TERUMO BCT, INC.

STATISTICAL ANALYSIS PLAN

Investigational Product:	Trima Accel system
Protocol No.:	CTS-5060
Protocol Title:	Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in 100% Plasma
Issue Date:	May 17, 2017
Version:	FINAL V2.0

Terumo BCT, Inc.

Protocol CTS-5060

Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in 100% Plasma
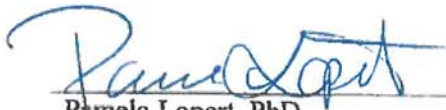
Signature Page

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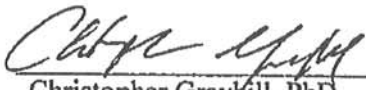Prosoft Clinical

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1.0   Introduction

This statistical analysis plan (SAP) is being developed after review of the protocol CTS-5060 and electronic case report forms (eCRFs). Reference materials for this SAP include the Clinical Investigation Plan (CIP) and the eCRFs.

The purpose of this plan is to prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the CIP. This plan explains in detail how the data will be handled or analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry.

The overall objective of this study will be achieved through descriptive analyses involving the device efficiency and safety variables collected in this study. All variables will be reported in listing format. All variables specified in this SAP will be analyzed and presented in descriptive tabulations and selected variables will be summarized and compared with criteria in FDA Guidance for Industry on Collection of Platelets by Automated Methods. The study objectives will be explored through the pre-specified primary, secondary, and safety endpoints.

This document contains information to support the generation of a Clinical Investigation Report (CIR) for Clinical Protocol CTS-5060, including detailed descriptions of the statistical methodologies to be applied, as well as the in-text tables, analysis summary tables, subject data listings, and descriptive graphics intended to present the analysis results.

The planned analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses that are performed but not identified in this SAP will be clearly identified in the CIR. The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

2.0   Study Objectives

The objective of this study is to verify that platelets collected on the Trima Accel System, Version 7.0 and stored in 100% plasma meet the FDA requirements for leukoreduction.

3.0   Statistical Methodology

All statistical analyses will be performed using SAS® software version 9.3. All testing and/or confidence intervals will be at a significance level of 0.05 unless stated otherwise.

3.1   Sample Size

As specified in the FDA guidance, for up to 1 allowed failure, 93 platelet products are required to show that the proportion of platelet units with an acceptable residual WBC level is at least 95% with 95% confidence. With 93 platelet products being collected, 16 failures or less is required to show that the proportion of platelet units with an acceptable platelet yield is at least 75% with 95% confidence.

Up to 450 healthy adult subjects will be enrolled in this study to complete 279 procedures (93 single, 93 double, and 93 triple platelet products).

3.2   Study Populations

Analysis populations for this clinical investigation will be the Full Analysis Set (FAS) and Safety Populations.

For all analyses by platelet product, the platelet product type (single, double, triple, or unassigned) will be determined from the calculated platelet yield (see Section 3.3) using the following.

- If the platelet yield, rounded to the nearest tenth, is $\geq 9.3 \times 10^{11}$, then the product will be analyzed as a triple.
- Otherwise, if the platelet yield, rounded to the nearest tenth, is $\geq 6.2 \times 10^{11}$, then the product will be analyzed as a double.
- Otherwise, if the platelet yield, rounded to the nearest tenth, is $<6.2 \times 10^{11}$, then the product will be analyzed as a single.
- Otherwise, if the procedure was not started, not completed or the platelet yield could not be determined for some other reason, as per the protocol analysis exclusion criteria, then the subject will be analyzed as "Unassigned".

The Safety Population will include all subjects enrolled in this trial for whom at least 1 apheresis procedure is initiated. A procedure will be considered to have been initiated if a Trima procedure start date and time are present. The Safety Population will be used for all summaries except the primary and secondary endpoints and the derived apheresis related parameters.

Due to the design of the study, a given subject may be enrolled in the study on multiple occasions. These subjects may also qualify for the Safety Population more than once. If this occurs, the subjects will be analyzed separately for each enrollment.

The Full Analysis Set (FAS) will be defined separately for single, double, and triple platelet products and will not include any repeat subjects. The FAS for a given platelet product will consist of all collections that do not meet any of the exclusion criteria specified below. The FAS will be used to examine the primary and secondary endpoints and the derived apheresis related parameters.

Data points will be excluded from the FAS analysis in the following situations:
1. Inability to collect a complete unit due to:
    a. Subject issues (inadequate access, reaction, needle abort, procedure disqualification upon Trima Accel device update of subject platelet count and hemoglobin or hematocrit).
    b. Decision to stop procedure by subject, Investigator, nursing staff or operator.
    c. Equipment failure or malfunction (unrecoverable system failure; plugged or malfunctioning filter[s]).
    d. Protocol deviation.

2. Decision to stop the procedure due to a change in the subject platelet count (i.e. subject qualifies for double, however day-of platelet count is for a single platelet product and 93 single platelet products have already been collected).

3. Failure or inability to update the Trima Accel system with the actual platelet count (platelet count performed on sample taken from Trima Disposable sample pouch) AND the actual platelet count differs from the entered platelet count by more than 10%. Updating the Trima Accel system with actual platelet count from the sample pouch is standard procedure for the Trima Accel system.

4. Incomplete or incorrect collection procedure or post-collection processing due to:
   a. Equipment failure or malfunction.
   b. Subject issues (inadequate access, reaction, needle abort).
   c. Unanticipated centrifuge stop during collection procedure.
   d. Failure to follow post-collection handling procedure outlined in the Trima Operator's Manual, and supplement(s).
   e. Subject and procedure samples are not taken as specified in protocol.
   f. Incorrect solution added to platelets prior to storage (eg platelet additive solution).
   g. Results of endpoint assays are not available.

3.3 Apheresis Related Parameter Calculations

Parent container:

$$Platelet\ Volume\ (mL) = \frac{Dual\ Bag\ Platelet\ Plus\ Product\ Weight\ (g) - Dual\ Bag\ Tare\ Weight (g)}{1.03\ (\frac{g}{mL})}$$

$$Plasma\ Volume\ (mL) = \frac{Plasma\ Bag\ Weight\ (g) - Plasma\ Bag\ Tare\ Weight (g)}{1.03\ (\frac{g}{mL})}$$

$$Average\ Platelet\ Concentration\ (x10^3/\mu L) = \frac{1^{st}\ CBC\ (x10^3/\mu L) + 2^{nd}\ CBC\ (x10^3/\mu L)}{2}$$

$$Platelet\ Yield\ (x10^{11}) = \frac{[Average\ Platelet\ Concentration] * [Dilution\ Factor] * [Platelet\ Volume]}{100,000}$$

$$Residual\ WBC\ Count\ (x10^6) = \frac{[Raw\ WBC\ Count\ (cells/\mu L)] * [Platelet\ Volume]}{1,000}$$

Individual components (Products A, B, and C, where applicable, from the eCRFs):

$$Platelet\ Volume\ (mL) = \frac{Bag\ Platelet\ Plus\ Product\ Weight\ (g) - Bag\ Tare\ Weight (g)}{1.03\ (\frac{g}{mL})}$$

$$Residual\ WBC\ Count\ (x10^6) = \frac{[Raw\ WBC\ Count\ (cells/\mu L)] * [Platelet\ Volume]}{1,000}$$

3.4 Primary Endpoints

- Proportion of platelet units with an acceptable residual WBC level for single platelet products.
- Proportion of platelet units with an acceptable residual WBC level for double platelet products.
- Proportion of platelet units with an acceptable residual WBC level for triple platelet products.

The acceptable residual WBC level is defined as following:

For single platelet products: residual white blood cell measurement, rounded to the nearest tenth, $< 5.0 \times 10^6$.

For double platelet products:
- Parent container has a residual white blood cell measurement, rounded to the nearest tenth, $< 8.0 \times 10^6$,
- If not met, each component residual white blood cell measurement, rounded to the nearest tenth, $< 5.0 \times 10^6$.

For triple platelet products:
- Parent container has a residual white blood cell measurement, rounded to the nearest tenth, $< 12.0 \times 10^6$,
- If not met, each component residual white blood cell measurement, rounded to the nearest tenth, $< 5.0 \times 10^6$.

3.5 Secondary Endpoints

- Proportion of platelet units with an acceptable platelet yield for single platelet products.
- Proportion of platelet units with an acceptable platelet yield for double platelet products.
- Proportion of platelet units with an acceptable platelet yield for triple platelet products.

Acceptable platelet yield is defined as following, where the platelet yield is calculated from the formula in Section 3.3:

For single platelet products: platelet yield, rounded to the nearest tenth, $\geq 3.0 \times 10^{11}$.

For double platelet products: platelet yield, rounded to the nearest tenth, $\geq 6.2 \times 10^{11}$.

For triple platelet products: platelet yield, rounded to the nearest tenth, $\geq 9.3 \times 10^{11}$.

3.6   Safety Endpoints

Safety will be monitored through collection of adverse events (AEs), serious adverse events (SAEs), unanticipated adverse device effects (UADEs), and device deficiencies.

3.7   Statistical Analysis

All data collected on the eCRFs will be presented in the listings. Missing data will not be imputed. All analyses will be based on observed data only.

3.7.1   Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by platelet products (single, double, triple, and unassigned) and overall. Categorical variables (such as gender and race) will be summarized by frequency and percentage. Continuous variables (such as weight and height) will be summarized by N (number of non-missing observations), mean, standard deviation, median, minimum, and maximum.

3.7.2   Disposition

Study completion status and reasons for discontinuation will be displayed by platelet products (single, double, triple, and unassigned) and overall using frequencies and percentages.

3.7.3   Efficiency Analysis

Primary Endpoints

Primary Endpoint Acceptance Criteria

Parameter	Measured	Acceptance Criteria
Residual WBC Count – Single Unit	Flow cytometry; BD Leukocount^{TM} or equivalent	Residual WBC count is $< 5.0 \times 10^6$
Residual WBC Count – Double Unit	Flow cytometry; BD Leukocount or equivalent	Residual WBC count is $< 8.0 \times 10^6$ or each component $< 5.0 \times 10^6$
Residual WBC Count – Triple Unit	Flow cytometry; BD Leukocount or equivalent	Residual WBC count is $< 12.0 \times 10^6$ or each component $< 5.0 \times 10^6$

Abbreviations: WBC = white blood cell.

Summary statistics will be provided separately for single, double, and triple residual WBC levels. The summaries will include N, mean, standard deviation, median, minimum, and maximum.

Frequencies and percentages of platelet units with an acceptable residual WBC level and the lower one-sided 95% exact binomial confidence intervals (Clopper-Pearson) will be calculated separately for single, double, and triple platelet products. If the lower one-sided confidence interval is greater than 95%, then it will be concluded that the

proportion of platelet units with an acceptable residual WBC level is at least 95% for the given platelet product.

Secondary Endpoints

Secondary Endpoint Acceptance Criteria

Parameter	Measured	Acceptance Criteria[a]
Platelet yield – Single Unit	Platelet concentration × volume	Platelet yield is $\geq 3.0 \times 10^{11}$
Platelet yield – Double Unit	Platelet concentration × volume	Platelet yield is $\geq 6.2 \times 10^{11}$
Platelet yield – Triple Unit	Platelet concentration × volume	Platelet yield is $\geq 9.3 \times 10^{11}$

[a] These yields represent typical lab minimums for splitting into double and triple platelet products.

Platelet yield will be summarized separately for single, double, and triple platelet products. The summaries will include N, mean, standard deviation, median, minimum, and maximum.

Separately for single, double, and triple platelet products, the lower one-sided 95% exact binomial confidence intervals (Clopper-Pearson) will be calculated for the proportion of platelet units with an acceptable platelet yield. If the lower one-sided confidence interval is greater than 75%, then it will be concluded that the proportion of platelet units with an acceptable platelet yield is at least 75% for the given platelet product.

3.7.4   Calculated Apheresis Related Parameters

The average platelet concentration, platelet yield, and residual WBC count as specified in Section 3.3 will be summarized by N, mean, standard deviation, median, minimum, and maximum for each platelet product type.

3.7.5   Safety Analysis

All adverse events will be coded using MedDRA and reported by SOC and preferred term. The focus of the adverse event summaries will be on treatment-emergent adverse events. Adverse events will be considered treatment-emergent if they occur on or after the start of the apheresis procedure, as defined in Section 3.2. Adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs) will be summarized with frequencies and percentages. Additional summaries of AEs will be presented for the maximum reported severity and relationship to device and procedure. AEs leading to study or procedure discontinuation will also be tabulated. Summaries will be presented by platelet products (single, double, triple, and unassigned) and overall.