**RESEARCH PROPOSAL**

**1. Specific Aims, including a statement on impact (one page)**

**Statement of impact:** Successful use of fibrinogen replacement with fibrinogen concentrate (FC) in patients with acquired fibrinogen deficiency has been described in the trauma literature in several observational and randomized studies [1, 2, 3, 4]. Several systematic reviews [5-8] have been published and included studies addressing feasibility, efficacy and safety on the use of FC in trauma and other bleeding settings. All combined, these studies demonstrate that the use of FC to replace fibrinogen in acquired hypofibrinogenemia improves coagulation and decreases the number of allogeneic blood products (ABPs) (red blood cells [RBC], frozen plasma [FP] and platelets [PLT]) transfused without safety concerns. Similarly, successful use of coagulation management algorithms including the use of prothrombin complex concentrate (PCCs) has been described in trauma [9-12, 13, 14]. In these studies, PCC use has also demonstrated decreased number of ABP units used and improvement of laboratory or viscoelastic tests parameters, without safety concerns. However, the efficacy and safety of early replacement of FC and PCC in trauma patients has yet to be demonstrated in a large multi-center randomized study.

The FIIRST-2 trial, a pragmatic multi-center study, will demonstrate the impact of rapidly infusing FC and PCC as an early hemostatic therapy in bleeding trauma patients, as compared to standard massive hemorrhage protocols (MHP) packs with RBC:FP:PLT at a 1:1:1 ratio. This trial will provide efficacy data on the impact on plasma fibrinogen levels, coagulation, and other clinical and transfusion endpoints and, additionally, will provide data on safety.

FC and PCC have important advantages over ABPs: they are faster to prepare, easier to administer, do not require an ABO blood group, have a more predictable response, are less likely to cause volume-related complications, can be prepared and administered in the pre-hospital/transport phase of care, and have a superior safety profile as are pathogen-reduced. The finding that FC and PCC are superior to the standard of care, with plasma and replacement of fibrinogen based on laboratory fibrinogen levels, would make them the preferred option for trauma resuscitation, which has the potential to improve the quality, reduce the logistical complexity, and increase speed of care offered to trauma patients. This would have several important consequences: (1) Possibility of administration of less fluid volume, leading to less hemodilution and fewer complications due to fluid overload; (2) Reduction of requirement for AB plasma, reducing the dependence on this product in short supply; (3) Potential ability to store FC and PCC in the trauma bays obviating the need to wait for ABPs; (4) Potential for use in the pre-hospital setting (e.g. land/air transport) or in distant/austere environments; (5) Mitigate the risk of future pathogen outbreaks by reducing the donor exposure to non-pathogen reduced products by more than 50%.

**Specific aim 1 (primary endpoint):** To evaluate whether a combination of FC + PCC administered in patients with hemorrhage due to trauma reduces the need for ABPs within the first 24 hours post admission.

**Specific aim 2 (secondary endpoints) - Efficacy endpoints:**

1. To evaluate whether a strategy using FC + PCC is associated with earlier hemorrhage control and less blood loss as measured by the total use of RBCs within the first 24 hours post hospital admission.
2. To evaluate physiological and hematologic endpoints among patients receiving a transfusion strategy based on early administration of FC + PCC compared to standards of care:
    a. Plasma fibrinogen levels
    b. International normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT)

    c. Hemoglobin levels
    d. Platelet count
    e. Base deficit, pH and lactate
    f. Thromboelastometry values for ROTEM clotting time (CT), EXTEM A10, EXTEM Maximum clot firmness (MCF), FIBTEM A10, FIBTEM MCF, and EXTEM LY30
3. To evaluate the total volume of crystalloids, albumin (5% and 25%) or other colloids administered within the first 24 hours after admission.
4. To evaluate the time from admission to transfusion of last RBC (within the first 24 hours after admission).
5. To evaluate the total and individual number of ABP units transfused within the 7 days post admission
6. To evaluate the total use of coagulation factor concentrates (PCC and FC) within the first 24 hours after admission.
7. To evaluate 24-hour and 28-day mortality.

**Specific aim 3 (secondary endpoints) - Safety endpoints:**

1. Incidence of acute respiratory distress syndrome (ARDS), defined by the Berlin Classification, before Day 28 after admission.
2. Incidence and severity of multi organ failure (MOF) as measured by the Sequential Organ Failure Assessment (SOFA) score, at Days 7, 14, 21, and 28 after admission.
3. ICU-free days.
4. Ventilator-free days
5. Incidence of abdominal compartment syndrome before day 28 after admission.
6. Incidence of limb compartment syndrome before day 28 after admission.
7. Incidence of thromboembolic events, as defined by evidence of any of the following, from admission to 28 days after admission:
    a. Deep vein thrombosis (DVT)
    b. Pulmonary embolism (PE)
    c. Myocardial infarction (MI)
    d. Ischemic stroke
    e. Arterial or venous thrombosis at other sites.
8. Incidence of transfusion reactions as defined by the International Society of Blood Transfusion over the first 28 days.
9. Incidence of treatment-emergent adverse events.

## 2. Research Strategy

### Significance

The FIIRST-2 trial will address several important points related to current clinical practice in hemorrhaging trauma patients: (1) Risk of pathogen transmission in the currently used allogeneic blood products (plasma and cryoprecipitate); (2) Plasma and cryoprecipitate require thawing and pooling by blood banks before issuing which lead to long preparation times, and thus delays in administration; (3) Cryoprecipitate and plasma contain variable amounts of fibrinogen and clotting factors, respectively; (4) Impact of faster coagulation factor replacement on patient outcomes; (5) Impact of lower volume products on volume related complications in the

massive transfusion setting. We believe that replacement of fibrinogen and clotting factors with FC + PCC instead of using plasma will be superior in this population. FC and PCC have important advantages: they are faster to prepare, easier to administer, do not require an ABO blood group, have a more predictable response, are less likely to cause volume-related complications (e.g., abdominal compartment syndrome), can be prepared and administered in the pre-hospital/transport phase of care, and have a superior safety profile. The finding that FC and PCC are superior to the standard of care, would make them the preferred option for trauma resuscitation, which has the potential to improve the quality and speed of care offered to trauma patients, leading to changes in evidence-based guidelines for early hemostatic therapy in trauma. A consensus conference held in 2007 [14] recommended implementation of pathogen reduction strategies as soon as available and found to be as efficacious to mitigate the risks of transfusion-transmitted pathogens. This will be offered by using the intervention conducted in the FIIRST-2 trial. Additionally, the RETIC trial (Reversal of Trauma Induced Coagulopathy) using first-line coagulation factor concentrates of fresh frozen plasma) [8], reported more rescue therapy in the arm treated only with plasma. This study suggests that use of clotting factors via FC and PCC is a superior strategy compared to the ratio based transfusion. The FIIRST-2 trial will answer this question as a definitive trial.

This trial will provide evidence on the clinical efficacy and safety on early administration of FC and PCC as first line hemostatic therapy in trauma care. Early FC and PCC supplementation in this population has the potential to result in reduced exposure to the number of units of AB plasma used, with improvement of clinical outcomes and possibly cost reduction. These data will have important implications for both civilian and military trauma care. Should this intervention be superior, we believe that these products may be carried to the battle field, in the military setting. FC + PCC may be feasible to have in the pre-hospital phase, in land ambulances and air transportation. We also believe that FC + PCC will be kept for easy and fast access in the trauma bays, to be used as early as possible during the resuscitation process without the need for delivery from a pharmacy or blood bank.

**Innovation**

The FIIRST-2 trial aims to refine and improve the current standards for treatment of severely bleeding and coagulopathic trauma patients. Currently, these patients are treated according to a damage control resuscitation approach, where volume is given to restore oxygen carry capacity (avoiding crystalloids); a hemostatic resuscitation approach is conducted emphasizing the need for replacement of clotting factors with plasma and cryoprecipitate; and the use of anti-fibrinolytics (tranexamic acid). Concomitantly, the source of bleeding is identified and stopped. The innovation that this brings is an entirely new approach to replacement of factors that is faster, offers more precision and is lower risk (pathogen-free) compared to standard care. Additionally, this intervention will decrease the amount of fluid volume received by these patients, which may decrease the complications of over resuscitation. The intervention will be novel in the field of trauma, yet also is more broadly applicable in other settings with bleeding and coagulopathic patients, such as in cardiac surgery, postpartum hemorrhage, and liver transplantation.

**Approach**

**Design:** The FiiRST-2 is a multicenter, pragmatic, randomized, parallel-control, superiority trial, utilizing a conventional two-armed, with an adaptive two-stage design, performed at eight Level 1 trauma centers in Canada. The study is designed to examine the effect of replacing fibrinogen and clotting factors via FC and PCC within the first hour of hospital arrival on the number of ABP units in trauma patients with severe

hemorrhage, versus the current standard of care at each participating site (ratio-based plasma resuscitation at 1:1:1).

**Patient enrollment:** Upon admission to the trauma unit, patients will be enrolled once the MHP has been triggered within first hour of hospital arrival, according to the MHP activation criteria at each study site. Once eligibility is confirmed, the blood bank technologist will randomize the patient to one of two groups: the intervention group, which will receive FC and PCC, or the control group which will receive hemostatic therapies as per the current standard of care at all participating sites (ratio-based plasma resuscitation).

**Randomization:** A computerized random number generator will be used to generate sequences of random block sized with sealed enveloped generated by Ergomed (Guildford, Surrey, England). Sealed envelopes containing these numbers for treatment allocation will be maintained in the blood banks of the participating sites. In order to assure balanced groups, the randomization will be stratified by hospital sites.

**Blinding:** Blinding of treatment will be performed by blood bank technologists. FC and PCC will be placed in a tamper-sealed container, with the first set of RBCs and will be open in the trauma bay only immediately before transfusion. Similarly, the control group will receive the standard MHP pack 1 in a tamper proof cooler and will only be opened immediately before transfusion. Patients and outcome assessors will be blinded to the intervention by standard study blood labels for the patient chart (FIIRST-2 pack 1 and pack 2). The FC and PCC will be issued as lyophilized powder to increase speed of delivery to the bedside.

**Primary endpoint:** The primary endpoint is an efficacy endpoint is a composite number of units of all ABPs transfused within 24 hours post admission, as compared to the current standard care (RBC, FP, and PLT administered in a 1:1:1 ratio), and fibrinogen concentrate (FC) administered in response to low fibrinogen levels at the discretion of the clinical team. The primary comparisons will be conducted in the modified intention-to-treat (mITT) population.

**Number of Patients:** The study will aim to enroll 350 trauma patients with approximately 175 assigned to each of the two treatment groups. Due to the inherent variability in the primary endpoint and a yet substantial uncertainty about the effect size, an adaptive design approach will be used. Adaptive trials add a review–adapt loop to the linear design–conduct–analysis sequence. Scheduled interim look at data of the first 120 patients will permit the pre-specified changes (the sample size re-calculation) to the trial's course, after analyses of the data; however, maintaining the validity and integrity. For this, a planned unblinded analysis will be performed after about 120 patients have completed the study (by the independent data safety monitoring committee), to calculate the conditional power of test statistics and perform a sample size re-assessment.

**Funding:** The FIIRST-2 study will be funded by grants from Canadian Institute for Military and Veteran Health Research (CIMVHR) and the Defense Research & Development Canada (DRDC) in a total of 800,000.00 CAD$. Additionally, Octapharma Pharmazeutika Produktionsges.m.b.H., manufacturer of Fibryga™ and Octaplex™ will provide 400,000.00. Finally, PCC and FC costs will be covered by the Canadian Blood Services (CBS).

**Patient Selection Criteria**

**Inclusion Criteria**: Severely injured (penetrating or blunt) trauma patients who are at risk of significant hemorrhage, defined as: (1) Estimated age greater than 16 years old; (2) Severely injured (penetrating or blunt) trauma patients who are at risk of significant hemorrhage; (3) Triggered massive hemorrhage protocol (MHP) within first hour of hospital arrival

**Exclusion Criteria:** Patients who meet any of the following criteria are not eligible for the study: (1) Known pregnancy; (2) Have an elapsed time from injury of more than 3 hours; (3) Refuse blood transfusion due to religious or other reasons; (4) Have a penetrating traumatic brain injury with Glasgow Coma Scale (GCS) of 3; (5) Are suspected or known to be on anticoagulants; (6) Have received more than 2 U RBCs within the first hour post admission or pre-hospital arrival; (7) Have known congenital or acquired bleeding disorder

**Test Products, Dose, and Mode of Administration:**

**Intervention group:** Patients will receive 4 g of Fibryga, 2000 IU of Octaplex and 4 U RBCs in both the first and second MHP packs. Patients will also receive 4 U of PLT (1 adult pool of buffy-coat prepared platelets in Canada) in the second MHP pack.

**Control group:** Patients will receive 4 U RBCs, and 4 U FP, in the first pack and 4 U RBCs, 4 U FP and 4 units of PLT in the second MHP pack, and FC will be administered if the fibrinogen level drops below 1.5–2.0 g/L or FIBTEM A10 drops below 8-12 mm at the discretion of the clinical team.

If a third MHP pack is required, and thereafter, patients in both groups will receive MHP packs according to MHP guidelines at each participating site, or revert to a laboratory or viscoelastic-guided transfusion as per the local guidelines once bleeding is controlled. TEG and ROTEM will not be used to guide transfusion of FC and PCC in the first 2 packs. ROTEM will be used at the Vancouver General Hospital, as the method is part of their protocol. The MHP will be terminated once bleeding stops and the MHP criteria are no longer met.

**Duration of Treatment:** The duration of treatment is from randomization after activation of the MHP, until the second MHP pack has been administered (or before if the MHP is terminated before pack 2). The maximum time frame for administration of the second MHP pack is 24 hours from admission to the trauma bay.

**Study Procedures:** Upon admission to the trauma room, the blood bank technologist will confirm the following criteria: (1) The time of injury and arrival to the trauma bay; (2) The patient's age; (3) The inclusion and exclusion criteria are met. The blood bank technologist will then randomize patients according to the randomization schedule and prepare and release the products.

**Study Visits:**

**Visit 1: Upon admission to the trauma room: (1)** Collect baseline and injury data; (2) Record time to admission of last RBC unit transfused in first 24 hours; (3) Collect laboratory data; (4) Collect thromboelastometry measurements, where available; (5) Collect mortality rate by exsanguination and other causes; (6) Record adverse (AE) and severe adverse events (SAE).

**Visit 2: 24 hours following arrival at the trauma bay: (1)** Obtain deferred consent by SDM or patient if recovered; (2) Collect total number of ABPs (RBCs + FP + platelets) transfused within 24 hours post admission; (3) Collect time to admission of last RBC unit transfused; (4) Record crystalloid and colloid requirement; (5) Record hemostatic therapies (FC, PCC, rFVIIa); (6) Collect laboratory values assessments; (7) Collect viscoelastic tests measurements, where available; (8) Record AEs and SAEs; (9) Record 24-hour all-cause mortality

**Visit 3: Days 2–27 following arrival at the trauma bay: (1)** Obtain deferred consent by SDM or patient if recovered; (2) Collect total and individual number of ABPs transfused (Day 7); (3) Time to admission of last RBC unit transfused; (4) Leg Doppler ultrasound or other imaging for thromboembolic complications where performed for clinical indications; (5) Record AEs and SAEs.

**Visit 4: Day 28 (in person if in hospital or by phone); (1)** Record AEs and SAEs; (2) Record ventilatory-free days; (3) ICU-free days; (4) Record 28-day all-cause mortality.

**Statistical Analysis Plan:**

To demonstrate that the early administration of FC and PCC is clinically superior to the standard of care, with respect to the mean number of units of ABPs administered within 24 hours of admission to the trauma bay, a two-sample, one-sided test of the pair of hypotheses will be carried out with a type I error probability of $\alpha = 0.025$. We considered a mean difference in 5 U of the composite outcome (mean 15 U in the control group and mean 10 U in the intervention group) to be as a clinically meaningful difference that should be detected with at least 80% power. Testing of the hypothesis will be performed in the context of a counting regression model (generalized linear model for count data with log-link function and a negative binomial error term), with treatment group as main effect. Inferences will be based on the one-sided 97.5% confidence interval (CI) for the ratio of mean units of ABPs in the intervention to control group derived from the estimated least square means of this model. Superiority will be concluded if the upper limit of this CI is strictly less than = 1.0 (i.e. the mean number of ABPs is larger in the standard of care). Sample size estimations based on these assumptions were performed with the software nQuery (version 8.3). Empirical estimates of the mean number of ABPs units within the first 24 hours and its dispersion were based on results of the FIIRST-1 Study [1] with the same endpoint in the same indication and similar treatment. A net sample size of 297 patients would suffice to demonstrate the superiority under the stated assumptions. The FIIRST-1 study had a 10% patient drop-off (exclusions post randomization). Hence we will inflate our sample size to account for a drop-out percentage of up to 15%. For this reason the study plans to enroll up to 350 patients.

Summary data for continuous variables will be presented as means and standard deviations, or medians and interquartile ranges, depending on the distribution. Discrete variables will be summarized as frequency and percentages. All-cause 24-hour and 28-day mortality will be analyzed by the intention-to-treat and per-protocol populations. Differences in binary outcomes will be assessed using exact tests for proportions. Likelihood ratio test in the context of a generalized linear model (GLM) for count data will be used to analyze ratios of blood and blood products. For categorical clinical endpoints, relative risks (RR) and 95% confidence interval (CI) will be calculated. ARDS-free survival will be used to account for deaths and lost-to-follow-up and will be analyzed using log-rank tests.

To verify the assumptions on the primary endpoint and potentially adapt the sample size of the study an unblinded (IDSMB only) interim analysis will be performed after a total of 120 evaluable patients have completed the study. The primary analysis will be performed on the modified intention to treat population. A secondary analysis will be performed for the per protocol population. The safety analysis population (SAF) will include all randomized patients who receive any of the non-RBC products in the first MHP pack or beyond of the intended first-line treatment and agree to remain in the study after consenting.

**External Validity:**

The FIIRST-2 trial will be performed in eight academic centers in Canada, with different characteristics. Moreover, patients will be recruited and randomized after the clinical team activates the MHP, as determined by local hospital practice. The change to routine practice is the administration of coagulation factor concentrates FC and PCC instead of the current standard of care (balanced ratio) and FC administered in response to low fibrinogen levels. Thus, patient management in the control group will reflect current practice and in the intervention group will reflect how FC and PCC will be used in practice. For these reasons, the study will have good external validity.

**2. Establish portability of the study to multiple sites and institutions. Delineate how many sites would be necessary and likely and how many subjects, subjects/site would be expected.**

The eight participating sites are all Level 1 trauma centers and are affiliated with Canadian Universities and medical schools. These centers have consolidated Trauma Programs, accredited by the Trauma Association of Canada standards. Furthermore, all centers have been involved with previous clinical trials in the field of trauma, and have the research structure necessary to conduct the FIIRST-2 trial as participating site. Most of the sites participated in the FIBRES trial (not yet published) completed by our team (FC vs. cryoprecipitate for cardiac surgery-related hemorrhage). The 350 patients are expected to be enrolled over a period of maximum 2 years. The average number of MHPs/year activated in each study site for trauma is as follows: Sunnybrook Health Sciences Centre, Toronto – 100; Saint Michael's Hospital, Toronto – 100; Montreal General Hospital, Montreal – 80; Foothills Medical Centre, Calgary – 86; Vancouver General Hospital, Vancouver – 35; The Ottawa Hospital, Ottawa – 43; Hamilton General Hospital, Hamilton – 45; London Health Sciences Centre, London – 91. The total number of MHPs in across all sites is 548 per annum.

Prior to study commencement, educational sessions will target trauma team members from the departments of emergency medicine, surgery, and anesthesiology. Furthermore, educational sessions will target blood bank technologists (based on REB requirements to assess eligibility criteria) and nursing from the emergency departments, and interventional radiology suite. The educational sessions will review the hypothesis of the study, study intervention and expected outcomes, but will focus on patient eligibility criteria. As well, posters with eligibility criteria and contact information for participating research staff will be posted in the trauma rooms, operating rooms, CT scanner suites, intervention radiology suites, and emergency departments in all participating sites.

**3. Relate how communication would occur between participating and principal sites. Attempt to predict difficulties and problems that may arise in these multi-institutional interactions and suggest how these may be solved (IRB issues, consent, data safety monitoring, etc.).**

The first phase of the trial, prior to the analysis of the first 120 patients will be conducted in 3 participating sites (Sunnybrook Health Sciences Centre, Hamilton General Hospital and London Health Sciences Centre). These centres were chosen to be part of the initial phase due to an easier operationalization. They will offer enough number of patients for the interim analysis and are all located in Ontario, which will facilitate frequent site visits by the study PI.

We have a strong team of research coordinators at the central coordinating center and at each site. These research coordinators/assistants participated in two large randomized transfusion studies in cardiac surgery (FIBRES [15] and TACS [16]) and have proven ability to complete multicenter trials with high degrees on compliance with study procedures.

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 *Fibryga* and *Octaplex*. The IB will be updated at regular intervals by Octapharma and whenever relevant new information concerning the IMPs 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 Investigator and study sites. The Investigator will be kept informed of important data that relate to the safe use of the IMPs as the study proceeds.

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.

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

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.

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.

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