TITLE: Assessing the Hemostatic Efficacy of Pathogen Reduced Platelets in Children Undergoing Cardiopulmonary Bypass Surgery: A Pilot Clinical Trial

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Principal Investigator:
Marianne Nellis, MD, MS
525 East 68th St, M512, New York, NY 10065
(212) 746-3056
Man9026@med.cornell.edu

Co-Investigators:
Sophia Hsien, MD
Fellow in Pediatric Cardiology
Soh9031@med.nyp.org

Liliko Chung
Clinical Data Coordinator, PICU
lhc4027@med.cornell.edu

Margaret Cormack
Regulatory Coordinator
Mac4035@med.cornell.edu

Robert Desimone, MD
Chief Transfusion Medicine Services
Rod9096@med.cornell.edu

Pranesh Rajendran
Transfusion Medicine Research Coordinator
Prr4005@med.cornell.edu

Statisticians:
Charlene Thomas, MS, cht2028@med.cornell.edu
Linda Gerber, PhD, lig2002@med.cornell.edu

Medical Monitor:
Weill Cornell Medicine DSMB

Participating Sites: Komansky Children's Hospital at Weill Cornell (PI – Marianne Nellis, man9026@med.cornell.edu), Morgan Stanley Children's Hospital (PI – Brett Anderson, bra2113@cumc.columbia.edu)

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Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from all investigators and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

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Institution Name

_____	_____	_____
Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

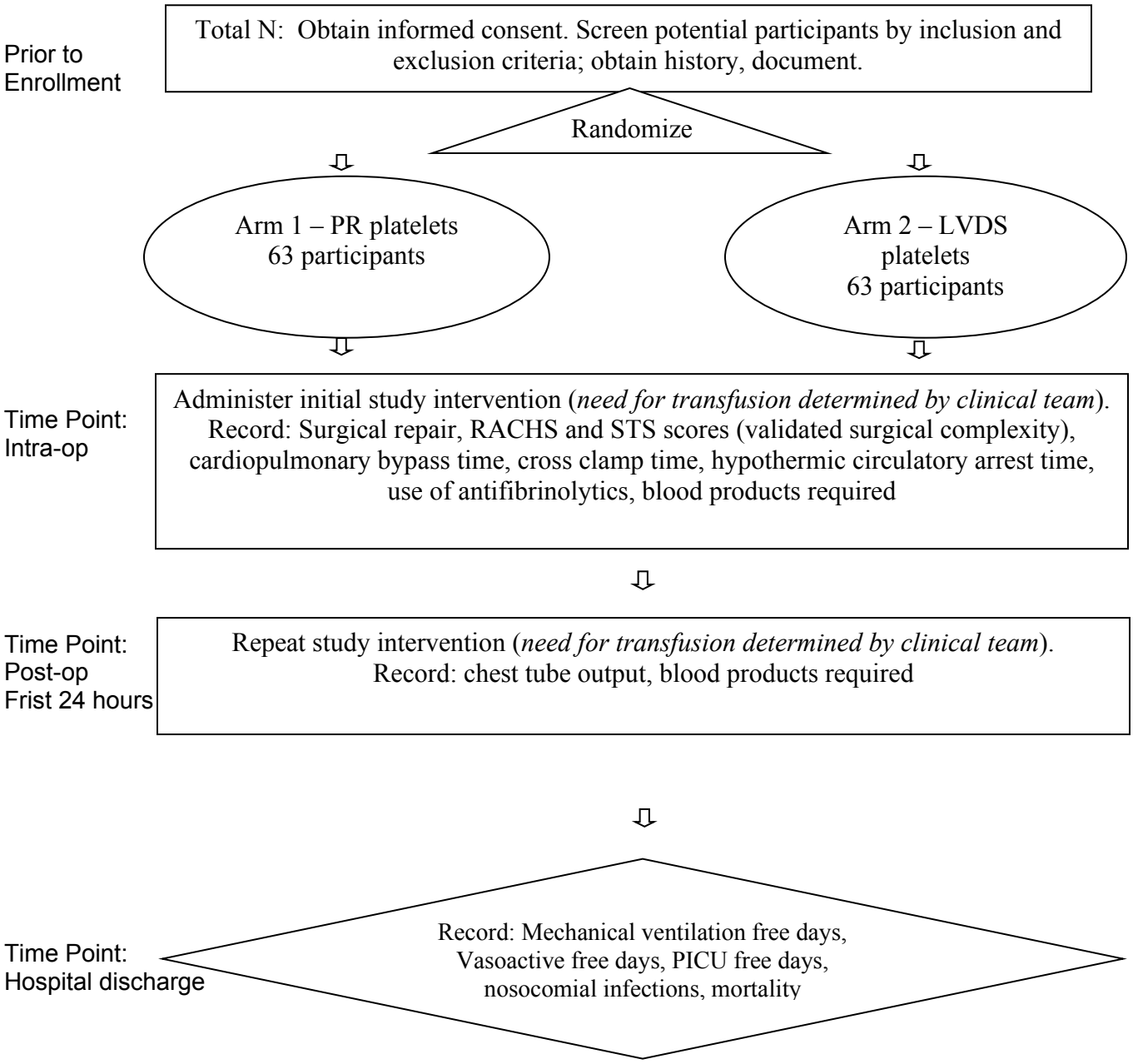
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	Assessing the Hemostatic Efficacy of Pathogen Reduced Platelets in Children Undergoing Cardiopulmonary Bypass Surgery: A Pilot Clinical Trial
Short Title:	Hemostatic Efficacy of Pathogen Reduced Platelets
Clinical Phase:	IV
Principal Investigator:	Marianne Nellis, MD, MS
Study Description:	This is a pilot clinical trial to assess the post-operative bleeding in children who receive pathogen-reduced (PR) platelet transfusions versus standard (large volume delayed sampling – LVDS) platelet transfusions both during and for 24 hours following. cardiopulmonary bypass surgery.
Sample Size:	126 (63 per group)
Enrollment:	This study will enroll approximately 252 subjects and screen up to 500 subjects. Though the sample size is 126, since the decision to transfuse platelets is at the discretion of the clinical team, and our preliminary data shows approximately 50% of children are transfused, we will need to enroll double the sample size, or 252 children (see full protocol for further explanation).
Study Population:	Children (ages 0-18 years of age) undergoing cardiopulmonary bypass surgery
Enrollment Period:	Length of hospitalization
Study Design:	This is an open label, randomized clinical trial of children undergoing cardiopulmonary bypass surgery at either Komansky Children's Hospital/Weill Cornell or Morgan Stanley Children's Hospital/Columbia. For children who require platelet transfusions either intra or post-operatively for the first 24 hours (decision to transfuse left at discretion of clinical team), they will receive either all PR or all LVDS platelet transfusions. Bleeding from the surgically placed chest tube will be recorded per hour for the first 24 hours post-operatively. In addition, the total volume of transfusion of any blood products will be recorded.
Description of Sites/ Facilities Enrolling Participants:	Komansky Children's Hospital/Weill Cornell and Morgan Stanley Children's Hospital/Columbia.
Study Duration:	6/30/2024
Participant Duration:	Length of hospitalization (no follow-up visits necessary)
Study Agent/Device Name Intervention Description:	Both PR and LVDS platelets are considered standard of care (currently whatever product is available is dispensed by transfusion medicine services). Platelets will be transfused in doses of 10mL/kg.

Primary Objective:	To determine the amount of post-operative bleeding in children receiving PR versus LVDS platelet transfusions during and following cardiopulmonary bypass surgery
Secondary Objectives:	To determine the blood product requirements and nosocomial infections in children receiving PR versus LVDS platelet transfusions during and following cardiopulmonary bypass surgery
Primary Endpoints:	Chest tube output for first 24 hours following cardiopulmonary bypass surgery
Secondary Endpoints:	Total dose red blood cell transfusions in first 48 hours, Total blood products transfused (intra and post-operatively) in first 48 hours, nosocomial infections

1.1 Schema


Prior to Enrollment
Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Arm 1 – PR platelets 63 participants
Arm 2 – LVDS platelets 63 participants
Time Point: Intra-op
Administer initial study intervention (*need for transfusion determined by clinical team*). Record: Surgical repair, RACHS and STS scores (validated surgical complexity), cardiopulmonary bypass time, cross clamp time, hypothermic circulatory arrest time, use of antifibrinolytics, blood products required
Time Point: Post-op Frist 24 hours
Repeat study intervention (*need for transfusion determined by clinical team*). Record: chest tube output, blood products required
Time Point: Hospital discharge
Record: Mechanical ventilation free days, Vasoactive free days, PICU free days, nosocomial infections, mortality

1.2 Study Objectives and End Points

1.2.1 Primary Objectives

To determine the amount of post-operative bleeding in children receiving PR versus LVDS platelet transfusions during and following cardiopulmonary bypass surgery.

1.2.2 Secondary Objectives

To determine the blood product requirements and nosocomial infections in children receiving PR versus LVDS platelet transfusions during and following cardiopulmonary bypass surgery.

1.2.3 Exploratory Objectives

Not applicable

1.2.4 Primary Endpoints

Chest tube output for first 24 hours following cardiopulmonary bypass surgery

1.2.5 Secondary Endpoints

Total dose red blood cell transfusions in first 48 hours, total blood products transfused (intra and post-operatively) in first 48 hours, nosocomial infections

2. Background

2.1 Disease

Pediatric patients undergoing cardiopulmonary bypass (CPB) are at high risk of ongoing bleeding due to hemodilution, platelet dysfunction, hypothermia and anti-coagulation [1]. Therefore, they often require post-operative hemostatic blood component transfusions, most commonly platelet transfusions, in order to prevent to stop bleeding [2, 3]. These children represent a unique patient population in that they each have mediastinal and/or pleural drains placed intra-operatively and therefore, their post-operative bleeding is quantifiable.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

Platelet transfusions are frequently prescribed to children to prevent or treat bleeding, but have been associated with increased transfusion reactions, as compared to their adult counterparts [4], as well as increased mortality [5]. Though red blood cells (RBCs) and plasma must be stored at lower temperatures, platelets are traditionally stored at room temperature with gentle agitation. Such conditions incur the additional risk of microbial contamination [6, 7]. To combat this, pathogen-reduced (PR) platelets, treated with either riboflavin or amotosalen and then exposed to ultraviolet illumination, have been developed [8, 9]. Studies have demonstrated that PR technology inactivates infectious agents [10] and lymphocytes [11]. In adult patients, PR platelets have been linked to increased platelet refractoriness and decreased platelet correct count increments, but no clinically significant

bleeding or increased risk of serious adverse events [12, 13].

Similar studies in the pediatric population have been limited. In an observational study of cohort of 240 neonates and children, patients who received PR platelets had an overall increase in total transfusion need as compared to those receiving non-PR platelets [14]. In a smaller cohort of children with oncologic diagnoses, those who received PR platelets had lower incremental increases in their platelet count following transfusion, but no significant increase in bleeding events [15]. The hemostatic efficacy of PR platelets has not been sufficiently examined in pediatric patients, particularly in those with ongoing bleeding.

Given the increased safety of PR platelets in regard to transfusion transmitted infections, the FDA encouraged all transfusion medicine services to provide either PR platelets or LVDS platelets to all patients in guidance issued in 2017. The transfusion medicine services at New York Presbyterian Hospital (on both the Weill Cornell and Columbia campuses) began introduction of PR platelets into the inventory in 2017 and maintain an inventory of both PR platelets and LVDS platelets currently. There is no difference in the risk of infection between PR and LVDS platelet products.

2.3 Rationale

Given the lack of evidence of hemostatic efficacy of PR platelets in children, we are seeking to characterize the hemostatic efficacy of PR platelets by comparing post-operative bleeding in children undergoing CPB who receive PR versus LVDS platelet transfusions.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

The need for the transfusion of any blood component, including platelet transfusions, will be at the discretion of the clinical team. Therefore, this study will not put an individual subject at increased risk of receiving a transfusion. In addition, if the platelet product to which the patient is assigned is not available, the patient will receive the available product without delay. Therefore participation in the study does not place the subject at risk of delayed transfusion.

The transfusion of any blood component carries the risk of transfusion transmitted infections, allergic reactions, transfusion associated acute lung injury, transfusion associated circulatory overload and transfusion related immunomodulation. However, these risks are known for both PR and LVDS products so that participation in the study, in which the subject will be randomized to either all PR or all LVDS platelet transfusions during cardiopulmonary bypass surgery and following for 24 hours, poses no increased risk as compared to not participating in the study.

PR platelets have been associated with a lower incremental rise in platelet count following a transfusion as compared to LVDS platelets in children with cancer. Therefore, subjects in this study are at risk of having a lower incremental rise in their platelet count if they receive PR platelets as compared to LVDS platelets. However, since platelets are transfused in the cardiac population not because of thrombocytopenia

but rather platelet dysfunction, this difference in platelet count should not affect the subjects' risk of bleeding.

It is unknown if either product (PR or LVDS platelet transfusions) is less efficacious in hemostasis, i.e. if one product leads to less bleeding.

De-identified clinical information (demographics, surgical characteristics, details regarding the platelet transfusion and clinical outcomes) will be collected on each subject. Though de-identified, there remains a risk of loss of confidentiality.

2.4.2 Known Potential Benefits

Both the FDA and the transfusion medicine services at Weill Cornell and Columbia Universities have determined that both PR platelets and LVDS platelets are equal in potential benefit of decreased transfusion transmitted infections.

Though it is unknown if one product is associated with improved hemostasis, if one product is, the subjects have the potential benefit of decreased bleeding.

2.4.3 Assessment of Potential Risks and Benefits

Given the minimal risks associated with this study (since the transfusions would be given regardless of participation in the study, the study is only ensuring a patient receives all PR or all LVDS platelets), the benefits of possible improved hemostasis, as well as the benefit to society, facilitating a greater understanding of the hemostatic efficacy, outweigh the risks.

2.5 Correlative Studies Background

Not applicable

3. Study Design

3.1 Overall Design

This is a multisite, open-label, randomized trial of PR versus LVDS platelet transfusions in children undergoing cardiopulmonary bypass surgery. The study will be conducted at at Komansky Children's Hospital at Weill Cornell and Morgan Stanley Children's Hospital at Columbia. Given that both products are FDA approved and already used in this patient population, it is a Phase IV study. Based on our preliminary retrospective data, we hypothesize that both products will have equivalent hemostasis, as measured by chest tube output in the first 24 hours, as well as total blood component requirements. Given the complexity of surgery is associated with bleeding risk, the two groups will be stratified on a validated score of surgical complexity (STS scoring). All subjects will be enrolled in the study for the length of their hospitalization.

The need for platelet transfusion will not be dictated by the study intervention, but rather the clinical team (both in the operating room and post-operatively, in the pediatric intensive care unit). Given that we do not want to delay the release of blood products from the blood bank, but rather have them available as standard of care in the operating

room, we cannot randomize the subjects at the time of the decision to transfuse platelets. Therefore, we will randomize subjects before the day of surgery. We recognize that there will be a significant number of randomized subjects (approximately 50%) who do not receive a platelet transfusion. Data will be collected on this group and analyzed both separately, and in an intention to treat model.

All platelet transfusions will be given as 10mL/kg as is considered standard of care.

Given the need to cross-check any transfusion of the blood component for patient safety, no area of the labeling will be disturbed and therefore the clinicians caring for the patients will be unblinded. Those responsible for data entry and data analysis will be blinded to the assigned groups of the subjects.

To minimize bias, we will perform subgroup analyses of neonates versus all other children given that the neonatal coagulation system is still under development and different than the coagulation system of the older child.

3.2 Scientific Rationale for Study Design

Limited data exists regarding the hemostatic efficacy of PR platelets in children. Our preliminary data, a retrospective study of 140 children undergoing cardiopulmonary bypass surgery, suggests that PR platelets are equally efficacious in terms of post-operative bleeding, as compared to non-PR platelets. However, retrospective studies are limited, and prospective randomized studies are needed to truly assess the primary outcome (the hemostatic efficacy).

3.3 Justification for Dose

Not applicable (the transfusions will be dosed equally as 10mL/kg as per standard of care)

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has been discharged from the hospital.

4. Subject Selection

4.1 Study Population

Children undergoing cardiopulmonary bypass surgery who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Male or female 0-18 years of age
2. Undergoing elective cardiopulmonary bypass surgery
3. Are planned to have a chest tube placed in the operating room prior to chest closure

4.3 Exclusion Criteria

1. > 18 years of age
2. Preterm infants (less than 38-week gestational age at time of surgery)
3. On extracorporeal membrane oxygenation (ECMO) or ventricular assist device prior to surgery
4. Family requests limitation of blood products (i.e. Jehovah's Witness)
5. Congenital bleeding disorder
6. Are planned to require ECMO post-op
7. Previously enrolled in the study

4.4 Lifestyle Considerations

Not applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. Demographics, screen failure details, and eligibility criteria will be collected on these individuals.

Though children undergoing elective cardiopulmonary bypass surgery do so only once during the course of 18 months (which will be the length of subject recruitment for this study), if a participant does meet inclusion criteria twice (undergoes a second elective cardiopulmonary bypass surgery in the course of 18 months), he/she can be rescreened and re-enrolled.

4.6 Strategies for Recruitment and Retention

All children scheduled to undergo elective cardiopulmonary bypass surgery are seen in the outpatient cardiothoracic (CT) surgery clinic setting approximately 3-5 days prior to surgery. Subjects and their families will be approached for assent/consent at this outpatient visit. Clinical staff at these outpatient sites (at Komansky Children's Hospital at Weill Cornell and Morgan Stanley Children's Hospital at Columbia) will be educated on the inclusion/exclusion criteria and consenting process. They will introduce the study to the families and if willing, the families will be approached by a clinical research coordinator for consent. The number of subjects eligible as well as those enrolled will be logged and reviewed on a monthly basis.

For neonates admitted for their birth and awaiting cardiac surgery, they will be approached in the neonatal intensive care unit by the CT surgery team. The families will be introduced to the study by the CT surgery team and if willing, will be approached by a clinical research coordinator for consent.

Subjects will be enrolled regardless of gender, race, and ethnicity. To demonstrate a difference of 1 mL/kg/hr of post-operative bleeding between the two study groups with 80% power, we will need 126 subjects enrolled and transfused platelets (63 subjects/group). Given the need for randomization prior to the decision to transfuse (as described above in Section 3.1), and the estimate that 50% of patients will not require any platelet transfusions,

we will need to consent and randomize approximately 252 subjects. Given that the two centers perform approximately 500 surgeries per year and the enrollment period will be approximately 18 months, we will require a consent rate of 34%.

We seek to enroll only children, who are considered a vulnerable participant, in order to understand the hemostatic efficacy of PR platelet transfusions in this population. The coagulation systems of infants and children are unique to adults and therefore children must be studied separately. Participants and/or their families will no be compensated for participation in the study.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Subjects will be registered as per the standard operating procedure for Subject Registration at Columbia. All data will be collected in a de-identified manner within REDCap hosted by Weill Cornell."

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Pre-Operative Visit	Operative Course	Post-Op Day 0	Post-Op Day 1	Post-Op Day 2	Off Study
Platelet Transfusion	*Given at discretion of clinical team (group assignment to be maintained only through first 24 hours post-operatively)*					
Informed Consent	X					
Demographics	X					
Medical History	X					
Physical Exam*	X		X	X	X	
Vital Signs*	X	X	X	X	X	
Weight*			X	X	X	
CBC*		X	X	X	X	

PT/PTT, fibrinogen*		X	X			
Outcome Evaluation		X	X	X	X	X
Medical Record Review and Data Collection		X	X	X	X	X
Adverse Event Assessment		X	X	X	X	

*all collected regularly as standard of care

6.1.1 Screening Visit

All children who are going elective cardiopulmonary bypass surgery are seen approximately 3-5 days in the CT surgery outpatient clinic as standard of care. This visit will also serve as the screening visit for these children. All neonates who are going elective cardiopulmonary bypass surgery during their birth admission are seen 2-3 days prior to surgery by the CT surgery team in the NICU. This consultation will also serve as the screening visit for these children. At this visit/consultation, the following events will occur:

- *Informed consent*
- *Demographics*
- *Medical history*
- *Physical exam*
- *Vital signs*

Once consented, randomization will occur at this phase, to allow for ordering from the New York Blood Center and so as not to delay the release of the platelet transfusion from the blood bank during the treatment phase. Eligible subjects will be randomly assigned to either PR or LVSD platelets (should they need a platelet transfusion) in a 1:1 ratio using a computer-generated randomization scheme stratified by surgical complexity (STS score) as developed by the statistical team.

6.1.2 Treatment Phase

Subjects will receive platelet transfusion(s) in the group to which they were randomized (PR vs LVDS) at the discretion of the clinical team for the time they are in the operating room through the first 24 hours post-operatively.

6.1.2.1 Operative Course

Data regarding the operative course, including vital signs, receipt of any hemostatic medications or blood products will be collected from the operative course. In addition, information regarding standard of care laboratory testing will be obtained. Of note, if testing is not performed as per standard of care, we will not obtain the laboratory assays only for the purpose of the study. Lastly, chest tube output in the OR and any adverse events in the OR will be collected. In summary, the following events will be recorded:

- *Vital Signs*
- *CBC, PT/PTT, fibrinogen (as obtained per standard of care)*

- *Outcome Evaluation*
- *Medical Record Review and Data Collection*
- *Adverse Events Assessment*

6.1.2.2 Post-Op Days 0-2

Because the primary outcome is the chest tube output in the first 24 hours, the intervention (PR versus LVDS platelet transfusions) will only be maintained for the first 24 hours post—op. In other words, if a subject requires a platelet transfusion after the first 24 hours post-op, they can receive whichever product is next available in the blood bank. During post-op days 0-2, the following events will be recorded:

- *Vital Signs*
- *Physical Exam*
- *CBC, PT/PTT, fibrinogen (as obtained per standard of care)*
- *Outcome Evaluation*
- *Medical Record Review and Data Collection*
- *Adverse Events Assessment*

6.1.3 Follow-up Phase

Subjects will be followed through the time of discharge to determine the following clinical outcomes: Mechanical ventilation free days, vasoactive free days, PICU free days, nosocomial infections, and in-hospital mortality. All “free days” will be calculated from the days a patient is alive in the PICU with 28-day max (i.e. a patient who is in the PICU for 10 days and ventilated for 4 days will have 3 mechanical ventilation free days, a patient who is in the PICU 30 days and ventilated 2 days will have 26 mechanical ventilation free days, and a patient who dies in the PICU on day 2 being mechanically ventilated the entire time will have 0 mechanical ventilation free days). All patients will be considered off study at time of hospital discharge. The following events will be recorded during the follow-up phase:

- *Outcome Evaluation*
- *Medical Record Review and Data Collection*

7. Study Intervention

7.1 Study Intervention/Device Description

Enrolled subjects will receive either PR or LVDS platelets based on the group to which they have been randomized. Both products are generally available in the blood bank, considered equally safe and efficacious, and used as standard of care.

7.2 Availability

As both products are already supplied to the blood banks at both Weill Cornell and Columbia, no special ordering will be required. Given shortages in the blood supply that are increasingly more common, the study coordinators in transfusion medicine at each site will work with the clinical research coordinators to ensure the product availability for the upcoming scheduled surgeries.

7.3 Acquisition and Accountability

Not applicable

7.4 Formulation, Appearance, Packaging, and Labeling

As the study is unblinded, the PR and LVDS platelets will maintained their normal appearance, packaging and labeling as required and approved by the FDA.

7.5 Product Storage and Stability

The blood products will be stored as per normal protocol in the blood banks at each site.

7.6 Preparation

The blood products will be prepared as per standard protocols maintained in the blood banks at each site.

7.7 Dosing and Administration

Platelets will be prescribed and administered at the discretion of the clinical teams. Each platelet transfusion will be dosed as 10mL/kg as per standard of care.

7.7.1 Dosing Delays/Dose Modifications

Not applicable

7.8 General Concomitant Medication and Supportive Care Guidelines

All hemostatic medications and blood products (such as anti-fibrinolytics, plasma transfusions and cryoprecipitate) will be prescribed at the discretion of the clinical team. All concomitant medications will be recorded in the REDCap data collection tool.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment may continue for the first 24 hour post-operatively or until one of the following criteria applies:

- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

A subject's follow-up in the study will end after one of the following applies:

- Subject's voluntary withdrawal
- Subject death
- Completion of all scheduled study follow-up appointments

7.10 Duration of Follow Up

Subjects will be followed until discharge from the hospital after removal from study or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

Stratified and permuted blocked randomization will be performed. A series of randomized blocks with a defined block size will be generated for each participating site with a 1:1 allocation ratio. This will allow for an equal number of patients in the PR platelets group and LVDS platelets group at each participating site (even in the event that full target accrual is not achieved). Randomization will be stratified by site (Komansky Children's Hospital/Weill Cornell vs. Morgan Stanley Children's Hospital/Columbia) and STAT score (STAT 1/2 vs. STAT 3/4/5). A biostatistician from the Weill Cornell CTSC Biostatistics, Epidemiology and Research Design (BERD) Core will create the randomization list and will not be involved with the study. The randomization list for each site will also reside in the Research Pharmacy at each site. Only the BERD statistician and the Research Pharmacies will have a copy of the blocked randomization list (for their respective sites). As this is an open-label study, all study personnel will be aware of the treatment assignments. The blocked randomization schemes for each participating site will be uploaded to a central REDCap database (housed at Weill Cornell Medicine) and each site's Research Pharmacy will be able to randomize a patient at their site by using the REDCap randomization module.

7.12 Study Intervention/Follow-up Compliance

No applicable

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. Patients will be discontinued if they require extracorporeal membrane oxygenation (ECMO) post-operatively (as the volume of platelet transfusions that a child requires on ECMO will likely not feasibly be supported by only one type of platelets). A dedicated Case Report Form (CRF) page will capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

8.1 Discontinuation of Study Intervention

Those children who unexpectedly require support from ECMO following surgery will be discontinued from the study intervention (as their need for platelet transfusions and risk of bleeding will be different due to the extracorporeal circulation of their blood). The decision to remain on ECMO is made in the operating room and the study team will be informed by the clinical team. Also, if a patient requires re-cannulation onto ECMO within the first 24 hours post-op (while in the PICU), they will be discontinued in the study intervention. There are no reasons for temporary discontinuation.

Discontinuation from platelet transfusion strategy does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following: Outcome Evaluation, Medical Record Review and Data Collection, Adverse Events Assessment.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

8.3 Lost to Follow Up

Not applicable (as the entire study occurs while the subject is admitted to the hospital)

9. Correlative/Special Studies

Not applicable

9.1 Laboratory Correlative Studies

Not applicable

9.2 Special Studies

Not applicable

10. Measurement of Effect

10.1 Response Criteria

The effect of the platelet transfusions received intra-operatively and in the first 24 hours post-op will be measured by (1) chest tube output in the first 24 hours post-op and (2) total transfusions required in the first t48 hours post-op

10.2 Duration of Response

Though transfused platelets typically stay in circulation for 5-7 days, we will be measuring the hemostatic efficacy for the first 24 hours post-operatively.

10.3 Progression-Free Survival

Not applicable

10.4 Other Response Parameters

Though not directly related, clinical outcomes, such as mortality, length of hospital stay, length of PICU stay, length of mechanical ventilation and length of vasoactive therapy will be collected.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF,

or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

Participants will be consented remotely using an electronic version of the informed consent form that follows federal, state, and local regulations, as applicable. We will

implement the following procedures for electronic informed consent.

The informed consent document(s) will be sent to the subject or their Legal Authorized Representative (LAR), if applicable, via secure email sent by REDCap prior to the scheduled consent discussion. The subject or LAR will be asked to review the consent document prior and during the consent discussion with a study staff member via an approved teleconferencing service (i.e., Zoom). The study staff member will confirm the subject or LAR has read and has the capacity to appreciate all aspects of the information presented in the consent process for the research study. The subject or LAR will be encouraged to ask questions. If agreeing to participate, the subject or LAR will sign the consent form using electronic informed consent (eConsent) via REDCap. A computer, tablet or touch screen phone will be used to capture digital signatures. If applicable, the person conducting consent will also sign the electronic informed consent (eConsent) document in a contemporaneous manner. Subjects will be provided with a digital copy of the completed form via email. The informed consent discussion and process will be documented by the study team in the subject's medical record or study record.

If a subject does not have access to a touch screen phone, computer or tablet, cannot work with remote electronic informed consent, or the remote electronic informed consent cannot be obtained for any other reasons, the consent may be conducted and documented at an in-person visit prior to study activities via paper consent form or through REDCap on an ITS tagged device.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

Due to feasibility and limited resources, a sample size of 126 patients will be included in this study. A sample size of 63 patients (126 total) in each group achieves 90% power

to detect a minimum difference of 0.2 mL/kg/hr in chest tube output 24 hours after the cardiopulmonary bypass surgery between the group receiving pathogen-reduced (PR) platelet transfusions and the group receiving standard (large volume delayed sampling – LVDS) platelet transfusions using a two-sample t-test assuming equal variance with a two-sided significance level of 0.05.

Based on preliminary data, only around 50% of children who undergo cardiopulmonary bypass surgery require platelet transfusions. Therefore, 252 patients will be enrolled and randomized to the study to take that into consideration.

Descriptive statistics (means, medians, standard deviations, interquartile ranges, proportions, frequency, and percent) will be calculated for baseline characteristics to assess and describe the study participants (by treatment group). Baseline comparability will be assessed using two-sample t-test (or Wilcoxon-rank sum test) for continuous baseline characteristics and the chi-square test (or Fisher's exact test) for categorical baseline characteristics.

Based on the understanding that 50% of the randomized participants will receive treatment, the following populations will be formed for the purpose of data analysis:

- An intent-to-treat cohort, defined as all participants who were recruited into the study, will be used for the primary and secondary analyses in the arm in which they were randomized, regardless of whether treatment was given.
- Per-protocol cohort, defined as all participants that continue with the platelet transfusion (PR platelets or LVDS platelets)

All analyses will be performed in R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). Note: The statistical considerations section was written in conjunction with Charlene Thomas MS, in the Division of Biostatistics, Department of Population Health Sciences.

12.1 Study Design/Endpoints

This is an open label, randomized, clinical trial that looks to compare the post-operative bleeding in children who received pathogen-reduced (PR) platelet transfusions versus standard (large volume delayed sampling – LVDS) platelet transfusions.

12.2 Sample Size/Accrual Rate

252 subjects will be randomized 1:1 to pathogen-reduced (PR) platelet transfusions or standard (large volume delayed sampling – LVDS) platelet transfusions Randomization will be done in REDCap using blocks of varying sizes and stratified by site and STAT score. We anticipate only 50% of children will require a transfusion, leaving evaluable 63 patients per arm. With 63 patients per arm (126 total), and assuming a standard deviation of 0.4, we will have 90% power to detect a minimum mean difference of 0.2 between the two treatment arms with a significance level of 0.050 using a two-sided two-sample equal-variance t-test.

12.3 Stratification Factors

Subjects will be stratified by site and STAT score (1/2 vs. 3/4/5).

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

The primary endpoint in this study is the chest tube output for the first 24 hours following cardiopulmonary bypass surgery. A two-sample t-test assuming equal variance or a non-parametric Wilcoxon rank-sum test will be used, as appropriate. All tests will be two-sided with an alpha level of 5%. Confidence intervals for the difference in means will also be calculated to assess precision.

12.4.2 Analysis of Secondary Endpoints

There are three secondary endpoints in this study. First, we will compare the total dose red blood cell transfusions in the first 48 hours between the two arms. Secondly, we will compare the total blood products transfused (intra and post-operatively) in the first 48 hours between the two arms. Lastly, rate of nosocomial infections between the two treatment arms will be compared. For the first two secondary endpoints, the two-sample t-test or non-parametric Wilcoxon rank-sum test will be used, as appropriate. For the last secondary endpoint, a Chi-square test or Fisher's exact test will be used as appropriate.

12.5 Interim Analysis

The DSMB will conduct regular reviews regarding the efficacy or futility of the treatment. If patients receiving PR platelets have > 20% bleeding as compared to LVDS platelets at the time of the interim analysis, the trial will be stopped. Interim analyses will be conducted by the study team three times during the course of the study with the enrollment and transfusion of every 42 patients.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with *Investigational Agent.* Consultation with the Biostatistics Office will allow for completion of this section.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least *XX* treatments. Consultation with the Biostatistics Office will allow for completion of this section.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Not applicable

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Not applicable

13.1.6 Events of Special Interest

Not applicable

13.1.7 Reporting of Pregnancy

Not applicable

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA

Not applicable

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an AE or SAE may come to the attention of study personnel during follow-up, medical record review or interviews with the clinical team. Because these subjects are inpatient and monitored closely, most AEs will be identified by clinical reports including laboratory findings, progress notes, nursing notes, etc. The local research team will monitor each subject daily for pre-defined AEs, particularly transfusion reactions. The research team will interview the clinical team and review the medical records daily for these events. The site PI or his/her designee will conduct prompt investigations of all reported AEs. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, initial assessment of relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of

relationship. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the trial, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. AEs will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 72 hours of the investigator becoming aware of the event.

- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within applicable policies of the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

The Weill Cornell DSMB will be responsible for subject safety and will have the authority to stop or modify the study. The DSMB will hold the principal investigator responsible for data quality and completeness, and for ensuring the safety of all children in the study. Members of the DSMB will be independent from the study conduct and free of conflict of interest.

The DSMB will meet at least semi-annually to assess safety and efficacy data (in terms of chest tube output, total transfusions and any transfusion reactions) on each arm of the trial. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The DSMB will provide its input to the principal investigator and IRBs.

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending or terminating party to the site PIs and regulatory authorities. If the trial is prematurely terminated or suspended, the PI will promptly inform the IRBs at Weill Cornell and Columbia, and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary outcome has been met
- Determination of futility

The trial may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the DSMB and IRBs. The trial will be stopped if children receiving PR platelets have > 20% more bleeding as compared to children receiving LVDS platelets.

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