of this CI is strictly less than $(1 + \delta)$.

The primary analysis will be performed on the ~~FFPmITT~~ population. A secondary analysis will be performed for the PP population to study the robustness of the results.

Only in case of demonstrated non-inferiority in the ~~FFPmITT~~ and the PP population subsequently the ~~pair of~~ hypotheses:

$$H'_0: \mu_F / \mu_c \geq 1$$

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vs. $H_1: \mu_F / \mu_c < 1$

will be tested, again by a two-sample, one-sided test, to demonstrate that treatment with *Octafibrin* is clinically superior to treatment with cryoprecipitate with respect to total number of ABPs. Since this test for superiority will only be performed if non-inferiority has been demonstrated previously, no adjustment of type I error is necessary and therefore the test will be done at the same type I error level as the test of non-inferiority.

5.7.2 Secondary efficacy endpoints

The secondary endpoints listed below will be analyzed in an exploratory manner only, presenting summary tables (frequency tables or sampling statistics according to data type) along with the presentation of 95 % confidence intervals and p-values for exploratory tests of treatment group differences. Results will be presented for the ~~FFMITT~~ and the PP population.

- Total number of units of ABPs administered from start of cardiac surgery until 7 days after surgery or discharge.
- Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets and plasma.
- Distribution of major bleeding type, using the validated universal definition of perioperative bleeding (UDPB) in cardiac surgery.
- Change in fibrinogen plasma level (measured using the Clauss assay) within 1 hour before and 1 hour after fibrinogen supplementation for first and subsequent doses.

The total number of ABPs within 7 days/discharge and the different subtypes of ABPs will be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.

Frequency distributions of the major bleeding type according to UDPB will be presented for each treatment group.

Change in fibrinogen plasma level will be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the *Octafibrin* and cryoprecipitate treatment groups and the corresponding 95% CI will be calculated.

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5.8 Pharmacokinetics / Pharmacodynamics

Not applicable.

5.9 Safety

All analyses will be performed for the MITT population. Only for analysis of SAEs the SAF population will be used additionally.

5.9.1 Adverse events

Adverse events (AEs) will be coded by the CRO according to the MedDRA thesaurus. Coding will be agreed upon with the Principal Investigator before database lock (cf. DMP).

Treatment-emergent adverse events (TEAE) will be analyzed, i.e. all new and worsening pre-existing adverse events occurring after first IMP administration up to postoperative day 28. 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 analyzed like different phases of the same AE.

A descriptive analysis will be performed. Global incidences of primary system organ classes (SOC) and preferred terms (PT) will be calculated for

- All TEAE irrespective of the causality assessment
- TEAE by relationship (likely and possible related)
- TEAEs by worst severity
- Serious TEAEs

This analysis comprises the following set of tables separated by treatment group:

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

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Multiple counts within a PT 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 subject identification, age, sex, AE descriptors, start and end of treatment will be prepared for the following types of TAEs:

- Serious adverse events (SAE)
- Adverse events which led to discontinuation
- Myocardial infraction
- Stroke
- Acute liver injury
- Acute kidney injury
- Thromboembolic events

The number of patients who died will be summarized. 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.

All adverse events recorded since enrollment will be listed in the data part of the report. Only TEAEs will be summarized in the tables.

5.9.2 Laboratory variables

In case of derived items in the database (i.e. after substitution of invalid values by missings, after transformation to standard units etc., see DMP), only the derived items will be analyzed. Results of all individual lab tests will be listed in original and standard units in appendix 16.2 to the clinical trial report.

All laboratory values will be classified as normal or abnormal according to the laboratories' normal 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:

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- 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. On 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 illustrating changes with respect to the laboratories' normal ranges between baseline and a defined scheduled time point.
- Number and frequency of patients with clinically significant laboratory values (e.g. > 3 x ULN).
- Patient listings will be provided showing individual lab abnormalities.

5.10 Other safety variables

The following additional safety variables will be summarized in tables separated by treatment group:

- Duration of mechanical ventilation up to postoperative day 28
- Duration of intensive care unit (ICU) stay up to postoperative day 28
- Duration of hospitalization up to postoperative day 28

5.11 Interim analyses

The study employs a group-sequential design that involves one pre-planned interim analysis after 600 patients have ~~completed the study~~ been enrolled

In addition, IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study. This data monitoring serves the purpose of an ongoing assessment of recruitment problems as well as the compatibility of the accumulating data with the assumptions made at study start. The extent of the information to be reviewed will be defined in the IDSMC charter. The IDSMC will keep all these data monitoring results in strict confidence. Only in case of identified

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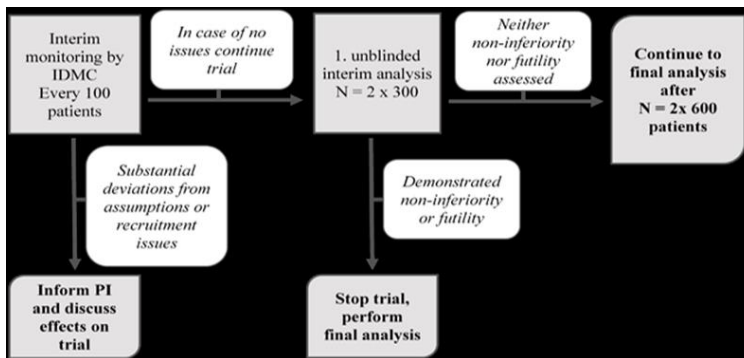
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issues during their data monitoring the IDSMC will advise the Principal Investigator in a non-treatment-disclosing manner on the problems.

The interim analysis will be an unblinded interim analysis with an adjusted type I error rate according to the O'Brien-Fleming method after 600 patients have been enrolled. After this interim analysis, a positive outcome may be claimed and enrolment may be stopped if the test of H_0 vs. H_1 in the ~~FFmTT~~ population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$ rejects the null hypothesis (efficacy stop). A full final analysis including all study data will be performed and reported if enrolment is stopped after the interim analysis. Also at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

Otherwise, the study will continue until the maximum sample size of $n = 2 \times 600$ patients, is reached. The final analysis will be performed as described above, but with an adjusted significance level of $\alpha_2 = 0.02242$ to maintain the overall one-sided significance level of $\alpha = 0.025$

The flow chart below illustrates the decision process underlying the interim analyses.





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6 QUALITY CONTROL

The SAP will be signed off only when approval by the Principal Investigator is received.

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 SAS programmer.

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

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7 REFERENCES

- [1] Cameron, A. C.; P. K. Trivedi (~~1998~~2014). Regression Analysis of Count Data, 2nd ed., New York: Cambridge University Press
- [2] Hilbe, J. M. (2008). Negative Binomial Regression, New York: Cambridge University Press
- [3] Karkouti K, Callum J, Wijeyesundera DN et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. Circulation 2016;pii: CIRCULATIONAHA.116.023956. [Epub ahead of print]

8 APPENDICES

8.1 Formulas for derived variables

Variable	Description
A detailed list of all derivations will be compiled upon protocol approval by Health Canada ΔBP_{24h}	Total units of Allogenic Blood Products administered within 24 hours of surgery, defined as: #RBCs + #FFPs + 4*#Platelets transfused in this time period
ΔBP_{7D}	Total units of Allogenic Blood Products administered within 7 days of surgery, defined as: #RBCs + #FFPs + 4*#Platelets transfused in this time period
Duration of mechanical ventilation	# of days on ventilation until postoperative day 28

Inserted Cells

8.2 List of Tables, Listings, Figures

A complete lists 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 both the Principal Investigator, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced. Therefore, this list will be approved by both parties before commencing the statistical programming.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.



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All output will be dated and have 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.

All statistical output will identify the underlying analysis populations and indicate the number of patients/events in this population (N) and the number of patient/events actually contributing to the particular output (n). All statistical output will be presented per treatment group and in total (if applicable).

All patient listings will contain additionally to the patient identification the analysis population and the treatment group.

8.3 Additional details on statistical methods

As the total number of allogenic blood products and similarly the number of RBCs, platelets and FFP transfused represent integer count data the use of statistical methods for count data is indicated for their analysis (see e.g. [1] and [2]).

Such methods are typically employed in the context of a generalized linear model (GLM) using the Poisson or Negative Binomial distributions as error terms.

As these models typically employ a logarithmic link function as a constituent part, it appears natural to state the null and alternative hypotheses in terms of the ratio of the treatment means. After such a logarithmic transformation these hypotheses take the form of a linear difference in the model parameters.

This allows the direct application of the GLM and their associated inferences (test and confidence intervals). The numerical analyses will be performed with the GENMOD procedure of the SAS system. During the analysis with PROC GENMOD the model assumptions (e.g. assumptions about the deviance) will be checked and all details of the analyses be reported in the appendix 16.1.9 to the clinical trial report.