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Trial Name: Efficacy of Mirasol-treated Apheresis Platelets in Patients With Hypoproliferative Thrombocytopenia (MIPLATE)

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Statistical Analysis Plan

Protocol Title:	Clinical Effectiveness of Conventional Versus Mirasol-treated Apheresis Platelets in Patients with Hypoproliferative Thrombocytopenia (MIPLATE)
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2. APPROVALS

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Sponsor Statistical Representative Approval		
Consultant Statistician	DocuSigned by: Richard Cook Signer Name: Richard Cook Signing Reason: I approve this document Signing Time: 02-Sep-2020 | 11:32 AM PDT E996A47EF631[illegible]D9528260AC5040B58 Richard Cook, PhD	02-Sep-2020 | 11:32 AM PDT Date

3. TABLE OF CONTENTS

4. LIST OF ACRONYMS

ABO	Blood Type
AE	Adverse Event
Aph	Apheresis
aPTT	Activated Partial Thromboplastin time
BDRC	Blinded Data Review Committee
BSA	Body Surface Area
BSRI	Blood Systems Research Institute
BP	Blood Pressure
CCI	Corrected Count Increment
CI	Confidence Interval
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CMV	Cytomegalovirus
CPC	CPC Clinical Research
DMC	Data Monitoring Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
HLA	Human Leukocyte Antigen
HR	Heart Rate
IA	Interim Analysis
IgG	Immunoglobulin G
INR	International Normalized Ratio
ISBT	International Standard for the Transfer of Information Associated with Tissue Transplantation, Cellular Therapy and Blood Transfusion

ln	Natural Logarithm
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MIR	Mirasol
mmHG	Millimeters of Mercury
NGB	Normalized Background
NI	Non-Inferiority
PLT	Platelet
PPS	Per Protocol Set
PT	Preferred Term
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
REF	Reference
Rh	Rhesus factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SMQ	Standard Medical Query
SpO_2	Blood Oxygen Saturation
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TFL	Tables Figures and Listings
UADE	Unanticipated Adverse Device Effects

WHO	World Health Organization
WHO DDE	World Health Organization Drug Dictionary Enhanced

5. PREFACE

5.1. CPC Clinical Research Representative

Data analysis will be performed by CPC Clinical Research (CPC). Responsibility for overall data analysis will be held by the Head of Biostatistics and Programming. Questions regarding data analysis or statistical resources should be directed to:

Head of Biostatistics and Programming
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5.2. Statistical Analysis Plan Drafts and Approval Process

This Statistical Analysis Plan (SAP) and any subsequent versions (e.g. amendments) will be developed, reviewed and approved in accordance with CPC's Standard Operating Procedures (SOPs). The SAP will be version controlled.

When departures from conventions described in CPC SOPs occur, the rules set forth in this SAP take precedence over the general conventions.

All approved original versions of the SAP (e.g., implemented over the course of the project) will be retained by CPC until the Clinical Investigation Report (CIR) has been signed, at which time files will be transferred to Terumo BCT Biotechnologies, LLC.

6. INTRODUCTION

This SAP is designed to provide a comprehensive understanding of the statistical analyses utilized in describing/assessing all study primary, secondary, and exploratory endpoints as well as analyses related to safety and the interim analysis (IA) identified in the MIPLATE Clinical Investigation Plan (CIP) version 9.0.

The key secondary study endpoint will be analyzed separately by Blood Systems Research Institute (BSRI), now Vitalant Research Institute. Blood Systems Research Institute will be wholly responsible for all analyses related to the key secondary study endpoint. The details of these analyses are provided in Appendix II of this document.

6.1. Study Design

This is a prospective, multi-center, controlled, randomized study in which a non-inferiority (NI) design will be employed to evaluate the clinical effectiveness of Mirasol (MIR)-treated versus Conventional (CONTROL) apheresis (Aph) platelets (PLTs) in subjects with hematologic malignancies with hypoproliferative thrombocytopenia expected to have PLT count(s) $\leq$ 10,000/µL and requiring $\geq$ 2 PLT transfusions. Subjects will be randomized by a ratio of 1:1 (MIRASOL vs CONTROL group) using a permuted-block schedule stratified by investigational site and type of treatment (allogeneic transplant vs autologous transplant vs chemotherapy). Randomization will occur as close to the initiation of the first study transfusion as possible, within five (5) days prior to the anticipated initiation of PLT transfusion(s).

Subject participation will be for up to eighty-one 81 days; a 14-day screening period, a 28-day treatment period, and a 28-day follow-up period. Study Day (also referred to in this document as 'Day') 0 of the treatment period is defined as the day of the first study transfusion following randomization. The primary, secondary, and exploratory endpoints will be based on data captured during the treatment period (Day 0 to transfusion independence or Day 28, whichever comes first). Transfusion independence is defined as ten (10) days without a PLT transfusion prior to date of last contact or Day 28 whichever is earlier. The date of transfusion independence will be the 10th day without a PLT transfusion.

Daily bleeding assessments assess bleeding for the previous day. The first bleeding assessment to be used for analysis of primary and secondary endpoints etc., will be collected on Study Day 1 which assesses bleeding at Study Day 0. Bleeding assessments are planned to occur on Study Days 0-27 and at the post transfusion follow-up visit. Consequently, there will be a maximum of 28 bleeding assessment days used for analysis. The bleeding assessments to be included in analysis are greyed out the in schematic below.

Study Day	0 (first transfusion day)*	1	2	3	4	5	6	27	Post transfusion/ Follow-up (in some cases Study Day 28)
Day bleeding assessed (24 hours previous to Study Day)	-1	0	1	2	3	4	5	26	27 + 2-day window allowed for visit

*The day the subject receives their first post-randomization PLT transfusion will be considered Day 0. If the subject's PLT transfusion episode spans two (2) calendar days, the day the transfusion started will be considered Day 0.

A single IA will be conducted after approximately 279 randomized individuals satisfying the inclusion criteria for the modified intent to treat (mITT) analysis have completed the Post-transfusion period Follow-up/Early Termination visit.

6.2. Subject Selection

Subject study selection is governed by the inclusion/exclusion criteria defined in the CIP. Subjects that meet all inclusion criteria and no exclusion criteria and who have signed an informed consent form will be eligible for enrollment.

6.3. Study Objectives

The primary study objective is to determine if the hemostatic efficacy of MIR-treated plasma stored Trima Accel® Aph PLTs (MIRASOL) is non-inferior to Conventional plasma stored Aph PLTs (CONTROL) in subjects with hypoproliferative thrombocytopenia requiring PLT transfusions.

The secondary study objectives include comparing other efficacy and safety endpoints between the MIRASOL and CONTROL groups.

Unless otherwise specified, comparisons of each endpoint will be presented as (MIRASOL vs CONTROL). The primary analyses will be based on the observed data in the mITT set. The secondary and exploratory endpoints are summarized below. An in-depth discussion of the analysis of these

endpoints is provided in Sections 8.1 to 8.3, respectively. The safety endpoints are also summarized below and are discussed in detail in Section 8.4

6.3.1. Primary Endpoint

The primary study objective will be assessed through examination of the Primary Efficacy Endpoint where clinical effectiveness will be measured by comparing the days of grade 2 or higher bleeding over the treatment period between the MIRASOL and CONTROL groups. Specifically, this study will investigate whether MIR-treated Aph PLTs (MIRASOL) are non-inferior to conventional PLTs (CONTROL) by testing the null hypothesis that the MIRASOL arm is inferior to the CONTROL arm. The null hypothesis will be tested using a one-sided alpha level of 0.025. If NI is established, superiority of MIR-treated Aph PLTs vs Conventional PLTs will be tested using a one-sided alpha level of 0.025 by employing a closed "gate keeper" multiple testing strategy. An in-depth discussion of the analysis of the primary efficacy endpoint is provided in Section 8.1 of this document.

6.3.2. Secondary, Exploratory, and Safety Endpoints

The Key Secondary Endpoint is human leukocyte antigen (HLA) alloimmunization defined as a binary response indicating the occurrence of alloimmunization.

Additional **Secondary Endpoints:**

1. Occurrence of World Health Organization (WHO) ≥ grade 2 bleeding
2. Time to first day of WHO ≥ grade 2 bleeding
3. Occurrence of WHO ≥ grade 3 bleeding
4. Occurrence of PLT refractoriness defined as 2 sequential transfusion episodes, each with corrected count increments (CCIs) < 5000 measured 1-hour post-transfusion
5. Occurrence of PLT refractoriness as defined above and with a positive antibody test within 14 days before or after the onset of PLT refractoriness
6. Number of PLT transfusion episodes per subject, i.e., frequency of transfusion
7. Days of PLT support; the number of days from the first to the last PLT transfusion
8. PLT utilization (average number of PLTs transfused)
9. CCIs at 1 hour and ≥ 18 but < 30 hours post-PLT transfusion(s)
10. Total number of red blood cells (RBC) transfusions (number of units)/subject

Exploratory Endpoints:

1. Total number of units of PLTs transfused/day of PLT support
2. Total number of PLTs (PLT dose) transfused/body surface area (BSA)/day of PLT support
3. Interval between PLT transfusion episodes (days)
4. PLT refractoriness defined as 2 sequential transfusion episodes, each with CCIs < 7500 measured 1-hour post-transfusion

Safety Endpoints

1. Treatment-emergent adverse events (TEAEs)
2. Transfusion-related adverse events (AEs)
3. Serious adverse events (SAEs)
4. Unanticipated adverse device effects (UADEs)
5. Pulmonary events
   a. Subjects on assisted ventilation
6. All-cause mortality
7. Death due to bleeding as the primary or contributory cause of mortality

6.3.3. Sample Size

A total of approximately 558 mITT subjects will be randomized in a 1:1 fashion to MIRASOL:CONTROL. This sample size estimate accounts for 10% of subjects who are randomized but will never receive an on-study transfusion and thus, will not be included in the mITT analysis set and, therefore, the primary analysis. A total of 558 mITT subjects in MIRASOL versus CONTROL will provide approximately 85% power for establishing non-inferiority at the 1-tailed 0.025 level of significance (using a 2-sided 95% CI) accommodating a 10% relative increase in the mean rate of WHO grade 2 or higher bleeding (i.e. $\mu T / \mu C = 1.1$).

7. Database Description

A comprehensive database description can be found by referencing the Terumo BCT CTS-5030 Data Management Plan (DMP). Two data sources will be used for study analysis, a clinical study database and a central laboratory database.

The clinical study database will be populated by an Electronic Data Capture (EDC) system which is developed and hosted by IBM Clinical Development using the eClinicalOS™ software platform. Data integrity will be maintained by conducting both internal and external data checks as described in the DMP. The clinical database will be used to create tables, figures, and listings (TFLs) for both the interim and final analyses.

Additionally, HLA antibody results are maintained exclusively by BSRI. Blood System Research Institute will be responsible for analyzing all data related to HLA and alloimmunization. Details of this analysis are provided in Appendix II of this SAP.

7.1. Creating Analysis Data Sets

To enable analysis of study data, it will be necessary to derive analysis datasets from raw variables in the clinical study database. All data and processing will be completed using SAS® version 9.4 or higher.

7.2. Validation of Data and Analysis Programs

All programs created by CPC to create analysis datasets, produce TFLs, or to perform statistical analysis will be generated according to CPC SOP-BDM-C-002: Developing Data Analysis Programs. Additionally, all datasets, output, and statistical analysis produced by CPC will be validated according to CPC SOP-BDM-C-003: Statistical Validation.

7.3. Archiving Data and SAS® Files

Following database lock, the SAS® programs used to analyze data for the final CIR will be executed and archived according to CPC SOP-BDM-C-002: Developing Data Analysis Programs.

The final analyses will be conducted on locked clinical study data using SAS® version 9.4 or higher. Unless specified otherwise, all analyses related to the primary, secondary and exploratory endpoints will involve the direct comparison of the MIRASOL and CONTROL arms.

To ensure integrity and internal consistency of all data points used for the IA, the biostatistics group will define data elements needed for the IA and work with the clinical data manager to determine which electronic case report forms (eCRFs) need to be cleaned. The identified data elements and timing of the IA will then be communicated to the appropriate study team members to facilitate timely collection and cleaning in preparation for the IA. All efforts will be made to fully monitor and resolve critical queries on the IA data elements. At the time of the data cut for the IA, all data in the clinical database will be used. As this is an ongoing study, outstanding queries may remain, and/or some data entered at the time of the data cut may not have been monitored.

7.4. Analysis Conventions

The following general conventions will be used for conducting all statistical analyses, where, departures from these conventions are defined in a more precise manner in specific sections of this SAP. In these instances, rules established in the specific sections take precedence over the general convention.

- Formal hypothesis testing will be performed on the primary outcome using a closed testing procedure with a first test of non-inferiority followed by a test of superiority if non-inferiority is demonstrated.
- Key secondary and secondary efficacy outcomes will be tested but viewed as supportive and exploratory.
- The distribution of continuous variables will be summarized using means, standard deviations (SD) and/or standard errors, medians, minimums (or 25th percentile), and maximums (or 75th percentile) and the number of subjects with non-missing data.
- Mean/median/quartiles are presented to one decimal more than the measured value. Minimum/Maximum are reported to the same number of decimals as the measured value. Standard deviation is presented to two decimals more than the measured value.
- Summary of discrete variables will consist of the number and percent of responses in each category. All percentages will be rounded to one decimal place. The count and percentage of responses will be presented in the form of "XX (XX.X%)", where the percentage is in parentheses. If the count is "0" then the percentage may not be presented to draw attention to the non-zero count cells. If zero percentages are displayed these will be shown as "0.0%". If the percentage is "100", the decimal place may be dropped. In addition, the decimal place may also be dropped due to space constraints within a table where this does not impact the interpretation of results.
- All Medical History and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1.
- All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) version dated 01Sep2016.
- Uncoded AE terms will be included with a System Organ Class (SOC) and Preferred Term (PT) of "Uncoded".
- Leading zeros will be used for decimal values less than one. For example, "0.05" will be used rather than ".05.
- All tables will clearly indicate the sample sizes contributing to the summary data in the column heading and labeled as "*Treatment* (N=)". For example, if a table reports data for the Full Analysis Set (FAS) population, N would represent all subjects in the FAS. If a table reports data for the Safety Set (SS), N would represent all subjects in the SS. Within the table the small "n" will represent the number of subjects within the population of interest who have non-missing data or data otherwise available for the summary measures of interest (i.e. the denominator for a subset of the overall population being presented in the summary). If no data are available for a TFL, the output will be produced with "No data to display". Footnotes which are data driven may be applied to the TFLs as needed. These changes will not necessarily be made to the mock TFLs.
- Percentages are calculated out of the header N unless otherwise footnoted.
- Duration of periods of time will be calculated in days as (stop date – start date + 1) in order to include both the starting day and final day of the periods of time. Conversions to weeks, months, or years will be calculated as days/7, days/30.4375, or days/365.25, respectively.
- In general, missing values will be handled as follows: for continuous variables at baseline, missing values will be excluded from calculation of summary statistics and the n of subjects reporting will be reported. For categorical values at baseline, the number and percent of subjects with missing values will be displayed. Handling of missing postbaseline values will depend on the analysis.

7.4.1. Dropouts and Missing Data

Handling of subject dropouts and other forms of missing data with regard to the primary endpoint will be discussed in Section 8.1. Handling of subject dropouts and other forms of missing data with regard to key secondary endpoints is the responsibility of BSRI. No imputation of missing data will be applied to secondary, exploratory or safety endpoints unless otherwise specified.

7.4.2. Adjustments for Covariates

Covariate adjustment will be utilized in both supporting and subgroup analysis of the primary endpoint and is discussed in Section 8.

7.4.3. Multi-center studies

Data from each of the study sites will be pooled for summarization and analysis unless otherwise specified.

7.4.4. Multiplicity Issues

As described in FDA's Guidance for Industry: Non-inferiority Clinical Trials, testing for superiority after successfully establishing non-inferiority is possible so long as Type I error control is maintained. For this study, a sequential testing strategy will be employed, whereby if the primary endpoint is positive in the sense that non-inferiority is concluded, a test for superiority will be performed for the primary endpoint with the same one-sided type I error rate.

No adjustments for multiple comparisons/testing will be performed for the key secondary, secondary or exploratory endpoints.

7.5. Analysis Populations

The study analysis populations (sets) are defined in Sections 7.5.1 thru 7.5.4.

7.5.1. Full Analysis Set

The FAS is defined as containing all randomized subjects, wherein subjects will be analyzed based on their assigned treatment group (MIRASOL or CONTROL) at the time of randomization.

7.5.2. Modified Intent-to-Treat Analysis Set

The mITT analysis set is defined as containing all randomized subjects who undergo at least one (1) study transfusion post-randomization based on the treatment group to which they were randomized. Subjects will be analyzed according to the treatment group (MIRASOL or CONTROL) they were assigned at randomization.

7.5.3. Safety Set

The SS is defined as containing all subjects who have been randomized and undergo at least one (1) PLT transfusion post-randomization, independent of the outcome or successful completion of the procedure. Subjects will be analyzed according to the majority treatment (transfusion type: MIRASOL or CONTROL) received. If there is a tie, i.e. no majority treatment exits, then the subject will be classified into the treatment group to which they were randomized.

7.5.4. Per Protocol Set

The Per Protocol Set (PPS) is defined as containing all randomized subjects who undergo at least 75% of post-randomization PLT transfusions as per the protocol treatment allocation and have not experienced any major protocol deviations (as described in Section 7.12). For instance, if a subject is randomized to

the MIRASOL arm and has 4 transfusions, 3 of those transfusions must contain MIR-treated Aph PLTs if the subject is to be included in the PPS. Similarly, if the subject had 3 transfusions, all 3 transfusions must contain MIR-treated Aph PLTs if the subject is to be included in the PPS. Subjects eligible for the PPS will be analyzed according to the treatment group to which they were assigned at randomization.

7.6. Definition of Baseline Value

Baseline is defined as the data point collected the closest, but prior to, the date and time when the first study transfusion is administered. In cases where the date is the same and the times are unknown, assessments taken on the same day are considered baseline.

7.7. Calculation of Study Day and Treatment Period

The day the subject receives their first post-randomization PLT transfusion will be considered Day 0. If the subject's PLT transfusion episode spans two calendar days, the day the transfusion started will be considered Day 0.

The treatment period is defined as the period of time from Day 0 through Day 27 or to the day of transfusion independence, defined as the last of ten (10) successive days after the last PLT transfusion (on- or off-protocol), whichever occurs first. Bleeding assessments are conducted at baseline and are to be conducted every day from Day 0 until the post-transfusion follow-up visit or early termination visit.

7.8. Definition of Visit or Windows

Visit labels, as collected in the database, will be used and no visit windows will be calculated.

7.9. Display of Treatment Groups

Unless specified otherwise, data will be summarized by study arm (MIRASOL vs CONTROL).

Treatment groups (arms) will be displayed as follows with respect to labels and ordering. Total columns may be provided for baseline assessments.

Groups	Definition
MIRASOL	Mirasol PLTs (MIR PLTs): LR-Trima Accel® Aph-pathogen reduced (PR)-plasma PLT
CONTROL	Reference PLTs (REF PLTs): LR-Aph-plasma PLT

7.10. Subject Demographics and Baseline Characteristics

Subject demographics including date of birth, age (years) at informed consent, age group (Age <18, Age 18-65, Age > 65), sex, ethnicity (Hispanic and non-Hispanic), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, and Multiple), height, weight, and body surface area (BSA) will be listed by subject and summarized. Childbearing potential/pregnancy information for females will be listed. Age will be calculated as a continuous variable, where, the calculated value will be used in creating the different age groups. All demographic and baseline characteristics will be listed, and summaries will be generated using the mITT set and the SS. Summary tables will be presented by treatment group.

7.11. Concomitant Medication, Medical History and other Baseline Data

Concomitant medications will be listed and summarized.

Diagnosis and treatment including treatment type strata of allogeneic transplant, autologous transplant, and chemotherapy will be listed and summarized.

Medical and surgical history and history of transfusions will be listed by subject.

Blood type (ABO), ABO incompatibility and Rhesus factor (Rh) will be listed by subject.

7.12. Protocol Deviations

Subjects who are randomized into the study but who do not meet all major inclusion/exclusion criteria will be considered as having major protocol deviations. All protocol deviations reported by hospital study sites will be summarized by deviation type (major/minor) the for the FAS population. All protocol deviations reported by hospital study sites including non-compliant transfusions and protocol deviations reported by blood centers will be listed for all screened subjects. Protocol deviations due to the COVID-19 pandemic can be identified through the standard text of 'Due to COVID-19' in the text of the deviation. A Blinded Data Review Committee (BDRC) will be formed and will review and classify possible protocol deviations for all subjects in the FAS as major or minor in a blinded fashion according to the BDRC Charter.

International Standard for the Transfer of Information Associated with Tissue Transplantation, Cellular Therapy and Blood Transfusion (ISBT) codes and corresponding definitions provided by the sponsor will be used in a read only manner to identify whether or not a platelet product meets the criteria either for the CONTROL group or the MIRASOL group transfusion per the CIP

Non-Compliant Transfusions are platelet transfusions that do not meet the platelet product requirements of the CIP. For subjects randomized to MIR treatment, ISBT codes categorized as anything other than 'MIRASOL' or 'Control Allowed' meet this criterion. For subjects randomized to Reference (REF), ISBT codes categorized as anything other than 'Control Allowed' meet this criterion. Non-compliant transfusions are protocol deviations, but they cannot be reported as protocol deviations in the database because that would potentially unblind users of the database. Instead, non-compliant transfusions are identified through ISBT codes and will be summarized and listed as separate protocol deviations.

7.13. Treatment Exposure

Exposure to platelet transfusions will be conducted on the mITT set and the SS by reason for transfusion.

One or multiple study platelet transfusions can occur anytime from Study Day 0 to Study Day 27 per subject. If a subject received a platelet unit within four (4) hours of completion of transfusion of the preceding platelet unit, these transfusions will be considered part of a single platelet transfusion episode in analyses.

Additional blood products transfused will be analyzed based on the SS. The number of blood products transfused (other than PTLs), type of blood product transfused, and for RBC transfusions, whether the RBCs were leukocyte-reduced, will be summarized.

7.14. On- Off-Protocol Transfusions

On- and Off-Protocol Transfusion definitions are as follows:

Off-Protocol Transfusion: any kind of PLT transfusion, other than those to which the subject was randomized (MIR PLTs or REF PLTs), regardless of the reason for the transfusion. For subjects

randomized to MIR treatment (MIRASOL), ISBT codes defined by the sponsor as 'Control Allowed' or 'Control NOT Allowed' meet this criterion. For subjects randomized to CONTROL, ISBT codes defined by the sponsor as 'MIRASOL' or 'MIRASOL Not Used' meet this criterion.

On-Protocol Transfusion: non-MIR or MIR treated platelet product transfused according to randomization assignment. For subjects randomized to MIR treatment (MIRASOL), ISBT codes defined by the sponsor as 'MIRASOL' or 'MIRASOL Not Used' meet this criterion. For subjects randomized to CONTROL, ISBT codes defined by the sponsor as 'Control Allowed' or 'Control NOT Allowed' meet this criterion.

On- and off-protocol platelet transfusions will be reported on the SS and summarized by treatment group and reason for transfusion, i.e. prophylactic, therapeutic (bleeding event), and other. The total number of platelet transfusions and the number of transfusions on- and off-protocol will be reported. The mean, median, minimum and maximum number of transfusions per subject will be reported. The number and percent of subjects with at least 1 on-protocol transfusion will be reported along with the median, minimum, and maximum duration of the transfusion period in days. The number and percent of subjects who had at least 75% of transfusions on-protocol (part of the PPS definition) will also be reported.

Each subject's transfusion will be listed along with on- or off-protocol and non-compliance status described in Section 7.12.

7.15. Subject Disposition

Subject disposition will be listed and summarized. The number of subjects screened, number of subjects in the FAS, mITT set, PPS and SS, the subject's final study status, and the number of subjects terminating the study early with reasons for early termination will be summarized for all subjects.

Subjects with Inclusion/Exclusion criteria deviations will be listed by subject.

8. Efficacy Analysis

A single primary efficacy endpoint will be considered and investigated using a NI design. The primary efficacy endpoint is defined as the number of days on which bleeding was assessed and WHO grade 2 or higher bleeding was evident over the treatment period. The maximum number of days with bleeding assessments will be twenty-eight (28) as this is the duration of the treatment period. Bleeding events are defined using criteria according to the WHO Grading Scale for Bleeding. Appendix I contains the WHO Grading Scale for Bleeding annotated with the study's Bleeding Assessment (MIPLATE Annotated eCRFs) variable identifiers (Bx) and answers that correspond to the bleeding status. Subgroup analyses involving the primary efficacy endpoint will also be conducted.

8.1. Primary Endpoint

Bleeding assessments based on the WHO Grading Scale for Bleeding will be conducted at baseline to assess eligibility prior to randomization, as well as daily starting on Day 0 and continuing to the post-transfusion bleeding assessment OR until transfusion independence (the last day of ten [10] consecutive days without a PLT transfusion). Each bleeding assessment will document the WHO Bleeding Scale components observed over the course of the prior calendar day, from 00:00 to 23:59. As such, the analysis of the Primary Endpoint, and Secondary Endpoint #2, will be based on bleeding assessments collected on Day 1 thru Day 28 which represent bleeds which occurred on Days 0-27.

The total number of days with WHO grade 2 or higher bleeding is obtained by counting the total number of calendar days (00:00 to 23:59) on which bleeding was assessed and found to be present. For example, if a subject has WHO grade 2 bleeding on Day 1, grade 2 bleeding on Day 2, and grade 3 bleeding on Day 3, this is considered 3 days of grade 2 or higher bleeding. Hematomas (bruises), petechiae, and purpura

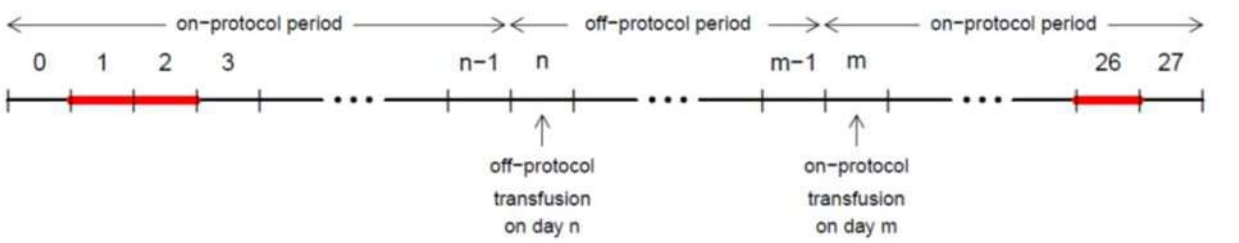
(e.g., types of bleeding that occur under the skin) represent unique cases in which they are only counted as additional days of bleeding if they are new or manifest in another anatomical location.

8.1.1. Primary Analysis

The MIRASOL vs CONTROL group will be compared with respect to the number of days of WHO grade 2 or higher bleeding. This will be carried out by fitting a negative binomial regression model with an offset defined as the natural logarithm (ln) of the number of days that bleeding was assessed in order to account for the fact that subjects may have different numbers of bleeding assessment days. As an example, if a subject had bleeding assessed on only 10 of 28 days, an "offset" of ln(10) bleeding assessment days is incorporated into the linear predictor of the model. Similarly, if bleeding is assessed on each of the full 28 days of the planned treatment period, an offset of ln(28) bleeding assessment days is incorporated. Adjustment using this offset will ensure that bleeding *rates* are calculated and compared between treatment groups and that the variable number of days with bleeding assessments across individuals is appropriately dealt with. Subjects who obtain transfusion independence prior to Day 28 will be assumed to have zero bleeding days between the date of transfusion independence and Day 27 and treated as if they had bleeding assessed on each of those days; these days will therefore contribute to the total number of bleeding assessment days used to calculate the offset. Subjects who drop-out of the study before Day 28 for reasons other than transfusion independence will contribute bleeding data for each of the days bleeding was assessed prior to the time of drop-out; bleeding status will not be simulated beyond the time of drop-out since the use of an appropriately computed offset deals with the variable duration of follow-up.

The handling of data following the administration of an off-protocol transfusion requires discussion. Here an off-protocol transfusion is defined as the transfusion of any kind of PLT product that differs from that to which the subject was randomized (i.e. MIRASOL or CONTROL).

The timeline diagram provided below demonstrates the definition of an off-protocol window, which we sometimes refer to as an off-protocol interval of time. Consider an individual who was recruited and received on-protocol transfusions as needed from day 0 to day *n-1*. On Day *n* they received an off-protocol transfusion and on Day *m* they received their first subsequent on-protocol transfusion; no off-protocol transfusions were received beyond Day *m*. In order to avoid attributing bleeding outcomes to the randomized treatment arm when an off-protocol product is delivered we partition the full treatment period as follows. We define the intervals from day 0 to *n-1* and *m* to Day 27 as *on-protocol intervals,* and days *n* to *m-1* as an *off-protocol interval*. In the figure below bleeds are represented by red lines on Days 1-2 and on Day 26 for illustration.



To mitigate against the effect of the off-protocol transfusions in the primary endpoint analysis, bleeding data will be simulated for the off-protocol windows (e.g. intervals such as *[n, m-1]* above) using an

individual-specific bleeding rate estimated as follows. If individual *i* has any off-protocol intervals of time, then an individual-specific bleeding rate will be computed as $r_i^{on}=B_i^{on}/N_i^{on}$ where B_i^{on} is the number of on-protocol days during which this individual experienced, and had documented, at least WHO grade 2 or higher bleeding. N_i^{on} is the number of days on which bleeding was assessed during the on-protocol intervals for this subject. Then a) the number of days bleeding was assessed during the off-protocol interval will be computed (N_i^{off}) and b) the number of these days during which WHO ≥ 2 grade bleeding is present will be simulated (B_s^{off}) based on a right-truncated Poisson distribution using the individualized bleeding rate (r_i^{on}). The right-truncation limit will be the total number of off-protocol days (N_i^{off}) since there cannot be more bleedings days than there are days at risk. Specifically, for each individual, counts will be simulated from a Poission distribution using r_i^{on} x N_i^{off} as the mean. A simple rejection sampling technique [1] will be used to sample from the right-truncation distribution whereby all values generated which exceed the right truncation limit will be ignored until one is generated that satisfies the right truncation condition. This value will be labelled B_i^{off}. Then the total $B_i^{on} + B_i^{off}$ will be taken as the number of bleeds for that individual experienced over $N_i^{on}+N_i^{off}$ days of assessments; then $\ln(N_i^{on}+N_i^{off})$ will be used as the offset.

If the bleeding rate estimated based on available data $r_i^{on} = 0$ then there will be no bleeding days simulated for the off-protocol days ($B_i^{off}=0$) and the offset will still be calculated as $\ln(N_i^{on}+N_i^{off})$. Note that for individuals whose last transfusion is off-protocol, at most 10 days of bleeding data after the last transfusion will be simulated as patients going ten (10) days without a transfusion will have acquired transfusion independence.

On occasions where a subject receives a mix of off-protocol and on-protocol units on the same day, they will be considered in an on-protocol period on that day. Transfusions can last more than one calendar day. The daily on- and off-protocol statuses will be assigned for the day the transfusion(s) starts. For subjects whose last transfusion is off-protocol, bleeding will be simulated until the subject completes the transfusion period or reaches transfusion independence. If the subject achieves transfusion independence prior to completing the transfusion period, the rules for transfusion independence will take over and subjects will be assumed to have zero bleeds and full follow-up from the day of transfusion independence until Day 27 inclusive (i.e. the remainder of the transfusion period).

Unless otherwise stated any subsequent analysis herein referring to the primary endpoint method will include the individualized simulated bleeding data for the off-protocol periods of time. This simulation will be done twice. Once at the IA and once at the final analysis. The set of simulations done for the primary efficacy analysis will be used for all subsequent analyses wherein off-protocol intervals are called to use simulated bleeding data.

8.1.2. Secondary Analyses

First Secondary Analysis: Off-Protocol Intervals Included with No Adjustments

In a secondary analysis of the primary outcome all available bleeding assessment data, whether collected on- or off-protocol, will be used and attributed to the randomized treatment in the spirit of an intention to treat analysis. No imputation will be carried out for bleeding status on days following drop-out as the offset deals with censoring and the resulting variation in the days at risk.

Second Secondary Analysis: Off-Protocol Intervals Excluded

In another secondary analysis of the primary outcome, bleeding data will be excluded during off-protocol intervals and the offset will be computed based on the number of on-protocol days which bleeding was assessed for the negative-binomial model. Subjects who obtain transfusion independence while on-protocol will be assumed to experience no further WHO grade 2 or higher bleeding and treated as if they

had bleeding assessed on each of those days. No bleeding data will be imputed following dropout if it occurs and the offset will accommodate different durations of time at risk.

First Sensitivity Analysis: Imputing Bleeding Status for Missing Data

In the analyses discussed to this point, on-protocol days without bleeding data recorded are not counted in the total number of days at risk. An additional sensitivity analysis will be carried out using a negative binomial model for imputing bleeding status on the on-protocol days when bleeding data is missing [2]. First, off-protocol periods of time will use the simulated bleeding rate simulated for the primary analysis in Section 8.1.1. Then the imputation for missing bleeding assessment days will be carried out by fitting an auxiliary negative binomial imputation model to the available data including these covariates: age, sex, treatment arm, treatment type strata, and pre-treatment platelet count. The imputation model will be run fifty (50) times and PROC MIANALYZE will be used to adjust variance estimates for multiply imputed data.

Second Sensitivity Analysis: Poisson Model with Robust Variance

In addition to fitting a negative binomial model to the data from completed and simulated observations, a Poisson model with robust variance estimation will be fit as a sensitivity analysis to the primary analysis.

8.1.3. Assessment of Non-Inferiority and Superiority

An NI analysis will be carried out to assess the primary efficacy endpoint with the null hypothesis being the MIRASOL arm is inferior to the CONTROL arm and the alternative hypothesis being the MIRASOL arm is non-inferior to the CONTROL arm. The null (H_0)and alternative (H_a) hypotheses are defined as:

$$H_0: \frac{\lambda_T}{\lambda_C} \geq \delta \text{ and } H_a: \frac{\lambda_T}{\lambda_C} < \delta \text{ respectively}$$

where λ_T is the mean rate of the MIRASOL group, λ_C is the mean rate of the CONTROL group, and, δ is the NI margin. To facilitate analysis, the null and alternative hypotheses are expressed on the natural logarithmic scale and take on the following forms.

$$H_0: ln(\lambda_T) - ln(\lambda_C) \geq ln(\delta) \text{ and } H_a: ln(\lambda_T) - ln(\lambda_C) < ln(\delta)$$

Specifically, a 95% confidence interval (CI) will be created about the point estimate (equivalent to a one-sided CI with an alpha level of 0.025) to test the null hypothesis, where the point estimate is defined as$ln\left(\lambda_T\right) - ln\left(\lambda_C\right)$. This parameter estimate will be obtained by fitting a negative binomial regression model with a natural log link, the response being the total number of WHO ≥ 2 grade bleeding days, a single treatment covariate which is 1 for individuals assigned to the MIRASOL product and 0 for those assigned the CONTROL, and with an offset of the ln(number the number of days bleeding was assessed).

If the upper bound of the 95% CI is less than$ln(\delta)$, then, NI of the MIRASOL arm relative to the CONTROL arm is inferred. Conversely, if the upper bound of the 95% CI is greater than or equal to $ln(\delta)$, NI is not demonstrated. In this study, the NI margin is 1.6. Justification of the value of 1.6 for the NI margin is provided in the CIP.

If NI is demonstrated, superiority of the MIRASOL arm versus the CONTROL arm will be examined. Superiority of the MIRASOL arm compared to the CONTROL arm will be demonstrated if the upper bound of the 95% CI is less than zero (ln(1)=0).

Results of the primary analysis will be displayed by treatment group and will include the average number of grade 2 or higher bleeds (including minimum and maximum), the average duration of on-protocol days or days of transfusion dependence (including minimum and maximum), the estimate of the mean rate, the natural logarithm of the estimate of the mean rate and the corresponding 95% CIs. The value of the point estimate, i.e. $ln\left(\lambda_T\right) - ln\left(\lambda_C\right)$, and its corresponding 95% CI will also be displayed.

An NI analysis will also be carried out to assess the secondary efficacy endpoint of proportion of subjects with ≥ grade 2 bleeding (Section 8.2.2 below). We let p_t and p_c represent the probability of a patient experiencing WHO >= grade 2 or higher bleeding in the MIR or CONTROL arm, respectively. With an NI margin of 1.2, the null hypothesis is H0: $p_t/p_c > 1.2$ (MIR has more than a 20% higher probability of a patient experiencing at least one WHO ≥ grade 2 bleed compared to CONTROL). The alternative hypothesis is HA: $p_t/p_c \leq 1.2$ (MIR has no more than a 20% higher relative bleeding rate compared to CONTROL). The risk difference will be calculated using the Wald Test.

8.1.4. Supporting Analyses

First Supporting Analysis: Study Site and Type of Treatment Included as Covariates

Supporting analysis will be conducted with regard to the Primary Efficacy Endpoint although no statistical inferences will be made regarding these analyses, i.e. p-values calculated will be considered descriptive only. A supporting analysis will be conducted by including the study site and type of treatment (allogeneic transplant vs autologous transplant vs chemotherapy) variables in the model. Treatment group by site and type of treatment interactions will be reported where other interaction terms may also be considered. To facilitate interpretation, exponentiated results will be provided.

Second Supporting Analysis: Analysis of Per Protocol Population

Additionally, in a supporting sensitivity analysis, a repeat of the process used to analyze the Primary Endpoint will be conducted based on the PPS.

Third Supporting Analysis: Analysis excluding data from a single site

In another supporting sensitivity analysis, data from John's Hopkins University will be excluded to assess the impact of data from this site. This sensitivity analysis of the primary endpoint is to assess the impact of data from this site due to non-compliance findings that have been audited and resolved.

8.1.5. Subgroup Analyses

After all primary, secondary, and supporting analyses are completed; a subgroup analysis of the primary endpoint will be conducted. All subgroup analyses will follow approaches for handling off-protocol intervals performed on the first analysis of the primary endpoint and described in Section 8.1.1. The following analyses, however, will include an interaction term between subgroup and treatment. The interaction p-value will be presented for each subgroup in summary table. The full model will be summarized for interactions significant at the 0.05 alpha level.

1. Age <18, 18-65, and >65 years)
2. Sex (Male/Female)
3. Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, and Multiple).
4. Ethnicity (Hispanic and non-Hispanic)

NOTE: Groups may be collapsed if an individual group represents <10% of the study population.

8.2. Secondary Endpoints

8.2.1. Key Secondary Endpoint

The Key Secondary Endpoint of HLA alloimmunization will be compared between the two groups using Fisher's exact test with a 2-sided test at the 0.05 level of significance. Blood System Research Institute will assume all analytic responsibilities of the Key Secondary Efficacy Endpoint for safety, interim and final analysis and details of this analysis are provided in Appendix II generated by BSRI.

8.2.2. Additional Secondary Endpoints

The additional secondary study endpoints and their corresponding analyses are discussed in detail below. All Secondary Endpoints will be compared based on study arm, (MIRASOL vs CONTROL), using the mITT set. Each of the ten additional Secondary Endpoints, as well as their respective analytic approaches is discussed as follows:

1. Proportion of subjects with ≥ grade 2 bleeding.

For each study arm, the proportion of subjects with at least 1 day of grade 2 or higher bleeding Day 0 through Day 27 (or until transfusion independence is achieved) will be calculated, where, p_t denotes the proportion of the MIRASOL group and p_c denotes the proportion for the CONTROL group. p_t and p_c will be calculated using the equations below:

$$p_T = \frac{Number of Subjects with \geq grade 2 Bleeding (Test Arm per mITT)}{Total Number of Subjects in the Test Arm per mITT}$$

$$p_C = \frac{Number of Subjects with \geq grade 2 Bleeding (Control Arm per mITT)}{Total Number of Subjects in the Control Arm per mITT}$$

The difference between the MIRASOL and CONTROL arms (p_T- p_C) will be reported along with the 95% CI about this difference. The 95% CI and the corresponding p-value will be generated using Fisher's exact test to test the superiority null hypothesis of p_t/p_c=1. Negative values of the reported difference favor the MIRASOL group.

2. Time to first grade 2 or higher bleed

The time to first grade 2 or higher bleeding will be analyzed using a log rank test comparing survival curves stratified by treatment group. The timeframe under consideration is defined from the day of the subject's first post randomization PLT transfusion to the day the subject experiences their first grade 2 or higher bleed. Subjects that do not experience a grade 2 or higher bleed will be censored at Day 27 or at date of transfusion independence (10th day without a PLT transfusion prior last follow-up day or Day 27 whichever is earlier), where appropriate. Subjects that do not complete the study or are lost to follow-up will be censored on the date of their last study visit in the treatment period. A Kaplan-Meier (KM) plot contrasting the two study arms will also be generated to provide a visual representation of probability of remaining free of a WHO grade 2 or higher bleed as a function of time since first post-randomization transfusion.

3. Proportion of subjects with ≥ grade 3 bleeding

This analysis will be identical to that conducted for Secondary Endpoint number 1 except proportions for each study arm will be calculated based on the number of subjects with grade 3 or higher bleeding.

4. Proportion of subjects with PLT refractoriness defined as 2 sequential transfusion episodes, each with CCIs < 5000 measured 1 hour post-transfusion.

PLT refractoriness is defined as 2 sequential transfusion episodes with CCIs < 5000 measured 1 hour post-transfusion for the transfusion episode. The count increment (CI) is calculated as follows: *CI =(Post-transfusion[1 hour] PLT (PLTs/µL) – Pre-transfusion PLT (PLTs/µL)).*

Typically, the platelet count is expressed in platelets/µl.

The CCI is calculated using the following equation considering a single transfusion episode at a time:

$$CCI = \frac{(\text{Post-transfusion[1 hour] PLT (PLTs/µL)} - \text{Pre-transfusion PLT (PLTs/µL))} \times BSA\ (m^2)}{\text{Number of PLTs in component (PLTs)} (\times 10^{11})}$$

where, BSA (m^2) = 0.007184 × Height (cm)$^{0.725}$× Weight (kg)$^{0.425}$

where, Number of PLTs in component (PLTs)(x10^{11})=Platelet yield

and where, Platelet yield = [Platelet Concentration (10^6/µL) x Platelet Unit Volume (mL)]/100

If the full transfusion volume was not transfused the partial volume transfused will be use in this calculation. The platelet concentration remains unchanged, regardless of volume transfused.

The value for the number of platelets transfused (infused dose) is always expressed in multiples of 10^{11}.

If two successive CCIs < 5000 measures are not observed, then PLT refractoriness is not attained. Based on these criteria among the patients in the mITT population, the proportion of subjects who experience PLT refractoriness for the MIRASOL (π_T) and CONTROL (π_C) groups are defined as:

$$\pi_T = \frac{NumberofSubjectswithpositivePLTrefractoriness(TestArm)}{TotalNumberofSubjectsintheTestArm}$$

$$\pi_C = \frac{NumberofSubjectswithpositivePLTrefractoriness(ControlArm)}{TotalNumberofSubjectsintheControlArm}$$

The difference between the MIRASOL and CONTROL arms (π_T- π_C) will be reported along with the 95% CI about this difference. Negative values of the reported difference favor the MIRASOL group. A test of the null hypothesis that this difference is zero will be carried out by Fisher's exact test.

NOTE: The pre-transfusion episode platelet count closest and prior to the transfusion episode should be used for all CCI calculations. The pre-transfusion episode platelet count should be collected within 24 hours of the start of the transfusion episode to be clinically meaningful in relation to the effect of the

transfusion on the post-transfusion platelet count. The post transfusion platelet count to calculate the 1-hour CCI is measured by a platelet count between 10 minutes and ≤ 4 hours post-transfusion episode. The post transfusion platelet count to calculate the 24-hour CCI (≥ 18 but < 30 hours post-transfusion episode) is measured by a platelet count within the defined window post-transfusion episode.

5. Immune PLT refractoriness will be subjects with PLT refractoriness as defined above and who also have a positive antibody test within 14 days before or after the onset of PLT refractoriness

Blood System Research Institute will assume all analytic responsibilities for this analysis. Details are provided in Appendix II.

6. Number of PLT transfusion episodes per subject, i.e., frequency of transfusion

The analytic approach used to investigate secondary endpoint # 6 will be based on a negative binomial model. The total number of PLT transfusion episodes (regardless of whether or not the transfusion is determined to be "off-protocol") will be calculated for each subject, and the negative binomial model will include only the covariate for treatment group which will give a regression coefficient; the exponentiated regression coefficient is an estimate of the ratio of the transfusion rate for the treatment groups. The offset in the negative binomial model will be the natural log of time in days from Day 0 to transfusion independence, study dropout or end of the 28-day treatment period for each subject.

7. Days of PLT support; the number of days from the first to the last PLT transfusion

The number of days from the first to the last PLT transfusion will be analyzed using a Cox regression model with the treatment group serving as the lone covariate. Subjects will be censored at Day 27 or on their last study visit in the treatment period. Reported results will consist of the hazard ratio along with the corresponding 95% CI and p-value. A hazard ratio greater than 1 will favor the MIRASOL group because it will correspond to a shorter duration of platelet support. A KM plot contrasting the two study arms will also be generated to provide a visual representation of survival probability as a function of study duration.

8. Platelet utilization rates (average number of PLTs transfused)

The platelet utilization rate will be calculated for each individual by adding the number of platelets transfused (10^{11}) during the treatment period divided by the total number of transfusion units for each individual. The number of PLTs transfused will be included regardless of whether or not the transfusion is determined to be "off-protocol".

The difference between the platelet utilization rate received in the MIRASOL (μ_T) and CONTROL (μ_C) groups will then be estimated as $\mu_T - \mu_C$, and a test of equality will be carried out using a pooled t-test. A 95% CI for $\mu_T - \mu_C$will also be reported; negative values of $\mu_T - \mu_C$ favor the MIRASOL group in the sense that it reflects a lower average number of platelets required in support of care.

9. CCIs at 1 hour and ≥ 18 but < 30 hours post-PLT transfusions

A linear mixed-effect model [3] will be fitted with a single covariate indicating the randomized treatment assignment and a subject-level random effect introduced to model the between-subject heterogeneity and accommodate a within-subject dependence in CCI values. The coefficient of the binary treatment covariate will be estimated and a 95% confidence interval for it will be computed along with a p-value for the test of no effect. These results will be supplemented by an estimate of the group means based on the linear mixed-effect model.

As per the CIP, collection of subject PLT count ≥ 18 but < 30 hours post-PLT transfusion episode is not mandatory. As a result, there may be limited amount of data available to fit the model proposed. If the model will not converge due to lack of data, the CCI data will be summarized at the subject level. That is, if the subject has only one transfusion episode, the single CCI value will be used; and for subjects who have multiple transfusion episodes, the average CCI across their transfusions will be used as their subject-specific number. These subject-specific (mean) CCI values will then be used to calculate group mean CCI values for both MIRASOL and CONTROL groups at both one (1) hour (measured between ≥10 minutes and ≤4 hours) at 24 hours (measured between ≥18 and < 30 hours). The mean subject-specific CCI estimate for each treatment group at each of these time points will be presented along with differences in means for the pairwise comparison (MIRASOL vs CONTROL).

10. Total number of Red Blood Cell transfusions (number of units)/subject

The analysis of this secondary endpoint, the total number of RBC transfusions (units), will be analyzed using the negative binomial regression model, mirroring the approach outlined for secondary endpoint #6. The only difference being that here, instead of the number of PLT transfusion episodes, the number of RBC transfusion units will be counted for each subject. Consequently, mean rate for the MIRASOL group(λ_T), and, mean rate for the CONTROL group (λ_C) will be based on the average number of RBC transfusion units. The offset in the negative binomial model will be the natural log of time in days from Day 0 to date of their last study visit in the treatment period completed. The natural log of the mean rate of the MIRASOL group minus the natural log of the mean rate of the CONTROL group, i.e. $ln(\lambda_T) - ln(\lambda_C)$, will be used to compare study arms. The corresponding 95% CI and p-value will be displayed such that negative values of difference between $ln(\lambda_T)$ and $ln(\lambda_C)$ favor the MIRASOL group by reflecting lower utilization.

8.3. Exploratory Endpoints

Four Exploratory Endpoints will be considered in this study, and, results of all analyses will be descriptive in nature. Each Exploratory Endpoint, as well as its corresponding analytic approach, is detailed below. All analyses will be based on the mITT population.

1. Total number of units of PLTs transfused/day of PLT support

For each subject, the number of units (a PLT unit is defined as one [1] single PLT bag) will be totaled and divided by that subject's number of days of PLT support. Consequently, each subject will have a value for the total number of PLT transfusion units started per day of PLT support. A day of PLT support is defined as any day in which a study PLT transfusion was started. Transfusions lasting more than twenty-four (24) hours will be counted as multiple days of PLT support. These values will then be averaged across subjects and will be displayed for each treatment group (MIRASOL vs CONTROL).

2. Total number of PLTs (PLT dose) transfused/Body Surface Area/day of PLT support

For each subject and transfusion episode, the PLT dose, i.e. the number of PLTs in a component (as defined in the denominator of the CCI equation), will be divided by the subject's baseline BSA which is calculated using the following equation:

BSA (m^2) = 0.007184 × Height (cm)$^{0.725}$× Weight (kg)$^{0.425}$

Similar to the analysis of the First Exploratory Endpoint, this value will be divided by the number of days that subject received PLT support. These values will then be averaged across subjects and displayed for each treatment group (MIRASOL vs CONTROL).

3. Interval between PLT transfusion episodes (days)

Only subjects with two or more transfusion episodes will be considered in this descriptive analysis. Additionally, if a subject has more than one transfusion episode in a day, this will be counted as a single transfusion episode for the purposes of this analysis. For each subject, the interval(s) between transfusion episodes will be recorded in days. If a subject has two transfusion episodes, the interval between PLT transfusion episodes will begin on the day after the initial transfusion episode ends and will end on the day prior to the start of the subsequent transfusion episode. For instance, if a subject has a transfusion episode on study Day 5, and then another transfusion episode on study Day 6, the interval is zero days. Likewise, if a subject has a transfusion episode on study Day 5, and then another transfusion episode on study Day 7, the interval will be 1 day. If a subject has three transfusion episodes, the two intervals between the three transfusion episodes will be determined using the same process described for a subject with two transfusion episodes, and the average length of the two intervals will then be calculated, i.e. (length of interval 1 + length of interval 2)/2. This average will be used in calculating the overall average. This pattern will be repeated for subjects with four transfusion episodes where the three intervals will be averaged, and so on for individuals with greater numbers of transfusions. The overall average number of days between PLT transfusion episodes will be summarized by averaging these subject-specific averages overall and for each treatment type (strata) by treatment group (MIRASOL vs CONTROL).

4. Platelet refractoriness defined as 2 sequential transfusion episodes, each with CCIs < 7500 measured 1 hour post-transfusion

This analysis will mirror the analysis performed on Secondary Endpoint # 4. The only difference being, PLT refractoriness is defined as 2 sequential transfusion episodes each with CCIs < 7500 measured 1-hour post-transfusion.

8.4. Safety Endpoints

All Safety Endpoints will be analyzed using the SS. Safety will be evaluated by assessment of physical examinations, vital signs, clinical laboratory values, and TEAEs.

8.4.1. Physical Examinations

Physical examinations are conducted at baseline and will be listed along with Medical and Surgical History. Results from physical examinations conducted through the course of bleeding assessments are reported as a part of the bleeding outcome.

8.4.2. Vital signs

Available data on vital signs (e.g., temperature [F°]), heart rate [HR] [beats/min], respiratory rate [breaths/min], systolic blood pressure (BP) (mmHg), diastolic BP [mmHg], SpO2 [%], and position [sitting, standing, supine]) will be reported utilizing appropriate thresholds by age group for each of the pre-, during, post- timeframes for each subject's transfusion. Data will be listed by treatment group and subject. See the CIP for information on the collection of vital signs.

8.4.3. Clinical Laboratory Values

All laboratory values will be reported in International System of Units.

Hematology is collected at baseline, Day 0 and daily when hospitalized and for clinical visits days. Hematology results include white blood cells ($10^3/\mu L$), RBCs ($10^6/\mu L$), hemoglobin (g/dL), hematocrit (%), and platelets ($10^3/\mu L$), and will be summarized by study day. Hematology data will be listed by treatment group and subject. Neutrophils and lymphocytes will only be included in the listing.

Coagulation laboratory tests (prothrombin time (seconds), International Normalized Ratio (INR), Activated Partial Thromboplastin time (aPTT) (seconds), and fibrinogen (mg/L)) are collected at baseline

and, if available, as part of routine care in follow-up. These labs will be summarized by study day. Coagulation laboratory tests will be listed by treatment group and subject.

Screening and Post-transfusion period Follow-up/Early Termination Cytomegolovirus (CMV) testing will be performed using an Immunoglobulin G (IgG) test. The results will be listed and summarized by study day.

8.4.4. Treatment Emergent Adverse Events

The following will be displayed.

- Overall TEAEs
- Platelet Transfusion Related TEAEs
- Medical Device Related TEAEs
- TEAEs by maximum severity
- SAEs
- UADEs
- Pulmonary events
  - Subjects on assisted ventilation
- TEAEs causing discontinuation from the study
- All-cause mortality
- Death due to bleeding as the primary or contributory cause of mortality

All TEAEs/SAEs identified during the reporting period (i.e. from initial post randomization platelet transfusion through seventy-two (72) hours following the transfusion end time of the last on-protocol PLT transfusion; for deaths including deaths due to bleeding through thirty (30) days following the transfusion end time of the last on-protocol PLT transfusion) will be followed until resolution, stabilization, or the end of subject's study participation, whichever is first.

Treatment Emergent Adverse Events are defined as those that occur during or following the first post-randomization PLT transfusion. The AE start date and time and transfusion start date and time of the first study transfusion will be used to identify TEAEs. The transfusion end time of the subject's final study transfusion will be used to identify the end of the 72-hour reporting period (or 30 days for deaths). AEs with missing/impartial start date and or time will be considered to be treatment emergent.

Treatment Emergent Serious Adverse Events (TESAEs) are defined as TEAEs marked serious by the investigator. Transfusion-related TEAEs are described through the reporting of TEAEs identified as related to the study treatment or those related to the medical device.

Unanticipated Adverse Device Effects are any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

Unanticipated Adverse Device Effects will be identified as treatment emergent adverse events reported by the investigator as serious, unanticipated, at least possibly related to study device or at least possibly related to study treatment.

Medical Dictionary for Regulatory Activities preferred terms in the associated SOC and Standard Medical Queries (SMQs) will be used to categorize TEAEs of "Pulmonary events" and additionally those pulmonary events requiring assisted ventilation as defined by the investigator.

Subject related TEAE counts will be summarized using frequencies and percentages. A subject will only be counted once per category of summarization (i.e. if a subject has multiple TEAEs, the subject will only be counted once in the overall 'Any TEAE' row but will be counted in each row for specific TEAEs). Event counts will be summarized using frequencies of events by treatment group.

A summary of TEAEs will be generated summarizing the number of TEAEs, TESAEs, unanticipated TESAEs, and UADEs. The number and percent of subjects with at least one TEAE, TESAE, TEAE related to study treatment, TEAE related to medical device(s), and TEAEs of pulmonary events and additionally those requiring assisted ventilation will also be included. The number of TEAEs by severity, relationship to study treatment (platelet transfusion) and relationship to the medical device, will be included.

Summary tables by SOC and PT will be reported for TEAEs, TESAEs, unanticipated TESAEs, UADEs, and Pulmonary related TEAEs as well as those pulmonary events requiring assisted ventilation. The number and percent of subjects with at least one event will be presented overall and, at most, once per SOC and PT.

All TEAEs will be listed by treatment group and subject. There will be a separate listing of TESAEs by treatment group and subject.

The timeframe for reporting death as part of AEs and death as a safety endpoint are different. The timeframe for reporting death as an AE is from randomization through thirty (30) days following the last per protocol PLT transfusion, where the timeframe for reporting death as a safety endpoint of death is through Day 56. The number of deaths through thirty (30) days following the last on-protocol PLT transfusion will be summarized by relationship to study treatment (PLT transfusion) and by relationship to medical device(s). The total number of deaths through Day 56 will be reported.

All deaths will be listed by treatment group and subject. This listing will include the investigator assessment of cause of death.

Deaths due to bleeding will be defined by the applicable bleeding grade and reported in the clinical study report. No listings or summaries will be produced as part of this reporting effort.

8.5. Tertiary Analyses

After all primary, secondary, supporting and exploratory analyses are completed; the following tertiary analyses of the primary endpoint will be conducted. All analyses will be performed at a group level with respect to the following subsets of such analyses will be considered exploratory. Due to their exploratory nature these analyses will be viewed as descriptive, hypothesis generating, and will not involve formal hypothesis testing.

8.5.1. Irradiation of Platelets

This exploratory analysis will summarize number and percent of irradiated PLTs transfused between arms. This may inform the effect of treatment with MIR PLTS versus Conventional PLTS that were irradiated between arms.

8.5.2. Washed Platelets

This exploratory analysis will summarize number and percent of washed PLTs transfused between arm. This may inform the effect of treatment with MIR PLTs versus Conventional PLTs that were washed between arms.

8.5.3. Age of Platelets

This exploratory analysis will summarize the age of PLTs transfused in days as a continuous variable between arms. This may inform the effect of treatment with MIR PLTs versus Conventional PLTs if there is a difference in the age of PLT units between arms. Platelet age is calculated as the date of the transfusion start recorded by the hospital site minus the Platelet Collection Date recorded by the blood center. For example, a platelet collected on the 10th of the month, and transfused on the 12th of the month would have an age of two (2) days.

8.6. Interim Analysis

An IA will be conducted at the 50% information fraction, i.e. when approximately 279 randomized mITT subjects have completed the post-transfusion period follow-up/early termination visit. The results of the IA will be presented to the study's Data Monitoring Committee (DMC). The DMC will assess efficacy, safety, and quality of trial conduct at the time of the IA.

Empirical conditional power [4] will be used in the IA to assess the futility in establishing NI. This will be carried out as follows.

A negative binomial model planned for the primary analysis will be fitted using unblinded data at the time of the IA following the convention for handling the off-protocol intervals prescribed in the primary analysis for each study arm. From these intercept only models, the estimates of β_0 and the variance parameter φ will be obtained. For an individual to be recruited in the second half of the trial, this person's duration of time (t_i) under observation will be drawn with replacement from each study arm's empirical distribution from the individuals who have completed their follow-up at the time of the IA regardless of on- or off-protocol intervals. The offset will be denoted as $\ln(t_i)$. Subjects whose time to transfusion independence is sampled and found to take place before Day 27 will be assumed to have zero bleeding days on the date of transfusion independence to Day 27 inclusive (which is assessed at the Post Transfusion follow-up visit). To simulate bleeding days over the period of transfusion dependence we first draw a random number V_i =RAND('GAMMA', $1/\varphi$), then compute $U_i = V_i * \varphi$ such that U_i will be a gamma distributed with mean 1 and variance φ . The count response is then to be drawn from a Poisson distribution with mean $U_i e^{\beta_0 + ln(t_i)}$. In order to simulate a count for the number of bleeding days which is guaranteed to be no greater than the number of bleeding assessment days for which bleeding data are required, a multinomial random variable will be generated with t_i+1 categories and probability vector P calculated based on the probability mass function of a right-truncated Poisson random variable. The resulting count will take on values 0, 1, 2, . . ., t_i while continuing to represent a realization of the bleeding data from the subject since it is using their estimated bleeding rate. When a cell probability for the multinomial is very small it will be set to 1×10^{-5} so that probabilities are > 0 and to avoid computational errors caused by very small floating-point numbers. The count response drawn in this way will be a realization from the truncated negative binomial distribution.

A completed dataset will then be available with the first half of the sample representing individuals for whom data are recorded and the second half of the sample representing simulated data representing contributions from individuals yet to be recruited. A negative binomial model will be fitted to this complete dataset as described for the primary analysis. A Wald-based two-sided 95% confidence interval will then be constructed for the regression coefficient of the treatment indicator based on this completed dataset. It will then be recorded whether the upper limit of this confidence interval includes the value of ln 1.6 which defines the non-inferiority margin on the scale of the natural logarithm.

Ten thousand datasets will be computed in this way and the proportion of completed datasets for which the upper limit of a two-sided 95% confidence interval is below the value of ln 1.6 will be taken as the empirical conditional power. If this empirical conditional power is below 0.30 the guidance would suggest termination for futility, but this would not be a binding rule. Factors other than the empirical conditional power will be considered when weighing the futility of the study as a whole.

The DMC will be fully unblinded in its assessment of safety and efficacy data at the time of the formal IA. The IA tables will be prepared semi-blinded by treatment codes (e.g. Treatment A and Treatment B) and the actual treatment assignments will be provided to the DMC under separate cover.

Note that the power calculation does not consider the minor power loss due to the futility analysis. The study will not be stopped at the IA for a positive primary efficacy outcome (e.g. non-inferiority or superiority of MIRASOL).

The DMC will receive their routine unblinded DMC report at the IA. In addition, the following data will be included in the IA report:

A summary of the mean, SD, minimum and maximum days of grade 2 or higher bleeding and days of bleeding assessments will be included by treatment group alone and by treatment group and treatment type.

For the primary outcome of days of grade 2 or higher bleeding first a basic summary table will be presented of the average days of grade 2 or higher bleeding, and the average days of bleeding assessments per treatment group. Then a summary of estimates from the negative binomial model with the natural log of the estimate, standard error, and 95% CI will be presented. Last, a table testing the non-inferiority hypothesis will be included showing the estimate of MIRASOL versus CONTROL from the model, the natural log of the NI margin, standard error, and 95% CI.

The mean CCI at 1 hour (measured between $\geq$10 minutes and $\leq$4 hours) and the mean CCI at 24 hours (measured between $\geq$18 and < 30 hours) after the end of every transfusion episode, when possible, will be calculated for each subject, and the mean of each treatment group will be presented along with differences in means for each pairwise comparison (treatment-control) at each time point (1 hour and >18-30 hours) as discussed in the analysis of Secondary Endpoint # 9. This will also be presented by age group (age <18, 18-65 and > 65 years) and treatment type (allogeneic transplant, autologous transplant, and chemotherapy).

Additionally, HLA antibody results are captured in a central laboratory database and will be maintained exclusively by BSRI. Blood System Research Institute will be responsible for reporting HLA results by treatment, age group, and treatment strata to the DMC.

9. REFERENCES

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10. APPENDIX I, ANNOTATED WHO GRADING SCALE

WHO Grading Scale for Bleeding annotated with the study's Bleeding Assessment (MIPLATE Annotated eCRFs) variable identifiers (Bx) and answers that correspond to the bleeding status.

	Grade 1	**Grade 2**	**Grade 3**
Oral and nasal	• Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤ 30 minutes* **B6a = No** • Petechiae of oral mucosa **B5 = Yes** • Epistaxis – total duration of all episodes in previous 24 hours ≤ 30 minutes* **B7a = No**	• Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* **B6a = Yes or Not Assessed or Refused or Don't Know** • Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes* **B7a = Yes or Not Assessed or Refused or Don't Know**	• Any bleeding requiring RBC transfusion over routine transfusion needs** **B8 = Yes**
Skin, soft tissue, musculoskeletal	• Petechiae of skin **B9 = Yes** • Purpura ≤ 1-inch diameter **B10a = No** • One or more spontaneous hematomas in the soft tissue or muscle > 1inch **B11 = Yes**	• Purpura > 1-inch diameter **B10a = Yes or Not Assessed or Refused or Don't Know** • Spontaneous hematoma in deeper tissues **B12= Yes** • Joint bleeding (confirmed by aspiration, imaging study or other accepted technique) **B13 = Yes**	• Any bleeding requiring RBC transfusion over routine transfusion needs** **B14 = Yes**
Gastrointestinal	• Positive stool occult blood test **B15a = Yes**	• Melanotic stool **B16 = Yes** • Hematochezia – visible red blood mixed in stool, not requiring a transfusion **B17 = Yes** • Hematemesis – Grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood) **B18a = Yes or B19a = Yes**	• Any bleeding requiring RBC transfusion over routine transfusion needs** **B20 = Yes**

Genitourinary	• Any biochemical or microscopic Hb/RBCs without red urine **B21a = Yes** • 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 **B23a = Yes**	• Gross/visible hematuria without need for transfusion **B22 = Yes** • 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 **B23b = Yes**	• Any bleeding requiring RBC transfusion over routine transfusion needs** **B24 = Yes**
Pulmonary		• Hemoptysis – Visible blood **B25 = Yes** • Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding) **B26a = Yes or B27 = Yes**	• Any bleeding requiring RBC transfusion over routine transfusion needs** **B28 = Yes**
Body Cavity		• Visible blood in body cavity fluid (eg red cells apparent in fluid aspirate) short of criteria for grade 3 or 4 **B29a = Yes**	• Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate), and/or need for transfusion **B30 = Yes**

Central Nervous System (CNS)		• Retinal bleeding without visual impairment **B31a = Yes** • Lumbar puncture with blood (> 5 RBC/ µL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color **B32a = Yes**	• Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap **B32b = Yes**
Invasive Sites		• Bleeding at invasive sites (venipuncture sites, IV lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours **B34 = Yes**	• Any bleeding requiring RBC transfusion over routine transfusion needs** **B35 = Yes**
Hemodynamic Instability			• Any bleeding associated with moderate hemodynamic instability (hypotension; > 30mmHg fall or > 30% decrease in either systolic or diastolic BP) and requiring RBC transfusion over routine transfusion needs** **B37 = Yes**

Abbreviations: RBC = red blood cell, Hg = hemoglobin, CSF = cerebrospinal fluid, IV = intravenous, mmHg = millimeters of mercury, BP = blood pressure.

*Count actual bleeding (ie. "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 BP, with associated tachycardia (HR increase of ≥ 20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs **B36 = Yes**
- Fatal bleeding from any source **B38 = Yes**
- 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) **B31b = Yes**

- Central nervous system (CNS) symptoms with non-traumatic bloody lumbar puncture **B32c = Yes**
- CNS bleeding on imaging study with or without dysfunction **B33a = Yes**

Grade 4 = (B31b=Yes or B32c=Yes or B33a=Yes or B36=Yes or B38=Yes)
Grade 3 = (B8=Yes or B14 or B20=Yes or B24=Yes or B28=Yes or B30=Yes or B32b=Yes or B35=Yes or B37=Yes)
Grade 2 = (B6a=Yes or Not Assessed or Refused or Don't know or B7a=Yes or Not Assessed or Refused or Don't Know or B10a=Yes or Not Assessed or Refused or Don't know or B12=Yes or B13=Yes or B16=Yes or B17=Yes or B18a=Yes or B19a=Yes or B22=yes or B23b=Yes or B25=Yes or B26a=Yes or B27=Yes or B29a=Yes or B31a=Yes or B32a=Yes or B34=Yes)
Grade 1 = (B6a=No or B5=Yes or B7a=No or B9=Yes or B10a=No or B11=Yes or B15a=Yes or B21a=Yes or B23a=Yes)
The maximum grade in the 24-hour assessment period will be the bleeding grade for that day

11. APPENDIX II, ANALYSIS OF THE KEY SECONDARY ENDPOINT

11.1. Introduction

Alloimmunization against the highly polymorphic human leukocyte antigens (HLA) has long been known to occur in oncology patients receiving platelet transfusions.[1,2] A major concern with HLA alloimmunization is the risk of HLA antibody formation contributing to platelet refractoriness, though it is known that alloimmunization is only one of many causes of platelet transfusion refractoriness.[3] The majority of HLA alloimmunization events following transfusion of oncology patients occurs within the first four weeks of induction chemotherapy.[2,4] Animal models show decreased alloimmunization in recipients of ultraviolet (UV) light treated platelets.[5,6] A definitive randomized control trial showed clear benefit of leukoreduction or UVB irradiation of platelet products in preventing both HLA alloimmunization and refractoriness to platelet transfusion.[4] The primary objective of MIPLATE is to determine if the hemostatic efficacy of Mirasol-treated plasma stored Trima Accel® apheresis platelets are non-inferior to conventional plasma stored apheresis platelets in patients with hypoproliferative thrombocytopenia requiring platelet transfusions. Secondary objectives include comparing other efficacy and safety endpoints between the treatment groups. One of the key secondary endpoints in the MIPLATE trial is to determine if receipt of Mirasol-treated platelets alter the risk for HLA alloimmunization after platelet transfusion.

11.2. Data Sources

Data and specimens from the enrolled patients in MIPLATE will be accessed for this assessment of alloimmunization.

Samples from enrolled patients will be screened for Class I and Class II antibodies at BSRI using the LSM12 kit manufactured by One Lambda. Samples will be tested at baseline (pre-transfusion) and on days 14 (± 5 days), 28 (± 7), and 56 (± 10 days). Blood System Research Institute laboratory staff will be blinded to MIPLATE treatment assignment.

11.3. HLA Antibody Testing

Test results will be reported as the normalized background (NBG) ratio for each bead in the assay, which corresponds to the strength of each HLA reaction. The NBG ratio and assay validity are calculated using the following set of abbreviations:

S#N	Sample-specific fluorescent value for bead #N
SNC bead	Sample-specific fluorescent value for Negative Control bead
SPC bead	Sample-specific fluorescent value for Positive Control bead
BG#N	Background NC Serum fluorescent value for bead #N
BGNC bead	Background NC Serum fluorescent value for Negative Control bead
NC Serum	Negative Control Serum validated for a given lot of LABScreen® beads

For an assay to be interpreted as valid, the following criteria will need to be met: SNC ≤ 1500, SPC ≥ 500, and SPC ≥ 2*(SNC).

The NBG value for each bead will be calculated as:

NBG = (S#N - SNC bead) / (BG#N - BGNC bead)

If any bead for a given sample yields an NBG ratio greater than the chosen cut-off the MIRASOL will be interpreted as positive, meaning evidence of alloimmunization. Cutoffs will be analyzed using a sensitive cutoff originally suggested by the manufacturer (NBG = 2.2) and cutoffs determined through studies of non-transfused males, using 3X or 5X the standard deviation above the mean value in that population.[7]

11.4. Analysis Objectives

The objective of the study is to compare the rate of HLA alloimmunization for recipients of Mirasol-treated platelets and recipients of conventional platelets. The treatment effect will be measured by the odds ratio (OR). The relative odds of alloimmunization (comparing Mirasol-treated to conventional platelets) will be estimated at each of the three assay cutoffs, along with associated 95% confidence intervals. In addition, HLA antibody data will be examined using KM plots to explore time to alloimmunization, with the outcome of interest being time to development of new HLA antibodies. Individuals not experiencing alloimmunization will have their follow-up censored. All analyses will be conducted both as intention to treat analysis and a per protocol analysis.

11.5. Populations

The two populations to be compared will be recipients of Mirasol-treated vs recipients of standard platelets.

11.6. Endpoints and Covariates

The endpoint for the HLA alloimmunization study will be development at any post-transfusion time point of a positive HLA antibody test at the given assay cutoff in a subject who had a negative HLA antibody test at that assay cutoff at baseline (pre-transfusion).

A relevant covariate that will be analyzed in a secondary analysis is the number of platelet transfusions received prior to the alloimmunization event, which will allow calculation of the rate of alloimmunization per unit of platelets transfused.

11.7. Handling of Missing Values and Other Data Conventions

Enrolled participants missing a baseline sample who do not have subsequent positive HLA antibody tests will be termed not alloimmunized. Participants missing a baseline sample who have subsequent positive HLA antibody tests will be termed unevaluable and will be excluded from analyses. Enrolled participants who have a baseline sample and have at least one subsequent post-transfusion sample will be used in the analysis.

11.8. Statistical Procedures

Odds ratios will be calculated to compare the risk of HLA alloimmunization in recipients of Mirasol-treated vs. conventional platelets. The exposure will be platelet type and the outcome will be development of a new HLA antibody. Development of HLA class I and HLA class II antibodies will be analyzed separately. The number of participants in each group at risk for alloimmunization will depend on the intention to treat and per protocol final categorization, but in general will be the number of participants who did not have detectable HLA antibodies at baseline at a given assay threshold.

In secondary analyses KM curves will be calculated using the longitudinal HLA antibody data to define subjects who are alloimmunized at baseline and the time to development of HLA alloantibodies post-transfusion. Development of HLA alloantibodies will be considered “failure” events during model specification, and the two arms of the study will be compared statistically using standard non-parametric tests, such as the log-rank test, with a p-value less than or equal to 0.05 considered evidence for significant difference

11.9. Approaches to Adjust for Multiplicity, Confounders, Heterogeneity

We do not plan to adjust for other potential covariates, unless evidence from the trial data suggest an unexpected imbalance between potential confounding factors such as the number transfused platelets or other patient characteristics. It is possible that platelet transfusion exposure will affect alloimmunization risk. In a secondary analysis, the risk of alloimmunization per platelet transfusion received prior to the alloimmunization event will be calculated.

11.10. Programming Plans

Data will be curated, cleaned, and analyzed using SAS® v9.4 software (SAS Institute Inc., Cary, NC).

11.11. REFERENCES

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