Determination of the Optimal Prophylactic Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients

PROTOCOL SYNOPSIS

As platelet use continues to increase at a rate disproportionately higher than that of red cells, it is important to identify the most cost-effective strategies for providing platelet support. Identification and implementation of the most safe and cost effective strategies for providing platelet support is crucial for effective disease management without depleting platelet supplies.

The two most important factors within the control of the ordering physician that will significantly influence the total amount of platelets transfused are: 1) the prophylactic platelet transfusion "trigger" selected for transfusion; and 2) the number of platelets given per transfusion. Informative clinical data have been provided in the last fifteen years concerning the platelet transfusion trigger. The optimal quantity of platelets to be used per transfusion remains a highly controversial subject. To date, no prospective platelet transfusion trials have been performed in which patients are randomized to an assigned platelet dose throughout their period of thrombocytopenia to evaluate the effects of different doses on transfusion outcomes.

There may be safety issues associated with different dosing strategies for platelet therapy. Maintaining a higher platelet count for a greater percentage of the time with higher dose platelet transfusion therapy might provide better hemostasis than lower dose therapy. On the other hand, trigger study data suggest that there may be no hemostatistically-related safety issues based on the dose of platelets transfused as long as a baseline level of $\geq$ 5,000 platelets/μl is maintained.

This study will investigate the safety of three different dosing strategies for inpatients with thrombocytopenia related to stem cell transplants or chemotherapy. The primary endpoint is the percentage of patients in each treatment arm who have at least one day with Grade 2 or higher bleeding. The most important secondary endpoints, capturing key data on costs and safety, are the total number of platelets dispensed, the total number of transfusion events, the highest grade of bleeding, and the bleeding severity score (if such a score has been validated and published by the end of the Platelet Dose trial, and the necessary information to calculate the score was collected). The results of this trial could have a major effect on standard medical practice.

The Platelet Dose Trial is a multi-site trial that will enroll 1350 patients in the United States. Patients will be randomized with equal allocation to three platelet transfusion therapy groups based on body surface area (BSA):

Lower dose: $1.1 \times 10^{11}/m^2$ (½ of the medium dose)
Medium dose: $2.2 \times 10^{11}/m^2$
Higher dose: $4.4 \times 10^{11}/m^2$ (twice the medium dose)

An acceptable dose will be a dose that is within a range of 25% either above or below the target dose. Patients will be prophylactically transfused at their assigned dose for morning platelet counts of ≤10,000/μl. If the post-transfusion platelet count is not ≥ 10,000/μl, the physician will be allowed to order another platelet transfusion but is not required to do so. The protocol allows for additional platelets in the case of invasive procedures or active bleeding.

Assessment of bleeding by study personnel will be performed daily by means of physical assessment of the patient, patient interview and review of patient chart and laboratory data. The actual assignment of the bleeding grades will occur at the Data Coordinating Center by a computerized algorithm programmed to evaluate the data from the case report forms, plus adjudication of death due to bleeding.

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1. BACKGROUND AND SIGNIFICANCE

As platelet use continues to increase at a rate disproportionately higher than that of red cells, it is important to identify the most cost-effective strategies for providing platelet support. Identification and implementation of the most safe and cost effective strategies for providing platelet support is crucial for effective disease management without depleting platelet supplies.

The two most important factors within the control of the ordering physician that will significantly influence the total amount of platelets transfused are: 1) the prophylactic platelet transfusion "trigger" selected for transfusion; and 2) the number of platelets given per transfusion.

Informative clinical data have been provided in the last fifteen years concerning the platelet transfusion trigger.[1-7] Three of these studies were randomized prospective platelet transfusion trials that demonstrated that a prophylactic transfusion trigger of 10,000 platelets/μl was as effective as the more standard trigger of 20,000 platelets/μl based on hemorrhagic morbidity and mortality.[3-5] The lower trigger significantly reduced the number of platelets transfused, and thus the costs of platelet therapy, by at least 20% to 30%.

In contrast, the optimal quantity of platelets to be used per transfusion remains a highly controversial subject. No prospective platelet transfusion trials have been performed in which patients are randomized to an assigned platelet dose throughout their period of thrombocytopenia to evaluate the effects of different doses on transfusion outcomes or platelet usage.

There may be safety issues associated with different platelet dosing strategies. Maintaining a higher platelet count for a greater percentage of the time with higher dose platelet transfusion therapy might provide better hemostasis than lower dose therapy. However, the previously discussed prophylactic platelet transfusion trigger trials, comparing triggers of 10,000 *versus* 20,000 platelets/μl, demonstrated no difference in hemorrhagic morbidity or mortality between the two arms of the study.[3-5] Furthermore, based on radiochromium-labeled red cell stool blood loss as a measure of bleeding through an intact vascular system, fecal blood loss was the same whether patients were transfused prophylactically at 5,000, 10,000, or 20,000 platelets/μl.[8] Overall, these data suggest that there may be no hemostatistically-related safety issues based on the dose of platelets transfused as long as a baseline level of $\geq$ 5,000 platelets/μl is maintained.

Platelets disappear from the blood stream by two distinct mechanisms:[9] 1) the majority of platelets are lost by senescence with a maximum platelet lifespan of approximately ten days; and 2) other platelets are likely involved in the maintenance of vascular integrity; that is, a fixed number of platelets (estimated at 7,100 platelets/μl/day) disappear from the circulation in a stochastic way, independent of their age. In steady-state thrombocytopenic patients, platelet lifespan is reduced proportionate to the circulating platelet count. This is because, at lower platelet counts, the fixed number of platelets removed randomly in the postulated endothelial supportive function represents an ever-increasing fraction of the circulating platelets causing a direct relationship between platelet count and platelet survival.

A model has been developed to predict platelet utilization using two different doses of pooled platelet concentrates prepared from whole blood.[10] Transfusion of pools of 3 platelet concentrates would decrease platelet utilization by 22% compared to pools of 6 platelet

concentrates using a prophylactic platelet transfusion trigger of 10,000 platelets/μl. Although overall use would be less, the frequency of transfusion would be predicted to be 2 transfusions *q* 3 days with a 3-concentrate pool and *qod* using a 6-concentrate pool. However, these assumptions have not been confirmed by a transfusion trial.

There have been two studies that have compared isolated transfusions of different doses of platelets given to the same thrombocytopenic patient. In both studies, higher dose platelet transfusions produced greater post-transfusion platelet increments resulting in longer intervals between transfusions as previously predicted.[9] In one study, 69 patients each received 3 sequential prophylactic transfusions with an average of 4.6×10^{11}, 6.5×10^{11}, and 8.9×10^{11} platelets/transfusion.[11] Platelet increments averaged 33,000 $\pm$ 22,000, 51,000 $\pm$ 29,000, and 62,000 $\pm$ 34,000 platelets/μl with platelet survivals of 2.6 $\pm$ 0.7, 3.3 $\pm$ 1.2, and 4.1 $\pm$ 1.4 days, respectively ($p<0.01$ for both of the higher doses compared to the lowest dose for both platelet increments and survivals). It can be predicted that the highest dose platelet transfusion therapy should reduce the number of platelet transfusion events by 35% compared to the lowest dose, but it would concurrently increase overall platelet use by 15%.

In another study, 46 patients[12] received 79 paired prophylactic transfusions of low dose 3.1×10^{11} *versus* high dose 5.0×10^{11} platelets/transfusion. Post-transfusion platelet increments were 17,000 platelets/μl *versus* 31,000 platelets/μl, and survivals were 2.2 days *versus* 3.0 days ($p<0.01$). In a cost-analysis of this study,[13] 88% of the costs of a platelet transfusion were attributed to the platelets themselves, 7% to the filter, and 5% to nursing and other costs of administration such as adverse event assessments, data tracking, etc. Therefore, reducing the number of platelets transfused rather than the number of transfusion events might be the most cost-effective strategy.

As platelets express the thrombopoietin receptor, transfusion of platelets would be expected to decrease the level of circulating thrombopoietin.[14] Therefore, high dose platelet transfusion therapy may be associated with substantial decreases in the levels of thrombopoietin, thereby prolonging the duration of thrombocytopenia and increasing platelet use as less thrombopoietin would be available to stimulate the return of marrow megakaryocyte platelet production.

In summary, with the costs of health care continuing to escalate, studies designed to determine how to safely improve the cost-effectiveness of medical therapy are of primary importance.

2. OBJECTIVES

2.1 Primary

To compare the three study arms of medium, lower and higher dose platelet therapy with respect to the percentage of patients experiencing at least one episode of Grade 2 or higher bleeding as determined by the Platelet Dose Trial Bleeding Scale (see section 6.3).

2.2 Secondary

To compare the three study arms with respect to the following outcomes:

Platelet Related:

1. Platelet utilization rates (total number of platelets transfused x 10^{11}).

2. Number of platelet transfusion events; i.e., frequency of transfusions. A transfusion event would be each separate platelet transfusion issued by the trial site's transfusion service.

3. Days of platelet support; the number of days from the first to the last platelet transfusion.

4. Frequency of platelet transfusions/day of platelet support.

5. Total number of platelets transfused ($x10^{11}$)/day of platelet support.

6. Total number of platelets transfused ($x10^{11}$)/Body Surface Area (BSA).

7. Total number of platelets transfused ($x10^{11}$)/BSA/day of platelet support.

8. Number of days with a morning platelet count of $\leq$10,000/μl.

9. Platelet response - corrected platelet count increment at ≤ 4 hours post-transfusion.

$$\text{Corrected count increment} = \frac{(\text{Platelet Increment}/\mu l) \times \text{body surface area } (m^2)}{(\text{number of platelets transfused}) \times 10^{-11}}$$

10. Platelet response - corrected platelet count increment based on the platelet count the morning following a platelet transfusion.

11. Incidence of platelet refractoriness (defined as two sequential transfusions, each with CCIs < 5,000 measured within 4 hours post-transfusion).

Hemostasis Related:

12. Number of days to first Grade 2+ bleeding.

13. Highest category of bleeding during time on study (Platelet Dose Trial Bleeding Scale Grades $\leq$1, 2, 3, 4 by arm).

14. Bleeding severity based on number of days with bleeding (total days of bleeding and bleeding/thrombocytopenic day), intensity of bleeding, and number of sites with bleeding, if such a severity score has been validated and published by the time this trial is completed.

15. Surrogate outcomes for hemostatic efficacy to include:
    a) Death due to bleeding as the primary or contributory cause of mortality.
    b) Number of platelet transfusions given above the 10,000/μl platelet transfusion trigger, number of platelet transfusions given more often than once/day, and/or number of platelet transfusions given above their assigned dose, in each case because of ≥ Grade 2 bleeding (as determined by the Platelet Dose Trial Bleeding Scale).
    c) Number of platelets (x 10^{11}), frequency of transfusions and duration of transfusions given because of ≥ Grade 2 bleeding (as indicated in 15b).
    d) Total number of RBC transfusions, and the mean per thrombocytopenic day for each patient.
16. Number of platelets (x 10^{11}), frequency of transfusions, and duration of therapeutic transfusions given for invasive procedures. For purposes of this study, invasive procedure is any type of surgical intervention or diagnostic procedure involving passage of an instrument; e.g. bronchoscopy, endoscopy, etc.

Other:

17. All cause mortality rates.
18. Cost Analysis: By varying the relative weight of cost per 10^{11} platelets and cost per transfusion event, data on how many platelets are transfused and the number of transfusion events will allow estimation of the relative costs of the transfusion strategies under varying pricing scenarios.

3. STUDY POPULATION

3.1 Inclusion Criteria

1. Patients with, or expected to have, hypoproliferative thrombocytopenia who are expected to have a platelet count of ≤ 10,000μl for ≥ 5 days, and be in the hospital for ≥ 5 days.
2. Weight between 10 and 135 kilograms.
3. Patients whose PT/INR, PTT and fibrinogen assays, measured within 72 hours before study entry, are as follows:
    a) PT ≤ 1.3 X upper limit of normal for the laboratory
    b) PTT ≤ 1.3 X upper limit of normal for the laboratory
    c) Fibrinogen ≥ 100mg/dL
4. Patients with any diagnosis undergoing or with completed hematopoietic stem cell transplantation, and patients with a diagnosis of acute or chronic leukemia, non-Hodgkins and Hodgkins lymphoma, myeloma, myelodysplasia, or non-hematologic malignancy undergoing or with completed chemotherapy.
5. During this hospitalization, the patient has not yet received any platelet transfusions related to the current or planned course of therapy. Individual platelet transfusions given prior to the study and unrelated to thrombocytopenia will not exclude the patient.

3.2 Exclusion Criteria

1. Evidence of ≥ Grade 2 bleeding (as determined by the Platelet Dose Trial Bleeding Scale) while being assessed for study entry.
2. Patients receiving antithrombotic drugs.
3. Patients who will receive bedside leukoreduced platelet transfusions.
4. Presently with or a history of platelet transfusion refractoriness within 30 days prior to enrollment in the study.
5. Pre-enrollment lymphocytotoxic antibody screen (PRA) known to be ≥ 20% based on prior data. If antibody screen not available, enroll patient.
6. Presently with or a history of acute promyelocytic leukemia (APML), immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), or hemolytic-uremic syndrome (HUS).
7. Patients who will be transfused at platelet trigger of >10,000 platelets/μl.
8. Patients with recent history of major surgery (≤ 2 weeks).
9. Currently taking, or participating in a clinical trial involving, platelet substitutes, platelet growth factors, or pharmacologic agents intended to enhance or decrease platelet hemostatic function.
10. Patients who are pregnant.
11. Patients previously enrolled in this trial.

4. TRIAL ENROLLMENT

4.1 Screening/Recruitment

Potentially eligible patients will be identified by the patient's physician or chart review by a TMH research staff member. Participating sites, in compliance with HIPAA regulations, will apply the Activities Preparatory to Research guidelines. The preparatory research provision allows a researcher to identify prospective research participants for purposes of seeking their authorization to use or disclose protected health information for a research study.

4.2 Stratification and Randomization

Treatment groups will be allocated using randomly permuted blocks within strata (Zelen, 1974). Four strata will be used: chemotherapy for hematologic malignancy, chemotherapy for solid tumors, stem cell transplant (allogeneic) and stem cell transplant (autologous or syngeneic). Treatment allocation will also be balanced within each clinical center using dynamic balancing (Zelen, 1974).

Patients will be randomized with equal allocation to three platelet transfusion therapy groups based on body surface area (BSA):

Lower dose: $1.1 \times 10^{11}/m^2$ (½ of the medium dose)
Medium dose: $2.2 \times 10^{11}/m^2$
Higher dose: $4.4 \times 10^{11}/m^2$ (twice the medium dose)

An acceptable dose will be a dose that is within a range of 25% either above or below the target dose.

4.3 Masking of Treatment Allocation

Treatment allocation will be masked. At enrollment, the patient's height and weight will be entered into the data management system. The computer will randomize the patient and the transfusion service staff at the trial site will be given the target platelet dose and acceptable dose range for the patient, but not the treatment arm the patient is assigned to. Although it is possible that the hospital staff caring for the patient, or the research staff performing the daily bleeding assessments, may be able to guess a patient's dose assignment based on the volume of platelets transfused, as well as the pre- and post-transfusion platelet counts, neither the hospital, research staff or transfusion service will be informed of a patient's randomization assignment.

5. INTERVENTIONS

5.1 Preparation

For each patient the physician can choose to use either apheresis or whole blood derived platelet products during the study to achieve the targeted platelet dose. The preferred type of platelets to be used for each study patient must be determined prior to randomization to prevent bias in product selection based on randomization assignment. However, it is recognized that, due to inventory problems, patients may not always receive the preferred platelet product.

All study transfusions – whether platelets or red cells – will be leukoreduced prior to transfusion. However, bedside white cell filtration will not be allowed, as a platelet count of the product actually transfused is needed to accurately determine post-transfusion platelet responses.

5.2 Administration

Patients will be prophylactically transfused for morning platelet counts of ≤10,000/μl. If the post-transfusion platelet count is not ≥ 10,000/μl, the physician will be allowed to order another platelet transfusion but is not required to do so.

For whole-blood-derived platelets, the transfusion service will determine from quality control (QC) data how many individual bags of whole-blood-derived platelets should be pooled to be within the target dose for that particular patient. That number of individual bags would be pooled and mixed in the usual way. Then a sample from the pooled bag would be taken to send off for platelet counting, and the weight or number of milliliters in the pooled bag that was sent to the patient would be recorded.

For apheresis platelets, the transfusion service will use the "at-collection" platelet count to decide which bag (or group of bags, or partial bag) to use for that particular patient. [If no single bag or set of bags would be in the target dose range, the transfusion service might have to sterilely split a bag and give half a bag, or one and a half bags, so that the total number of platelets would be in the target dose range.] At the time the transfusion service

releases the platelets to be transfused, they will take a sample of each bag or partial bag for platelet counting "at issue" and record the weight or number of milliliter in the bag.

The platelet count of any granulocytes transfused will be done at issue.

The transfusion service does not need to wait for the platelet count results before issuing the platelets or granulocytes to the patient. The sample(s) for the "at-issue" platelet count should be taken shortly before the units are sent to the patient. The actual dose measured at issue will be used for calculating Corrected Count Increments (CCIs). Platelet counts and volumes of all platelet and granulocyte products must be done after all processing has been completed.

If the patient develops active bleeding the physician will be allowed to obtain an additional platelet count and order more platelets. For an invasive procedure, the physician will be allowed to increase the transfusion dose pre- and post-procedure as per their usual practice. In both of these situations where therapeutic platelet transfusions are given, the patient should be returned to their assigned platelet dose as soon as possible.

If a patient develops platelet refractoriness (defined as two sequential transfusions, each with CCIs of < 5000 measured within 4 hours post-transfusion), a serum sample will be drawn for lymphocytotoxic antibody determination. If the PRA is ≥ 20%, the patient will be presumed to be alloimmune platelet refractory and may be given either HLA-matched or cross-match compatible platelet transfusions. Because of the difficulty and expense of obtaining these special products the full dose of the selected platelets may be transfused. Even though such patients will not necessarily remain in their dose arm, they will continue to be followed for study measurements and assessments. It is expected that alloimmune platelet refractoriness will occur infrequently, perhaps only 15% of the time since patients will be receiving leukoreduced blood products. Since alloimmunization is not considered related to transfusion dose or number of donor exposures, it should occur at the same rate among the arms. If the PRA is < 20%, local practice will be followed to treat the refractoriness. The patient will remain in the study and data will continue to be collected on the patient.

Patients receiving granulocyte transfusions will remain on study even though these patients will be receiving a variable number of platelets with these transfusions. Platelet counts of the transfused granulocytes will be obtained so that total platelets administered to each patient can be determined. In addition, a post-transfusion platelet count will be obtained with each granulocyte transfusion, similar to what is required for a platelet transfusion. Patients should remain on their assigned platelet dose arm while receiving granulocyte transfusions.

5.3 Concomitant Treatments or Interventions

Patients may require other treatments while enrolled in the protocol. Most platelets will be transfused in the second and third week after chemotherapy. The most common procedures that patients may require will be line placement, lumbar puncture, thoracentesis and bronchoscopy. Institutional transfusion criteria should be followed prior to the start of the procedure. In general, institutions may require a platelet count of ≥25,000/μl for line

placement and ≥50,000/μl for lumbar puncture, thoracentesis and bronchoscopy. For an invasive procedure, the physician will be allowed to increase the transfusion trigger and the transfusion dose pre and post procedure as per their usual practice. Such patients should be returned to their assigned platelet arm as soon as possible.

6. MEASUREMENT

6.1 Schedule of Measurement

Patients will be followed until 30 days after the initial platelet transfusion, until they have not received a platelet transfusion for 10 days after the most recent platelet transfusion (assumed to have had platelet recovery), or until hospital discharge, whichever comes first. Patients will be studied during only one episode of thrombocytopenia.

The following is a list of the data that will be collected while the patient is on study. Table 1 outlines the schedule of laboratory assessments.

At Baseline:

1. Demographics and Medical History:
   - Weight
   - Height
   - Date of birth
   - Gender
   - Ethnic origin
   - Race
   - Any prior pregnancies (*Yes – give #, or No*)
   - Any prior transfusions *(Yes or No)*
   - Diagnosis (disease and type of treatment; i.e., chemotherapy or type of hemopoietic transplant)
   - ABO type of patient
   - If receiving allogeneic transplant, ABO type of donor and whether donor is related (*Yes or No*),
   - Type and date of transplant, if any

2. Laboratory:
   - Platelet count
   - Hematocrit / Hemoglobin
   - PT, INR, PTT and Fibrinogen
   - HLA antibody screen

3. Hemostatic Assessment:
   - Assessment of bleeding by study personnel will be performed by means of physical assessment of the patient, patient interview (if possible) and review of patient chart and laboratory data. Research staff will perform the physical assessment and interview of the patient before reviewing the patient's chart and laboratory data to allow an objective patient assessment without the bias that

might be introduced by doing the chart and laboratory data reviews first. Research staff will perform the Hemostatic Assessment daily at approximately the same time each day.

Daily:

1. Laboratory:
   - Platelet count
   - Hematocrit / Hemoglobin
   - PT, INR, PTT and Fibrinogen - if available - as part of routine care
2. Hemostatic Assessment:
   - Research staff will perform the Hemostatic Assessment daily at approximately the same time each day. (See above)
3. Medications:
   - Anti-thrombotic and Fibrinolytic Inhibitor medications (name, dose, date started), if patient started either type of medication while on the study.

End of Study:

1. Laboratory:
   - Platelet count
   - Hematocrit / Hemoglobin
   - HLA antibody screen
   - PT, INR, PTT and Fibrinogen - if available - as part of routine care
2. Hemostatic Assessment (See above.)

With Each Platelet and Granulocyte Transfusion:

- Type of product transfused (granulocytes, apheresis platelets, pooled whole-blood-derived platelets, HLA or crossmatch compatible platelets)
- ABO type of the transfused platelets
- Platelets leukoreduced *(Yes or No)*
- Platelets volume reduced *(Yes or No)*
- Age of the apheresis platelets, or of pooled platelets if all same age
- Platelet count of platelets or granulocytes prepared for transfusion (at collection and issue if apheresis, at issue if whole-blood-derived platelets or granulocytes)
- Volume at issue of platelets or granulocytes transfused
- Post-transfusion platelet count between 10 minutes and 4 hours after each transfusion.

Tests for HLA and Platelet Specific Antibodies:

- With the development of suspected platelet refractoriness, a sample will be drawn for HLA antibody screening. Blood can also be drawn and tested for platelet specific antibodies depending on local practice. These tests will be considered part of routine patient care.

Table 1: Schedule of Patient Laboratory Assessments

TEST	Baseline	Daily	End of Study	Transfusion	Other
Hemoglobin	R	R	R		
Hematocrit	R	R	R		
Platelet Count	R	R	R	R (post)	S*
Lymphocytotoxic Antibody Screen	R		R		R (if refractory)
PT and INR	R	S	S		
PTT	R	S	S		
Fibrinogen	R	S	S		
ABO RH Typing	R				

R = required
S = lab results collected if available (done as part of patient standard care).
*Additional platelet counts will be collected if ordered by the treating physician (for active bleeding or invasive procedure)

6.2 Specimen Collection Procedures

Blood specimens will be collected from either a peripheral venipuncture site or central line using sterile technique. Specimens for coagulation tests will be drawn from peripheral sites whenever possible. A central line may be used if special procedures are in place to prevent compromise of coagulation study results. Specimens must be labeled with name and unique identifier as per institutional policies. Approximately 0.5mL to 10mL (capillary and pediatric specimens in pediatric "bullets") of blood will be collected at baseline and daily from patients for study laboratory assessments. After each transfusion, 0.5mL to 5mL of blood will be collected for a post transfusion platelet count. At the start of the study, an additional 2mL (pediatric patients) to 10mL of blood will be taken for ABO RH typing and/or a pregnancy test if necessary. At the end of the study, approximately 2mL (pediatric patients) to 10mL of blood will be drawn for final study laboratory assessments.

6.3 Definitions – Bleeding Scale

Table 2 describes the criteria that will be used to evaluate and grade bleeding.

Table 2: Platelet Dose Trial Bleeding Scale

	Grade 1	Grade 2	Grade 3
Oral and nasal	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤ 30 minutes* ➢ Petechiae of oral mucosa ➢ Epistaxis – total duration of all episodes in previous 24 hours ≤ 30 minutes*	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* ➢ Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes*	♦ Any bleeding requiring RBC transfusion over routine transfusion needs**
Skin, soft tissue, musculoskeletal	➢ Petechiae of skin ➢ Purpura ≤ 1 inch diameter ➢ One or more spontaneous hematomas in the soft tissue or muscle > 1"	➢ Purpura > 1 inch diameter ➢ Spontaneous hematoma in deeper tissues ➢ Joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	♦ Any bleeding requiring RBC transfusion over routine transfusion needs**
Gastrointestinal	➢ Positive stool occult blood test	➢ Melanotic stool ➢ Hematochezia – visible red blood mixed in stool, not requiring a transfusion ➢ Hematemesis – Grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood)	♦ Any bleeding requiring RBC transfusion over routine transfusion needs**
Genitourinary	➢ Any biochemical or microscopic Hb/RBCs without red urine ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle **OR** Bleeding heavier than normal **OR** Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting	➢ Gross/visible hematuria without need for transfusion ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle **OR** Bleeding heavier than normal **OR** Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting	♦ Any bleeding requiring RBC transfusion over routine transfusion needs**
Pulmonary		➢ Hemoptysis – Visible blood ➢ Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding)	♦ Any bleeding requiring RBC transfusion over routine transfusion needs**

	Grade 1	Grade 2	Grade 3
Body Cavity		➢ Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	➢ Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate), and/or need for transfusion
Central Nervous System		➢ Retinal bleeding without visual impairment ➢ Lumbar puncture with blood (>5 RBC/μL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color	➢ Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap
Invasive Sites		➢ Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours	♦ Any bleeding requiring RBC transfusion over routine transfusion needs**
Hemodynamic Instability			➢ Any bleeding associated with moderate hemodynamic instability (hypotension; >30mmHg fall or >30% decrease in either systolic or diastolic blood pressure) and requiring RBC transfusion over routine transfusion needs**

*Count actual bleeding (i.e. "running out" or need for basin, Kleenex, towel, etc.) not minor bleeding
**Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding

GRADE 4:

- ♦ Any bleeding associated with severe hemodynamic instability (hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of $\geq$ 20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs
- ♦ Fatal bleeding from any source
- ♦ Retinal bleeding with visual impairment (Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consult for documentation)
- ♦ CNS symptoms with non-traumatic bloody lumbar puncture
- ♦ CNS bleeding on imaging study with or without dysfunction

6.4 Assessment and Adjudication Procedures

The persons performing the hemostatic assessments will not be informed of the patient's treatment group. However, great care must be taken to ensure that these assessments are performed in a standardized manner across all sites. Training of staff will be documented. Patients will be assessed for bleeding daily during the study period. Assessment findings will be recorded on the appropriate case report form. The actual assignment of the bleeding grades will occur at the DCC by a computerized algorithm programmed to evaluate the data from the case report forms.

6.4.1 Purpose of Adjudication

The role of the adjudication panel is to assess whether bleeding was a contributory cause of a patient's death. A key secondary endpoint of this trial is grade of bleeding, and "death due to bleeding" is one way of reaching Grade 4 bleeding.

6.4.2 Selection of Subjects for Adjudication

In accordance with the Platelet Dose Protocol, adjudication will be carried out for all patients who die on study and have either:

- Bleeding judged to be a possible, probable or definite contributory cause of death according to the patient's physician
- Grade 3 or 4 bleeding, or
- A situation where Grade 3 or 4 bleeding can not be ruled out due to missing data.

6.4.3 Adjudication Panel

The adjudication panel will consist of at least three physicians. A minimum of three physicians will review each case.

6.4.4 Adjudication Process

The DCC will prepare a packet of materials to be express mailed to members of the panel. The packet will include: a summary of the patient's demographic information, diagnoses, and bleeding grade history. Before sending the materials, the DCC will remove any information that could identify the patient or disclose the treatment group assignment. The panel may request additional information including hospital records or autopsy reports. Panel members will complete Form P100 – Adjudication Form to indicate their conclusions. The P100 sheets will be sent to the DCC for entry into the data management system. If all panel members agree as to whether bleeding was a cause of death, no further action will be taken. If the panel members do not agree, a conference call will be scheduled to resolve the adjudication.

A summary of the panel's findings will be presented to the DSMB during their semi-annual meetings.

6.4.5 Adjudication Schedule

The adjudication panel will review cases once every 6 months, approximately 1 month before each scheduled DSMB review of the Trial. Cases to be included in each review include deaths that occurred at least 30 days prior to the review, meet one or more of the criteria listed in Section 6.4.2 and have not yet been reviewed by the panel.

7. ADVERSE EVENT CRITERIA AND REPORTING

Reporting of all adverse events will be consistent with standard TMH CTN procedures described in the Manual of Procedures (MOP), Chapter 6: Guidelines for Reporting Adverse Events. Reporting requirements are calibrated to the severity of the event and the perceived relationship to the individual transfusion. The TMH CTN will be using the descriptive terminology developed by the National Cancer Institute (Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 dated June 10, 2003) for use in reporting adverse events. The CTC includes a grading (severity) scale for each adverse event term. Grades were developed using the following guidelines:

Grade 0 - No adverse event or within normal limits
Grade 1 - Mild adverse event
Grade 2 - Moderate adverse event
Grade 3 - Severe adverse event
Grade 4 - Life threatening or disabling adverse event
Grade 5 - Fatal adverse event

7.1 Definitions

Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether or not it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Serious Adverse Event: Any adverse event that results in any of the following outcomes: Death, a life threatening event, prolongation of existing hospitalization, congenital anomaly/birth defect, and/or a persistent or significant disability/incapacity.

7.2 Data Collection and Validation

In general, data will be collected and entered into a web-based data management system (DMS) at each site participating in the Platelet Dose Trial, and transferred electronically to the Data Coordinating Center. The DMS is programmed to validate all data entry fields as the data is entered. Validations are question-by-question checks that give immediate

feedback to help catch data entry errors, form completion errors, or out-of-range values. Reports of outstanding edits, generated upon completion of data entry, will enable continuous cleaning of data at each site.

The DCC will regularly monitor all data for consistency and correctness. If the DCC observes inconsistent data or patterns of protocol violations or missing data, site staff will be contacted immediately to address the finding.

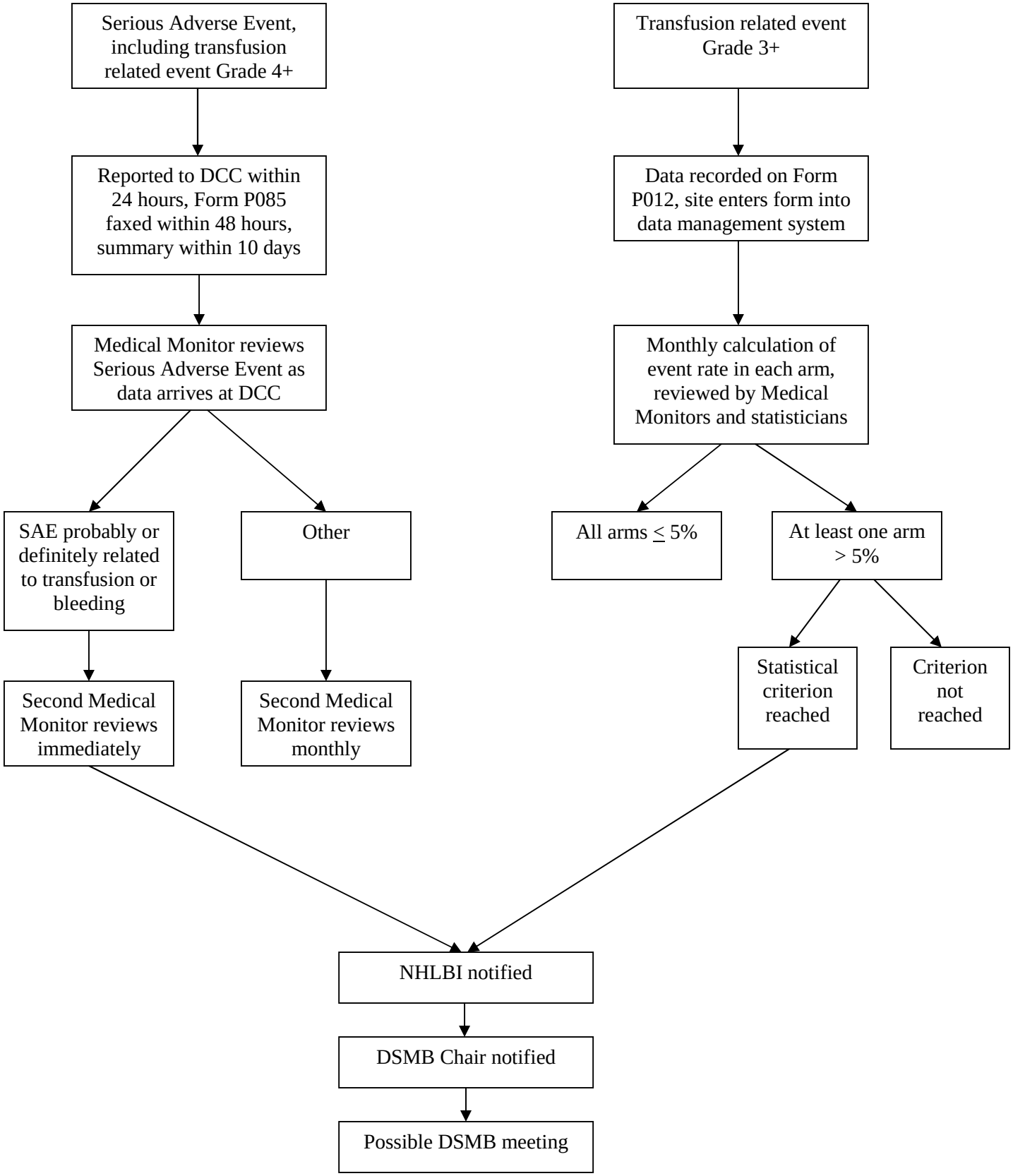
7.3 Monitoring of Adverse Events

Serious adverse events, including death, will be monitored continuously by the DCC as data are received. Transfusion related events of Grade 3 and higher will be monitored by the DCC at least monthly.

Whenever the continuous or monthly monitoring raises concern about event rates, the DCC will immediately contact NHLBI. Details are provided in subsections 7.3.1 and 7.3.2. The NHLBI TMH Executive Secretary will contact the DSMB Chair to discuss any concerns raised by the continuous and monthly monitoring of adverse events. After review of the concerns with the DSMB Chair, an interim DSMB conference will be scheduled if deemed necessary.

Figure 1 summarizes the monitoring plan for this study.

Figure 1: Monitoring Plan



7.3.1 Continuous Monitoring of Serious Adverse Events

Serious adverse events, including death of a subject participating in the Platelet Dose Protocol, must be reported to the DCC within 24 hours by phone or email. The Serious Adverse Event Form (Form P085) must be sent to the DCC via fax within 48 hours. The Serious Adverse Event Form will be entered into the Data Management System by the DCC. A summary of the adverse event must be submitted to the DCC within 10 days of the event. This category of events includes, but is not limited to, transient ischemic attack, myocardial infarction, stroke, Graft-versus-Host disease, venocclusive disease of the liver, seizure, TRALI, and death. It also includes other life-threatening and fatal (Grade 4 and 5) adverse events related to transfusion of blood products. These include life-threatening and fatal events related to allergic reaction/hypersensitivity, sinus bradycardia, sinus tachycardia, hypertension, hypotension, dyspnea, hypoxia, wheezing, cough, hemolysis, fever, and infection.

The DCC Medical Monitor assigned to the study will review all serious adverse events as data arrive at the DCC. In particular, the Medical Monitor will review the attributions listed on Form P085 regarding the relationships between the adverse event and transfusion, underlying disease and bleeding (unrelated, unlikely, possible, probable or definite). If an adverse event is reported on Form P085 as probably or definitely related to transfusion or bleeding, if the Medical Monitor thinks such an attribution might be warranted, or if other questions arise, the Medical Monitor will confer with a second non-study physician with expertise in transfusion medicine. In addition, each month these physicians will review together the attributions for serious adverse events that were not considered probably or definitely related to transfusion or bleeding.

The DCC will report all serious adverse events to the NHLBI Project Officer as described in the TMH MOP. Serious adverse events that are considered probably or definitely related to transfusion or bleeding (either on Form P085 or according to the Medical Monitor) will be flagged for special attention. In these cases, the Executive Secretary will contact the DSMB Chair to ask for advice on how to proceed.

7.3.2 Monthly Monitoring of Transfusion Related Events

Adverse events of all severity levels that are related to transfusion of blood products (i.e. events related to allergic reaction/hypersensitivity, sinus bradycardia, sinus tachycardia, hypertension, hypotension, dyspnea, hypoxia, wheezing, cough, hemolysis, fever, infection, and rigors/chills) will be monitored by the DCC using data reported on the Transfusion Related Event form (Form P012). Serious transfusion related adverse events are also reported within 24 hours, and monitored as described in Section 7.3.1.

At least monthly, the DCC Protocol Statistician will calculate the percentage of patients in each treatment arm with at least one transfusion related event of Grade 3 or higher. The Protocol Statistician and Medical Monitors will meet to review and discuss the results of this analysis. Transfusion related events of Grade 3 or higher

are expected to be rare. In this patient population, at most 1 – 3% of patients would be expected to have at least one such event. If any arm has more than 5% of patients with a Grade 3 or higher transfusion related event, and this percentage differs significantly from the percentage in at least one of the other arms as described below, the DCC will notify NHLBI. The Executive Secretary will contact the DSMB Chair to ask for advice on how to proceed. This monitoring plan is designed to identify a possible excess of transfusion related events in one or more study arms. It is not intended to serve as a formal stopping rule for this study.

Table 3 shows the p-values that would trigger notification of NHLBI if the 5% criterion were also met. For the first 14 months, the boundary p-value is 0.0010. At later months, the boundary p-values are similar to the O'Brien-Fleming boundaries at those months for a trial with a nominal p-value of 0.017 for each comparison. These boundaries were chosen, using simulations, to strike a balance between two goals: minimizing the chance of flagging a comparison for special attention when there is truly no difference between treatment arms, and maximizing the chance of flagging a comparison for special attention before the planned end of the trial when there truly is a difference between treatment arms and the highest rate is above 5%.

Table 3: P-values for interim monitoring of Grade 3+ transfusion related events

Month	p-value
1	0.0010
2	0.0010
3	0.0010
4	0.0010
5	0.0010
6	0.0010
7	0.0010
8	0.0010
9	0.0010
10	0.0010
11	0.0010
12	0.0010
13	0.0010
14	0.0010
15	0.0016
16	0.0022
17	0.0031
18	0.0042
19	0.0053
20	0.0066
21	0.0083
22	0.0098
23	0.0116
24	0.0137

When there is truly no difference between the treatment arms the percentage of times that a comparison is flagged for special attention should be low. This will help protect the study from a decision to stop early for an imbalance in transfusion related events that is actually due to chance differences. When there truly is a difference between the treatment arms, and the highest percentage is more than 5%, the percentage of times that at least one comparison is flagged for special attention should be high. This will help to ensure that a treatment arm with excessive Grade 3 or higher transfusion related events is identified for special attention.

Table 4 shows the operating characteristics of this monitoring plan for transfusion related events under several different scenarios, as determined by simulations with 10,000 replications per scenario. In the three scenarios where the true percentage of patients with Grade 3 or higher transfusion related events is the same in all three treatment groups, there is less than a 2.5% chance that NHLBI would be contacted. In all of the eight scenarios where there are treatment arm differences and the highest rate is above 5%, there is at least a 68% chance that NHLBI would be contacted, indicating reasonable power to detect excessive Grade 3 or higher transfusion related events. In six of the eight scenarios there is at least an 80% chance that NHLBI would be contacted.

Table 4: Operating characteristics for monitoring of Grade 3+ transfusion related events

Scenario	True percentage with Grade 3+ transfusion related events			Percent of replications with comparison flagged for attention				Median month for the comparison to be flagged, among replications where the comparison is flagged			
	Arm A	Arm B	Arm C	Any	A vs. B	A vs. C	B vs. C	Any	A vs. B	A vs. C	B vs. C
1	1%	1%	1%	0.00%	0.00%	0.00%	0.00%	n/a	n/a	n/a	n/a
2	2%	2%	2%	0.23%	0.15%	0.09%	0.04%	16	17	17	10
3	3%	3%	3%	2.04%	0.76%	0.71%	0.76%	19	19	19	19
4	1%	1%	6%	89.20%	0.00%	87.48%	87.64%	13	n/a	14	14
5	1%	3.5%	6%	89.23%	12.12%	87.96%	26.30%	14	16	14	20
6	2%	2%	6%	82.84%	0.04%	73.05%	73.11%	16	11	18	18
7	2%	4%	6%	75.64%	13.88%	72.66%	15.71%	18	19	18	20
8	2%	2%	7%	95.68%	0.03%	90.35%	90.48%	15	16	16	16
9	2%	4.5%	7%	91.54%	27.90%	90.09%	22.70%	16	19	16	20
10	3%	3%	7%	80.72%	0.71%	65.23%	65.85%	18	20	19	19
11	3%	5%	7%	68.90%	18.28%	65.34%	13.58%	18	20	18	20

7.4 Interim Analyses and Statistical Stopping Guidelines

Formal interim analyses of the primary endpoint and selected safety-related endpoints have been developed to monitor the study. These formal interim analyses are designed to assist the DSMB in overseeing the study. The DSMB may develop other criteria for determining when to intervene in the enrollment or treatment of patients in the study if deemed necessary.

The DSMB will make its recommendations based on the totality of evidence, taking into account the observed rates in each treatment arm of the primary bleeding endpoint, other safety-related secondary endpoints, and adverse events; the conduct of the study (accrual, compliance, etc.); and information from outside the study. Therefore, the interim analysis plan will provide guidelines rather than strict rules about whether the study (or one arm of the study) should be stopped before its planned conclusion.

The proposed plan is as follows.

7.4.1 Interim Analyses of Primary Endpoint

Sample size calculations have been based on the assumptions that

- There will be four equally spaced looks planned for the primary endpoint, i.e. interim looks after outcome data have been obtained for approximately 112, 225, and 337 patients per arm, and a final look at the end of the study;
- The primary endpoint will be analyzed at each look using separate pairwise comparisons between each pair of treatment arms still enrolling patients at that look; and,
- A Lan-DeMets alpha spending function similar to O'Brien-Fleming boundaries will be used for each pair of treatments, with a nominal p-value of .017 for each pair (i.e. using Bonferroni adjustment for the three pairwise comparisons).

This approach controls the Type I error for each pair of treatments to be no more than 0.017 even if a decision is made to discontinue one treatment arm partway through the study.

This approach means that an extremely large difference between two treatment arms in the percentage of patients with Grade 2 or higher bleeding would be needed to cross a stopping boundary at the first look. The boundary becomes less stringent at later looks. If the study continues to its planned number of patients, the treatment difference needed to declare statistical significance will be only slightly larger than the critical value that would be used if there were no interim looks. Table 5 shows the p-values that would be needed for each one-degree-of-freedom chi-square test at each look to declare that the boundary had been crossed. At an interim look, this would suggest that stopping the trial, or one arm of the trial, should be considered. If the study continues to the planned number of patients, crossing the boundary would be

considered necessary to declare a statistically significant difference between the two arms with an alpha level of 0.017.

Table 5: P-value boundaries using Lan-DeMets O'Brien-Fleming type boundaries

Look	p-value
1st interim look	< 0.0001
2nd interim look	0.0004
3rd interim look	0.0046
Final look	0.0155

If the DSMB meetings do not take place at exactly the planned number of subjects, the EAST-3 software package can be used to adjust the critical p-value at each look to ensure that the overall significance level of 0.017 for each pairwise comparison of the primary endpoint is maintained.

7.4.2 Interim analyses of safety-related secondary endpoints

Several of the secondary endpoints listed in Section 2.2 are related to patient safety. These include secondary endpoints 13 (highest grade of bleeding while on study), 14 (if a validated published severity scale which we can calculate from study data becomes available), 15a (death due to bleeding), and 17 (all-cause mortality).

At each scheduled DSMB meeting data will be presented regarding the proportion of patients in each treatment arm with death due to bleeding and with death from any cause. P-values for chi-square tests (or, for rare outcomes, Fisher's exact tests) comparing each pair of treatment arms will be provided. Data will also be presented regarding the proportion of patients in each treatment arm who reach each grade of bleeding, and Cochran-Mantel-Haenszel tests of trend (or similar exact tests, for rare outcomes) will be presented for each pair of treatment groups. If an ordinal severity scale is available, a similar approach will be taken. If an essentially continuous severity scale is available, it will probably be highly skewed. The mean, standard deviation, and quartiles of the score will be presented for each group. If a log transform or other suitable transform can be found, the data will be transformed before using t-tests to compare each pair of treatment arms. Otherwise, Wilcoxon rank sum tests will be used to compare each pair of treatment groups. For each of these secondary outcomes, the p-value boundaries in Table 5 will be used when considering whether to stop the trial or one arm of the trial.

Early stopping guidelines based on endpoints related to blood component usage or transfusion events are not proposed, because these endpoints are related to the economics of health care rather than patient safety.

7.5 Interim Reporting

7.5.1 Monthly Reports to Sites

Reports of accrual information, outstanding queries, and protocol violations will be distributed to the sites monthly.

7.5.2 Quarterly DSMB Reports

The DSMB will receive quarterly updates on:

- Site status;
- Accrual overall and by site;
- Study compliance issues; and
- The status of adverse event monitoring:
    - When the monthly summaries of Grade 3+ transfusion related events were prepared and discussed;
    - Whether the continuous review or monthly discussion raised issues which were reported to NHLBI as being of possible concern; and
    - Any actions taken in response to those concerns.

7.5.3 Semi-Annual DSMB Reports

The DSMB will meet every 6 months, either in-person or via teleconference. Reports will include:

- Baseline characteristics overall and by treatment arm;
- Formal interim looks at:
    - Primary study endpoint,
    - Highest grade of bleeding,
    - Death due to bleeding,
    - All cause mortality,
    - Bleeding severity (if validated scale available);
- Serious adverse events overall and by treatment arm;
- Transfusion-related events of all severity levels overall and by treatment arm;
- Site status;
- Accrual overall and by site; and
- Study compliance issues.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis Plan

The primary analysis for the primary endpoint, the percentage of patients with at least one episode of Grade 2 or higher bleeding, will be three one-degree-of-freedom chi-square tests, each comparing a pair of treatment groups. These tests will be carried out at the .017 significance level to adjust for the multiple comparisons.

These analyses will be done on an intention-to-treat basis. That is, patients will be counted in the treatment arm to which they were randomly assigned, even if they actually received transfusions that were not according to their assigned dosing strategy. Any such "crossovers" between treatment arms will tend to make the observed percentages of patients with Grade 2 or higher bleeding more similar between treatment arms than they would have been if all patients had been treated according to their assigned dosing strategy. Thus, an intention-to-treat analysis is conservative.

The most important secondary endpoints, capturing key data on costs and safety, are the total number of platelets dispensed, the total number of transfusion events, the highest grade of bleeding, and the bleeding severity score (if such a score has been validated and published by the end of the Platelet Dose trial, and the necessary information to calculate the score was collected). These endpoints capture the main components of transfusion costs and seriousness of bleeding. Differences between each pair of treatment arms for these three or four pre-specified key secondary outcomes will be tested, each at the .017 significance level, also on an intention-to-treat basis. For other secondary outcomes, only descriptive data will be presented.

Platelet usage, number of transfusion events, and the severity score (if continuous) are expected to have highly skewed distributions, so for these endpoints a log transform (or other suitable transform) will be carried out before using a t-test to compare treatment arms. If no acceptable transform can be found, a Wilcoxon rank sum test will be used instead of the t-test.

In the analysis of highest grade of bleeding, some grades are expected to be quite rare. Proc StatXact will be used for each of the 2x4 tables to obtain precise Monte-Carlo estimates of the p-value for an exact Kruskall-Wallis test for treatment differences, where the bleeding grades are considered ordered. If the severity score is ordinal, similar analyses will be carried out for that outcome.

Per-protocol and covariate-adjusted analyses will also be performed as secondary analyses.

8.2 Sample Size and Power

The primary endpoint for the study is the percentage of patients with at least one episode of bleeding at Grade 2 or higher, as determined by the Platelet Dose Trial Bleeding Scale.

Eighty-five percent power was desired to detect an absolute difference of 12.5% between any pair of dose strategies. The estimated percentage of patients who will experience Grade 2 or higher bleeding is 50%. Sample size for a chi-square test at the .017 level was calculated for a scenario with true percentages of 43.75% and 56.25%, assuming an interim monitoring plan with three interim looks and one final look. (See section 7.2.) Without taking into account loss to follow-up, 389 patients per arm (1167 patients in all) would be needed to achieve 85% power. This sample size would also provide 80% power to detect a treatment arm difference if the true percentages were 44.1% and 55.9% (an absolute difference of 11.8%) and 90% power to detect a treatment arm difference if the true percentages were 43.3% and 56.7% (an absolute difference of 13.4%). A sample size of 445 per arm would be needed for 90% power to detect a difference with true percentages of 43.75% and 56.25%.

Because the patients in this study will be hospitalized, loss to follow-up is expected to be no more than 10%. Conservatively allowing for 13.5% loss to follow-up, the target sample size is 450 patients per arm (1350 patients in all).

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