TITLE: Transfusion of Pathogen Reduced Cryoprecipitated Fibrinogen to Expedite Product Availability in Perioperative Bleeding

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Pilot Observational Study of Transfusion of Pathogen Reduced Cryoprecipitated Fibrinogen (INTERCEPT Fibrinogen Complex) in Patients with Bleeding to Expedite Product Availability in Perioperative Bleeding

SUMMARY

Immediately replacing fibrinogen in perioperative bleeding patients with acquired fibrinogen deficiency improves outcomes. The product that is primarily used for fibrinogen replacement in the US, cryoprecipitate, must be stored frozen and expires six hours after thawing, resulting in a delay in transfusion of approximately 50 minutes from the time it is ordered, as well as unnecessary transfusion of more readily available but not indicated blood components that are transfused while the patients waits for cryo . A modified version of the product, pathogen reduced (PR) cryo, is now FDA approved and can be thawed and stored for 5 days, allowing the product to be available immediately when needed. No clinical studies are available for this product. In this quality improvement study, we will compare the effect that readily available, pre-thawed PR cryo has on transfusion practice in cardiovascular and liver transplant patients who receive PR cryo versus those who receive traditional cryo by randomizing cryo transfusions in the blood bank by month to all cryo or all PR cryo. All clinical decisions, including the need for cryoprecipitate, and laboratory testing will occur per standard of care.

INTRODUCTION

Cryoprecipitated AHF product (cryo), a pooled product from 5-10 blood donors, is the primary source of fibrinogen replacement for bleeding patients in the United States. When stored frozen, it has a shelf life of one year; however, it must be thawed prior to use. Thawing, labeling and dispensing cryo can take 28-97 minutes and then it must be transfused within 6 hours due to a theoretical risk of bacterial contamination.

The competing need to have cryo rapidly available for urgent transfusions and the need to avoid wasting product has led to the development of pathogen reduced (PR) cryo, which recently received FDA approval. This product is also called Intercept Fibrinogen Complex (IFC) and can be kept thawed at room temperature for up to 5 days after thawing.

PR cryoprecipitate is derived from a traditional cryoprecipitate product that is treated with amotosalen. [redacted] The inactivation of pathogens allows thawed PR cryo to have a shelf-life of 5 days without the risk of microbial contamination. Furthermore, multiple studies have shown that fibrinogen is stable when thawed at room temperature for up to 35 days. The longer shelf-life should reduce product wastage which

would offset the increased cost of PR cryo over traditional cryo. In vitro studies have shown no differences in efficacy between traditional and PR cryo. No safety differences are expected between the two products, as evidenced by the FDA approving PR cryo without any clinical studies.

The same pathogen reduction process used for PR cryo/IFC that was developed by Cerus Corporation has been in use in the United States since 2014 for platelet and plasma products. Cryoprecipitate is a derivative of plasma, and the pathogen reduction process was already FDA approved. Therefore, the FDA approved this blood product and its pathogen inactivation process, without any clinical trials or observational studies. [redacted]
PR cryo/IFC, the product we are studying, is a biological blood component and the process used to treat PR cryo, known as INTERCEPT® Blood System for Cryoprecipitation (package insert included in IRB application) is the same process used for PR platelets and PR plasma. The pathogen reduction process occurs at the blood supplier and then the product is received by our hospital. T[redacted]

Since PR cryo can be kept at room temperature for 5 days, similar to thawed plasma, the blood bank can opt to have a PR cryo supply thawed and immediately available for use. This can prevent delays in treatment in bleeding patients.

BACKGROUND OF CRYO USE AT NYP/WC

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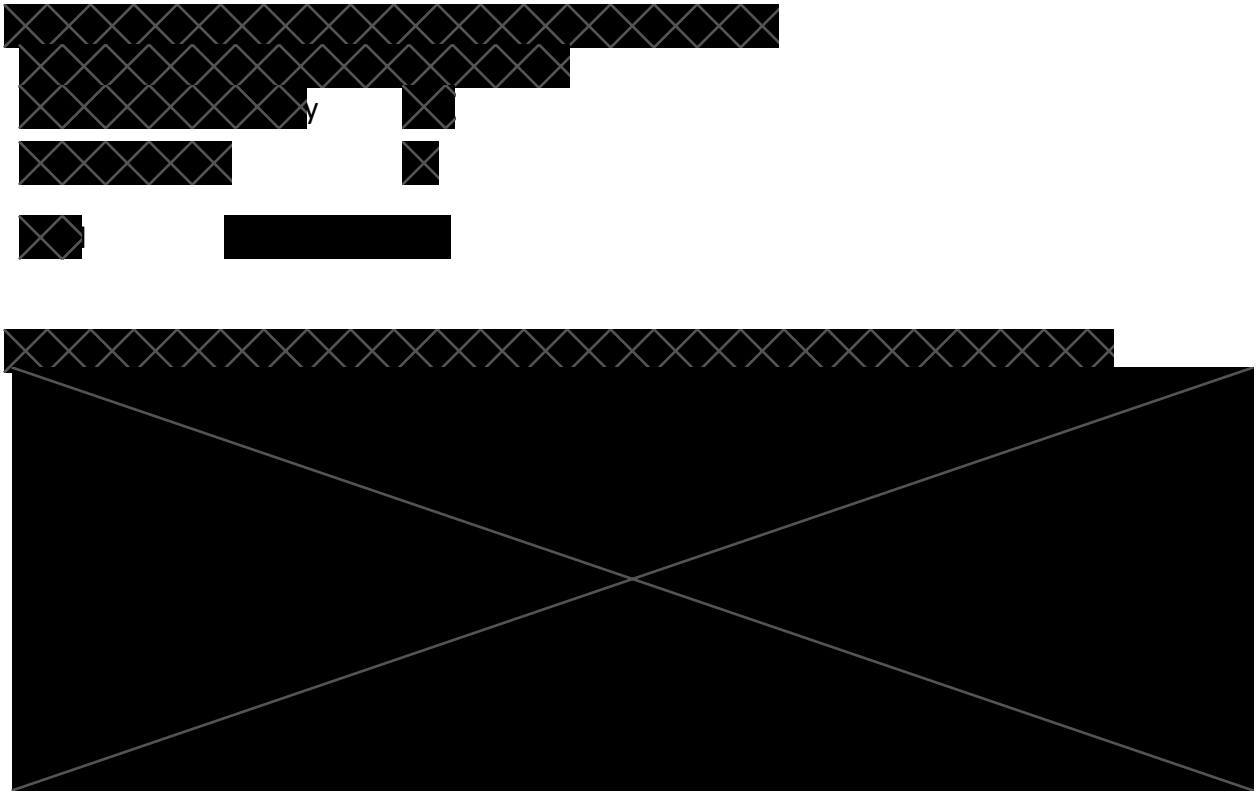

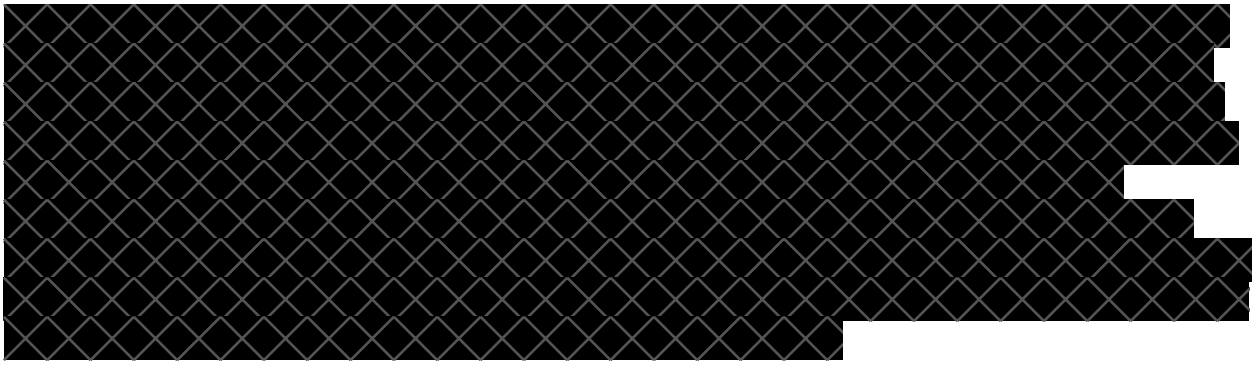

Given PR cryo's recent FDA approval, no real-world studies or clinical trials exist directly comparing conventional cryoprecipitate and pathogen reduced cryoprecipitate use in the perioperative setting. The relative frequency of cryoprecipitate usage in our large cardiac and

liver transplant programs at Weill Cornell provides an ideal setting to compare the two products.

STUDY DESIGN

Given that PR cryo can be more readily available for urgent perioperative need, the transfusion medicine service and anesthesiologists at NYP/WC would like to transition to this product. PR cryo is a more expensive product, so it is necessary to evaluate whether its availability will reduce the need for other blood products or reduce traditional cryo wastage, prior to fully converting to this product. A single center prospective, pilot cluster randomized study with an adaptive design will be used to compare the availability and cost effectiveness of cryo and PR cryo when it is ordered for standard clinical indications. In this design, the intervention and randomization are not made at the level of the individual patient, but rather on clusters of patients by month. The clusters will include all patients at NYP/WC for whom pooled cryo is ordered during a single month, not just liver transplant and cardiovascular surgery patients.

Since both products are considered clinically equivalent, the blood bank will alternate use of PR cryo and regular cryo each month for all patients with a cryo order over a one year period during the transition to the use of this new product. All patients will receive either traditional cryo or PR cryo in a given month; however, only a subset (CV and LT patients) will be studied.

Data from the EMR and lab systems will be collected from the NYP data warehouse during the one-year QA study and included in the data analysis. The following demographic variables will be collected: age, ethnicity, race, gender, underlying diseases, surgery type, medications given within 5 days of surgery.

The primary outcome will be the total number of blood components (RBCs, platelets, plasma) used over the admission within the first 30 days after surgery.

REDCap will be used for data collection/storage. Our data scientist, who is an Epic Clinical Data Navigator (CDN), will use SQL queries through the NYP Jupiter data warehouse for automated data extractions of clinical and laboratory data. A TRAC request will be submitted once the IRB is approved. Any variables not available through Jupiter will be extracted manually from the electronic medical record by the research coordinator and entered manually in REDCap. We will use the Safe Harbor method for de-identification of data. We will remove all 18 PHI elements referenced by HHS that could identify a patient.

The secondary outcomes, which are all routinely available in the EMR per standard of care, will include:

1. Number of cryo or fibrinogen concentrate products used perioperatively (defined as anesthesia start time to 3 days post-procedure)

2. Number of RBC, plasma, and platelet products used perioperatively (defined as anesthesia start time to 3 days post-procedure)
3. Time from OR start time to start of cryo transfusion
4. Time from cryo order to start of transfusion
5. Number of cryo units wasted by blood bank per month during study periods.
6. Laboratory measures, as available in the medical record, related to the indications for cryo: pre and post transfusion FIBTEM amplitude at 10 mins and maximum clot firmness & fibrinogen level within 10 minutes to one hour after the end of the first cryo transfusion.
7. Highest and lowest fibrinogen level or ROTEM FIBTEM within 24 hours after surgery.
8. Volume in drains (e.g. chest tube for CV surgery) at 24 hours or until removed, whichever is sooner.
9. Time from end of bypass pump until end of surgery (reflects time to hemostasis) for CV surgery
10. Length of stay (OR, ICU and hospital)
11. Need for ventilator
12. Time on ventilator
13. Overall cost of cryo vs PR cryo, when factoring wastage, during each 1-month period
14. Adverse events: fevers, infections, transfusion reactions within 5 days of surgery start time, need for surgical re-exploration, multiorgan system failure
15. Fibrinogen level most proximal to end of procedure

STUDY PATIENT POPULATION

Liver transplant and cardiovascular surgery populations were chosen because they are the 2 patient populations which receive cryo during massive blood loss most frequently in the operating room. Although they don't have the same mechanisms of injury and coagulation dysregulation, they both are prone to severe and early hypofibrinogenemia, hyperfibrinolysis, thrombocytopenia, platelet dysfunction and dilutional coagulopathy during surgery. The CV surgery and liver transplant anesthesiology groups at Weill Cornell faithfully use ROTEM for real time goal directed blood product therapy. Other patient populations may receive cryo, but cryo tends to be less predictably used in these populations, less evidence based (i.e., less based on immediately available point of care coagulation lab results) and more of a last resort option, rather than an early planned intervention. The other groups of patients who require cryo are smaller, more heterogeneous and have more covariates that will make data analysis more difficult to interpret. Thus, the focus is on two fairly homogeneous patient groups at high probability to require cryo transfusion.

Inclusion criteria: Adult patients undergoing cardiovascular surgery or liver transplant who receive cryo during surgery during the two year study period. Cardiovascular surgery includes the following procedures: coronary artery bypass grafting, valve repair or replacement, open thoracic aortic and thoracoabdominal aortic surgery, atrial or ventricular septal defects, ventricular assist device implantation or revision, or any combination of the above.

Exclusion criteria:

1) Patients who do not receive any cryo product in the OR.
2) Patients who are not cardiovascular surgery or liver transplant patients
3) Cardiac transplantation surgery
4) Patients who receive a product in error within either the cryo time period or the PR cryo time period. For example, PR cryo during a cryo month or cryo during a PR cryo time month.
5) Patients who receive less than 1 pool (5 units) of cryo
6) Pediatric patients (less than 18 years of age).
7) Patients who received both PR cryo and traditional cryo
8) Pregnant women

Investigators:
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Anesthesiology: Dr. Natalia Ivascu, Dr Meghann Fitzgerald, Dr. Shanna Hill, Dr. Christine Lennon
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Data scientist: Sophie Rand
Research coordinator: Pranesh Rajendran
Statistician: Caroline Andy

LABORATORY TESTING

Patients requiring transfusions intraoperatively or post-operatively are currently already assessed via ROTEM pre and post product transfusions to guide product selection for clinical purposes. A ROTEM transfusion algorithm is already in use for both cardiovascular surgery and liver transplant. All laboratory testing will be standard of care for labs and ROTEM. Patients will have a ROTEM performed on the ROTEM Delta instrument either in the blood bank or in the OR.

CONSENT

Consent will not be obtained at the level of the individual patient prior to transfusion because both products are FDA approved and considered standard of care. This is a quality improvement study to understand whether improved logistics (i.e. more ready and immediate access to cryo) can avoid the use of other unnecessary blood products and decrease costs associated with those products. In addition, there is no accurate method to predict the need for fibrinogen replacement in bleeding patients during surgery so consent could not be obtained prior to surgery. The decision to transfuse cryo during surgery occurs urgently during hemorrhage while patients are under anesthesia.

All CV and LT patients will be retrospectively provided with a patient information sheet about the study after the transfusion in the OR. [redacted] All decisions about when to transfuse will be made by clinical providers according to their clinical judgement and unrelated to the study.

[redacted]

STATISTICAL ANALYSIS

RATIONALE FOR A CLUSTER RANDOMIZED TRIAL

Individual patient efficacy clinical trials are useful to establish the clinical efficacy of an intervention amongst a carefully selected population under optimal conditions following detailed protocols. However, such trials do not address questions about how an intervention or logistical change affects clinical practice in the real world.

The surgical care of patients in our hospital is undertaken using standardized procedures that optimize outcomes, such as standard preoperative assessment and pre-and postoperative care pathways. Because our cardiac surgery and liver transplant services deliver care through standard institutional policies, it is appropriate to address whether either of the two FDA-approved blood products for fibrinogen replacement in acquired hypofibrinogenemia used during surgery to treat bleeding would reduce the total amount of blood products transfused. Testing the effects of the two products mandates a pragmatic trial done with randomization of product used by month rather than by patient. It is extremely difficult to predict which patients will receive fibrinogen replacement during surgery and thus impossible to predict which patients to consent ahead of time. At the time the decision is made to transfuse cryoprecipitate, a patient is already bleeding and under anesthesia, and thus there is no opportunity to consent in real time. Thus, this study will use a cluster randomization treatment assignment design with a calendar month time period as the cluster; specifically addressing whether the use of cryoprecipitate or PR cryoprecipitate reduces overall blood transfusions without any contamination of study groups by the inability to fulfill the appropriate cryo use if individual randomization had been used.

The main challenge of a cluster-randomized trial is the need for inflated sample size (relative to a non-clustered design) that results from clustering. Individuals within a cluster tend to have a smaller degree of variation compared to the variation between clusters, which is measured statistically by the intra-cluster correlation coefficient (ICC) (Arnup SJ et al). If the ICC is greater than 1, then this cluster effect will incorrectly reduce the standard error of the model estimates

if it is not properly accounted for in the analysis. This study will use randomization between intervention arms each month with a design known as the cluster randomized trial. This allows for the ability to assure that all research subjects in a given month will receive a particular cryo product and ensure the reduction in contamination of the two study arms (one of the primary reasons for designing studies in this fashion). In the planned trial, each month the Weill Cornell blood bank will be randomized to one of the two cryoprecipitates as part of a quality improvement study, the randomized product will be used as standard institutional policy for an entire calendar month. At the end of each month, the blood bank is re-randomized to a new standard policy that is used for the subsequent calendar month. This design is methodologically rigorous and tests the effect of a change in standard policy as it would actually be used in the clinical setting.

SAMPLE SIZE ANALYSIS

The primary endpoint of the study is total number of blood components other than cryo (RBCs, platelets, plasma) used over the hospital admission within the first 30 days after surgery. The goal of the trial is to demonstrate a 20% reduction in this total blood product use for PR cryo compared to the total observed with conventional cryo. In order to determine this effect size and the patient variability associated with this outcome, data were collected from 150 cardiovascular surgery and liver transplant cases at the study center during 6 months in 2021. Because the number of units used was clearly right-skewed and, therefore, possibly log-normally distributed, the sample size determination was based on the hypothesized ratio of means (effect size) of 0.8. In addition, the coefficient of variation is the key determinant of variability with log-normal data, and this was seen with the recent data to be a value of 1.1. The other issue to consider in this calculation is the cluster randomization. However, the cluster in this study is the month when the surgery is performed. The assumption is made that the intra-cluster correlation of the primary outcome within a given month should be very small, say 0.0001. As a result, this would have very little effect on the sample size (the Kish design effect is about 1.01 assuming approximately 100 subjects per month). Then with 80% power and 5% significance (two-sided), the number of subjects per group would be 251.

However, there is a possibility that the effect size has been overestimated. Thus, a sample size re-estimation will be conducted after 60% of the subjects have been included in the trial. The method of Gould (Gould AL. Interim analyses for monitoring clinical trials that do not materially affect the type I error rate. Stat Med 1992; 11:55-66.) will be used to re-evaluate the sample size.

EQUIVALENCY BETWEEN COHORTS

In order to control for possible patient population variations between the patients transfused with cryo and PR cryo, clinical scoring systems will be utilized to ensure the two groups are similar: MELD score for liver transplant patients and EUROSCORE for cardiovascular surgery patients.

EVALUATION OF PRODUCT SUPERIORITY

The primary outcome of total number of blood components (RBCs, platelets, plasma) used over the admission within the first 30 days after surgery will be evaluated using a two-sample t-test on the log-transformed values or the Wilcoxon rank-sum test if the log-transform does not result in an acceptable comparability to a normal distribution. This will be based on an intent-to-treat paradigm (all subjects randomized will be evaluated and in the group they were randomized to). However, it is assumed that all of the subjects will be appropriately evaluated for this endpoint.

There are a number of secondary endpoints, and the specific statistical method is indicated below:

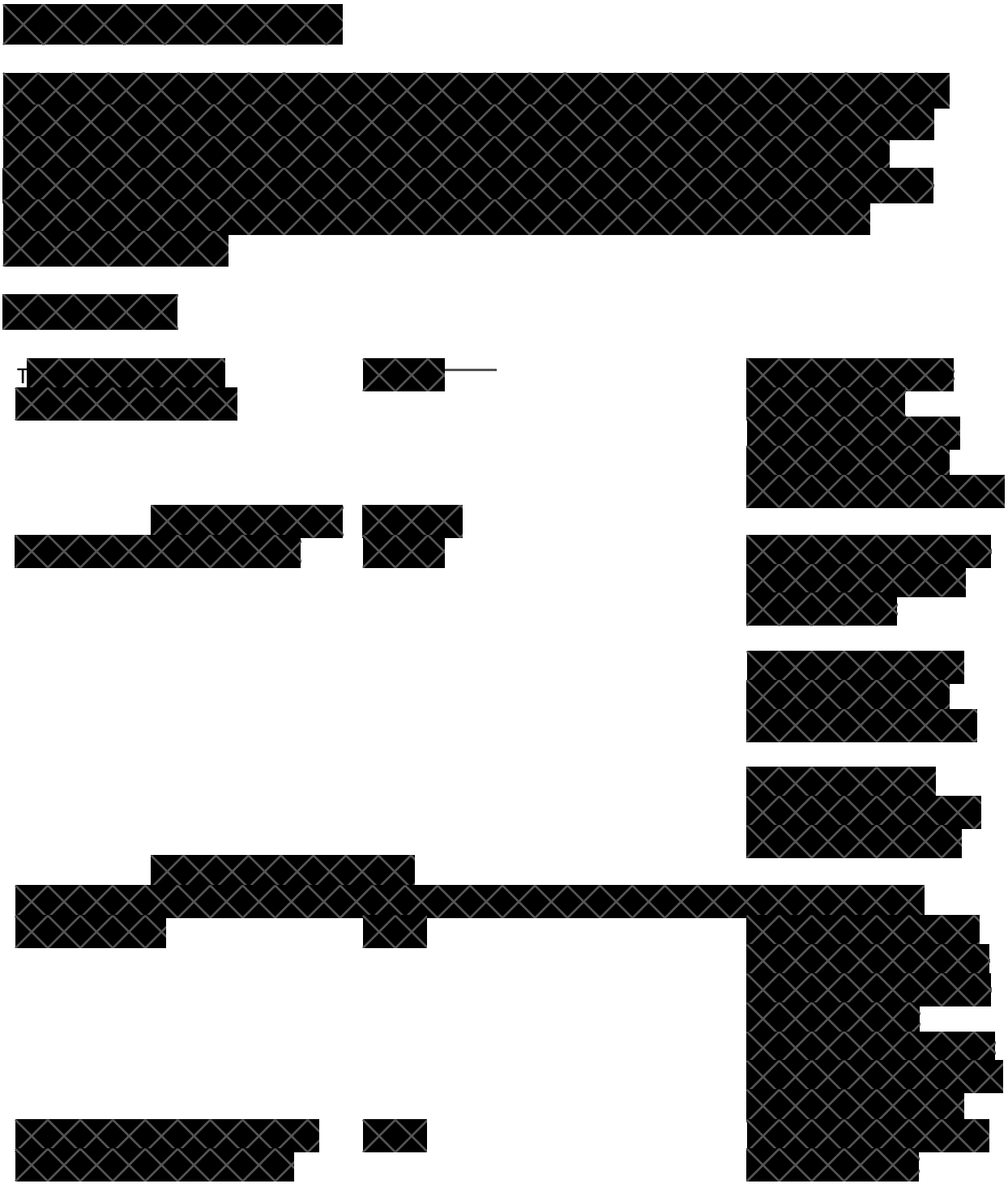
1. Number of cryo or fibrinogen concentrate products used perioperatively (defined as anesthesia start to 24 hours post-procedure): Wilcoxon rank-sum test
2. Number of RBC, plasma, and platelet products used perioperatively (defined as anesthesia start to 24 hours post-procedure): Wilcoxon rank-sum test
3. Time from cryo order to ready in the blood bank: Wilcoxon rank-sum test
4. Time from cryo order to start of infusion: Wilcoxon rank-sum test
5. Number of cryo units wasted by blood bank per day during study periods: Wilcoxon rank-sum test
6. Laboratory measures for cryo and PR cryo (pre and post transfusion FIBTEM amplitude at 10 mins and maximum clot firmness, fibrinogen): Wilcoxon rank-sum test
7. Volume in mediastinal drains (e.g. chest tube for CV surgery) at 24 hours (or until removed): Wilcoxon rank-sum test
8. Length of stay (OR, ICU and hospital) & time on ventilator: log-rank test, particularly if there is any censoring
9. Overall cost of cryo vs PR cryo, when factoring wastage, during each 1-month period: Wilcoxon rank-sum test
10. Fibrinogen level most proximal to end of procedure, with adjustment for fibrinogen dose administered (if known): without adjustment the Wilcoxon rank-sum test can be used; with adjustment a properly selected linear model (depending on the link function required)

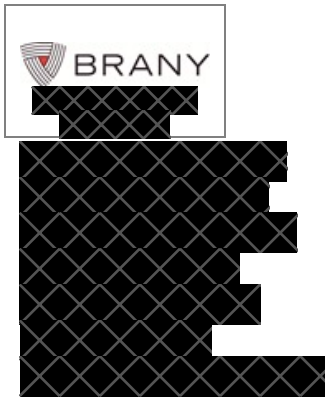
In order to control statistical significance for this number of endpoints, the Holm procedure will be used.

Many of the endpoints noted above can be evaluated after adjustment with selected covariates using a properly selected linear model (depending on the link function required).

INTERIM ANALYSIS

A separate interim analysis for futility will be conducted on the primary endpoint when 60% of the subjects have completed the trial. Sixty percent of 502 (251 per group) is 302. We expect to accrue 302 patients in approximately 1 year. During the interim analysis we will decide if the study will continue or stop. This will involve the calculation of conditional power and a potential stopping rule of a value for this calculation of <10%.





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