CLINICAL INVESTIGATION PLAN

Study Title:	Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in Platelet Additive Solution
Study Number:	CTS-5059
Study Device:	Trima Accel® system
Manufacturer:	Terumo BCT, Inc. 10811 West Collins Avenue Lakewood, CO 80215 USA Phone: (303) 231-4832
Sponsor:	Terumo BCT, Inc. 10811 West Collins Avenue Lakewood, CO 80215 USA Phone: (303) 231-4832
Sponsor Contact:	Heather Pidcoke, MD, PhD Phone: (303) 231-4805 Email: Heather.Pidcoke@terumobct.com

This study will be conducted according to this protocol, Good Clinical Practice as described in the International Conference of Harmonisation Guidance for Industry E6, and as applicable, United States Food and Drug Administration 21 CFR 600-680 and 21 CFR 812, International Organization for Standardization 14155:2011(E), and other regulatory requirements of the regions where the study is conducted. All essential documents will be archived.

Version/Date: 4.0/22 NOV 2016

Confidentiality Statement

CLINICAL INVESTIGATION PLAN APPROVAL

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AMENDMENT 3 SUMMARY OF CHANGES

Study Title:	Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in Platelet Additive Solution	
CIP #:	CTS-5059	
CIP Version / Date:	Version 4.0/22 NOV 2016	
Replaces CIP Version / Date:	Version 3.0/19 FEB 2016	
Rationale:	This amendment was made to increase the number of healthy adult subjects enrolled in this study from up to 350 subjects to up to 450 subjects. After study initiation, it was noted that the number of screen failures and procedures excluded per Section 15.4 Protocol Analysis Exclusions was higher than originally anticipated. Therefore, in order to ensure 93 evaluable single, double, and triple products are collected from 279 individual subjects, the total number of subjects enrolled in the study will be increased from up to 350 to up to 450. Additionally, typographical error corrections, sponsor contact information, and minor wording changes for clarity have been made and will not be reflected in the table below.	
Section(s)	**Used to Read:**	**Now Reads:**
Synopsis, Section 8.1 Study Design, and Section 9.1 Number of Subjects and Selection	Up to 350 healthy adult subjects will be enrolled in this study to ensure 93 single, 93 double and 93 triple platelet product evaluable data points	Up to **450** healthy adult subjects will be enrolled in this study to ensure 93 single, 93 double and 93 triple platelet product evaluable data points

SYNOPSIS

Sponsor:	Terumo BCT, Inc.
Study Title:	Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in Platelet Additive Solution
Study Number:	CTS-5059
Target Population:	Healthy Adults
Device Description:	The Trima Accel system is an automated blood component collection system that uses centrifugal force to separate donor blood into platelet, plasma, and red blood cell (RBC) components and uses Anticoagulant Citrate Dextrose, Solution A (ACD-A) as the anticoagulant. The device is comprised of three major sub-systems, 1) the Trima machine itself, 2) sterile, single-use disposable blood tubing sets and, 3) embedded software. There are additional optional accessories such as plasma bags, platelet bags, a seal safe system, and barcode scanner kit. The Trima Accel system received United States Food and Drug Administration (FDA) 510(k) clearance for hyperconcentrated platelet collections stored in platelet additive solution (PAS) on 17 December 2012 (BK120049).
Intended Use:	The Trima Accel system is an automated blood cell separator intended for use in collecting blood components for later transfusion into patients.
Study Centers Planned:	At least 2 and up to 8 Blood Centers in the United States
Objective:	To verify that platelets collected on the Trima Accel system with Version 7.0 software enhancements and stored in PAS meet the FDA requirements for leukoreduction ($< 5.0 \times 10^6$ residual white blood cells [WBC] per transfusable unit).
Rationale:	The study is designed to evaluate changes to the Trima Accel software to ensure the modified software meets the FDA acceptance criteria for leukoreduction and platelet yield. The operating range for the system flow rates, anticoagulant ratios, storage conditions, and centrifugal forces are the same as the currently cleared Trima Accel system. There are no changes to the environment or storage conditions for platelets; therefore, no in vitro or in vivo platelet quality data will be collected.
Outcome Measures:	Primary Endpoint: The proportion of platelet units with an acceptable residual WBC level. Acceptable residual WBC counts are: singles = residual WBC level $< 5.0 \times 10^6$; doubles = residual WBC level $< 8.0 \times 10^6$ or $< 5.0 \times 10^6$ for each transfusable unit; and triples = residual WBC level $< 12.0 \times 10^6$ or $< 5.0 \times 10^6$ for each transfusable unit. Secondary Endpoint: The proportion of platelet units with an acceptable platelet yield. Acceptable platelet yield for single, double and triple platelet products are: platelet yield $\geq 3.0 \times 10^{11}$ for singles, platelet yield $\geq 6.2 \times 10^{11}$ for doubles, and platelet yield $\geq 9.3 \times 10^{11}$ for triples.
Safety Measures:	Safety will be monitored through collection of adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs).
Inclusion Criteria:	1. Age 18 years or older. 2. Meets the inclusion criteria defined by the Blood Center for an apheresis platelet with PAS collection on the Trima Accel system. These criteria are based on FDA guidance and American Association of Blood Banks (AABB) standards. Note: subjects who are deferred from volunteer community donations because of travel restrictions, piercings, or tattoos may participate in the study, as products are not transfused. 3. Has given written informed consent.

Exclusion Criteria:	1. Has previously donated an evaluable platelet product in this study (CTS-5059).
Number of Subjects Planned:	Up to 450 healthy adult subjects will be enrolled in this study to complete 93 single, 93 double and 93 triple collections.
Study Design:	This is a prospective, open-label, multi-center controlled study to evaluate the leukoreduction of platelets stored in PAS collected on the Trima Accel system Version 7.0 software enhancement. Up to 450 healthy adult subjects will be enrolled in this study to ensure 93 single, 93 double and 93 triple platelet product evaluable data points. Evaluable is defined as a completed platelet product that does not meet any of the protocol analysis exclusion criteria. Plateletpheresis will be per site standard practice and per applicable FDA guidelines such as the FDA Collection of Platelets by Automated Methods, December 2007 Guidance for Industry and Pre-storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion, September 2012.
Study Duration:	Study participation will be up to 30 days and will consist of 1 to 2 visits. Screening may be done within 30 days of the apheresis procedure or combined as a single visit, which includes screening and the apheresis procedure all in 1 day. The entire study should be completed in approximately 16 months.
Statistical Methodology:	Counts and percentages of success rates and the lower one-sided 95% exact binomial confidence intervals will be calculated separately for success rates of single, double, and triple platelet products. If 0 or 1 failure is observed, then the confidence interval will suggest that the true success rate is at least 95% with 95% confidence for the given platelet product. This approach will be applied independently to single, double, and triple platelet products. Also applied independently to single, double, and triple platelet products, the lower one-sided 95% exact binomial confidence intervals will be calculated for the proportion of platelet units with an acceptable platelet yield. If 16 or fewer failures are observed, then the confidence interval will suggest that the true success rate is at least 75% with 95% confidence for the given platelet product.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AABB	American Association of Blood Banks
ACD-A	Anticoagulant Citrate Dextrose, Solution A
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
CV	Coefficient of Variation
DCF	Data Clarification Form
DVT	Deep Venous Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELF	Extended Life Platelet
ESC	Extent of Shape Change
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HSR	Hypotonic Shock Response
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Standard
ITT	Intent-to-Treat Population
Kg	Kilogram(s)
L	Liter(s)
LOC	Loss of Consciousness
LRS	Leukoreduction system
MedDRA	Medical Dictionary For Regulatory Activities
mL	Milliliter(s)
mmHg	Millimeter of Mercury
MNC	Mononuclear Cell
PAS	Platelet Additive Solution
PHI	Protected Health Information
PIR	Platelet Inventory Recovery
RBC	Red Blood Cell
RPM	Revolutions Per Minute

SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TA-GvHD	Transfusion Associated Graft-versus-host Disease
TBV	Total Blood Volume
TRIM	Transfusion-related Immunomodulation
UADE	Unanticipated Adverse Device Effect
UCL	Upper Confidence Limit
USID	Unique Study Identification
USP	United States Pharmacopeia
WBC	White Blood Cell

1 INTRODUCTION

1.1 Background

Platelet transfusions are used extensively for the treatment and prophylaxis of bleeding associated with major trauma, surgery, or chemotherapy, and in individuals that are thrombocytopenic (have low platelet count) or have other platelet dysfunctions.

Currently, the majority of platelets transfused in the United States are collected by apheresis.[1] Platelets collected by apheresis are separated from donor blood using advanced techniques and the remaining blood components (red blood cells [RBC], white blood cells [WBC] and/or plasma) can be cycled back to the donor. The use of platelet concentrates obtained from single donors by automated apheresis has grown steadily as the collection instruments have improved to enable collection of double or even triple doses of platelets (hyperconcentrated) in a single apheresis collection. This practice maximizes the amount of platelets collected from each donor in a manner that is time and cost efficient, and it has the benefit of exposing the recipient to as few individual donors as possible, thereby potentially minimizing the risk of transfusion related adverse events (AEs) such as pathogen transmission and immune reactions.[2]

The risks posed by WBCs in transfused blood components are recognized as an additional and substantial problem in transfusion medicine. Residual WBCs in blood components have been implicated in transfusion complications, including transfusion-associated graft-versus-host disease (TA-GvHD), alloimmunization, febrile nonhemolytic transfusion reactions, transmission of intracellular viruses (eg, cytomegalovirus, human immunodeficiency virus [HIV]), and transfusion-related immunomodulation (TRIM). To reduce the risk of WBC induced transfusion complications, leukoreduction is employed and removes the majority of WBCs from blood component products.[3,4]

In addition to leukoreduction in platelet products, platelets can be stored in platelet additive solution (PAS). In Europe it is common practice to replace part of the plasma with PAS. The rationale behind this practice is that diluting the plasma may reduce the risk of deleterious reactions such as allergic reactions and immune reactions triggered by cellular mediators present in the plasma.[5] Substituting PAS for plasma may have other advantages as well. It has a more consistent composition than plasma from different donors, it can be optimized for longer storage, and it allows for a more frugal use of blood components since more plasma can then be used for other applications instead of platelet storage.[6,7]

Platelet additive solution has been used for over 20 years in Europe. In the United States, the first Food and Drug Administration (FDA) approval for the use of PAS was in 2009. This first approval was for the use of the PAS InterSol™ (Fenwal™, a Fresenius Kabi company) as a replacement of 65% plasma in platelet components. Subsequently, approval was received in 2012

for Isoplate™ solution use with the Trima Accel® Automated Blood Collection system (Trima Accel system).

2 DEVICE DESCRIPTION

Terumo BCT, Inc. (Terumo BCT) is a corporation that develops and markets the Trima Accel system, an apheresis medical device for the collection of blood products, including platelets. The Trima Accel system is an automated blood component collection system that uses centrifugal force to separate donor blood into platelet, plasma, and RBC components using Anticoagulant Citrate Dextrose, Solution A (ACD-A) as the anticoagulant. The device is comprised of 3 major sub-systems: 1) the Trima machine itself; 2) sterile, single-use disposable blood tubing sets; and 3) embedded software. There are additional optional accessories, such as plasma bag, platelet bag, seal safe system, and barcode scanner kit.

The Trima Accel system consists of a functionally closed disposable set (sterile, nonpyrogenic) used in conjunction with equipment and software to collect combinations of blood products. Collections for this study will be performed per the Version 6.0 Trima Accel Operators Manual and the Version 7.0 user change summary which is provided to the study site by the Sponsor.

The Trima system 4.0 was initially cleared for the collection of platelets by the FDA on 13 October 1998 (BK970023). The Trima Accel system was cleared under BK010046 and BK010050 and additional Trima Accel embedded software modifications have been submitted and cleared by the FDA with the most recent approval on 29 August 2014 (BK140158) for Version 6.4 software.

Terumo BCT has developed new Trima Accel embedded software (ie, Version 7.0) to enhance the collection of platelets stored in PAS.

2.1 Version 7.0 Software

The Trima Accel system Version 7.0 software is intended to consolidate multiple enhanced software versions with the additional value of creating improvements relevant globally. These improvements include enhancing the leukoreduction, reducing the procedure time, and improving the overall experience for the operator and donor.

The configuration of the device (software update to Version 7.0) will be provided to the Investigator by Terumo BCT. These configurations will be within the normal operating range of the Trima Accel system Version 6.4, as cleared by the FDA. The operating range for the system flow rates, anticoagulant ratios, storage conditions, and centrifugal forces are the same as the currently cleared Trima Accel system software.

The following modifications have been made in Version 7.0 software to be used with the Trima Accel system:

1. The blood prime procedure has been modified to increase the inlet pump speed during specific portions of prime, allowing the system to reduce the time of the blood prime procedure by improving the blood flow rates through the channel during the priming process.

2. Modifications to the leukoreduction system (LRS) chamber clearing procedure to clear excess WBC content from the LRS chamber in a more efficient manner.

3. Changes to the platelet inventory recovery (PIR) phase to reduce the platelet inventory in the separation channel and LRS chamber at the end of the procedure when sufficient platelets remain.

4. The platelet collection algorithm has been modified to improve the control of the concentration of platelets delivered to the LRS separation chamber, thereby improving the leukoreduction potential of the LRS chamber.

5. The platelet collection algorithm for hyperconcentrated platelets has been modified to improve the control of the concentration of platelets within the LRS separation chamber, also improving the leukoreduction potential of the LRS chamber.

6. Improvements to the venous access pressure monitoring algorithms have been made that adjusts the draw flow rate in response to a venous access alarm (autoflow). Specifically, this algorithm allows for longer pump pauses in response to a venous access alarm by automatically lowering the flow rate and will automatically increase the flow rate when no venous access alarms occur.

7. Maintenance modifications to the software to upgrade the operating system from VxWorks 5.5 to VxWorks 6.9.

2.2 Arm Cuff

It is standard practice during phlebotomy to use a tourniquet or blood pressure cuff approximately 2 inches above the antecubital area for venipuncture.[8] The American Association of Blood Banks (AABB) recommends applying 60 mmHg of pressure either via a tourniquet or blood pressure cuff and have the donor squeeze a hand-gripper several times and hold during the process of obtaining venipuncture.[8] After venipuncture, it is recommended to have the donor relax their hand and give the gripper a slow, firm squeeze every 5-10 seconds and loosen the tourniquet or blood pressure cuff to 40 mmHg.[8] In regards to the apheresis procedure, the AABB recommends sites follow their standard operating procedures (SOPs), which generally state to maintain appropriate pressure (20 to 40 mmHg) and blood flow (ie, squeeze a hand-gripper) during the apheresis procedure.

Terumo BCT has developed an arm cuff which can be used as an alternative to maintain pressure on the arm and blood flow during apheresis procedures. Specifically, this arm cuff has a pressure control valve which allows the cuff to be fully inflated for use in obtaining venipuncture, an inline relief valve which allows the cuff to maintain the desired donation pressure (20 to 40 mmHg), and an inflation bulb which the donor may squeeze to maintain the donation pressure.

The arm cuff is not connected or linked to the Trima Accel system and will be submitted for FDA clearance as a standalone device as an alternative method to the standard methods of maintaining arm pressure and blood flow for apheresis procedures. In the current study, half the study sites will receive the arm cuff and the remaining will utilize their standard method of maintaining donation pressure as indicated by the Site SOP. The use of the arm cuff is not expected to impact the leukoreduction, volume, or yield of single, double or triple platelet products.

2.3 Platelet Additive Solution

InterSol solution was FDA approved for the storage of hyperconcentrated platelets (BN080041) on 07 December 2009 for use with the Amicus™ Separator system (BK090065). InterSol PAS is an isotonic solution designed to replace a proportion (65%) of the plasma used in the storage of leukoreduced apheresis platelets under standard blood banking conditions.

The solution contains constituents that are naturally occurring components present in many cellular systems: sodium acetate as a nutrient, sodium citrate to prevent platelet clumping and activation, sodium phosphate for buffering, and sodium chloride for osmolarity. InterSol solution does not have a pharmacological effect in vivo, but rather acts to provide the appropriate environment for platelet storage in lieu of a portion of the plasma.

InterSol solution is provided as a 500 mL sterile and non-pyrogenic solution in a non-polyvinyl chloride plastic container with a sterile and non-pyrogenic fluid path.

Each 100 mL of InterSol contains 305 mg dibasic sodium phosphate, anhydrous, United States Pharmacopeia (USP); 93 mg monobasic sodium phosphate, monohydrate, USP; 318 mg sodium citrate, dihydrate, USP; 442 mg sodium acetate, trihydrate, USP; 452 mg sodium chloride, USP; Water for Injection, USP quantity sufficient.

Currently, the use of InterSol solution for storage of platelets with the Trima Accel system has not been cleared by the FDA. The FDA has recently approved a prospective in vitro study of platelets collected on the Trima Accel system and stored in InterSol solution (IDE 16145).

2.4 Disposable Sets

The collection of single, double, and triple platelets stored in PAS will be done with the Trima Accel Platelet + Sampler + AutoPAS, MultiPlasma, RBC disposable set (catalog number 80370). This disposable set was cleared by the FDA (BK120049) on 17 December 2012.

3 INTENDED USE STATEMENT

The Trima Accel system is an automated blood cell separator intended for use in collecting blood components for later transfusion into patients. Depending on the tubing set used, the Trima Accel system may collect multiple blood components, alone or in combination. For the purposes of this study the following products will be collected under this protocol:

- Platelets Pheresis, Leukocyte Reduced in 65% InterSol PAS (single, double, and triple units) with or without concurrent plasma.

4 NONCLINICAL STUDIES

Laboratory assessments using human and bovine whole blood pools to test software changes related to procedure time and platelet leukoreduction have been conducted at Terumo BCT. Specifically, modifications to previously released versions of Trima Accel software regarding the blood prime and the PIR algorithm have been tested to confirm the software changes in Version 7.0 maintain product volume accuracy and reduce the overall time of the apheresis procedure. These software modifications tested in whole blood pools resulted in a product volume accuracy ± 6% indicating the system was properly primed for the collection procedure and decreased the overall procedure time.

Additionally, the in vitro quality of double hyperconcentrated platelets collected from a single donor on the Trima Accel system, split and then stored in plasma via gravity drain and InterSol solution via auto PAS-metering was tested. The acceptance criteria[9] of $pH_{(22°C)} > 6.2$ was met for all units in this study through 7 days of storage. In vitro cell quality of platelets stored in InterSol solution (determined by extent of shape change [ESC], hypotonic shock response [HSR], membrane-bound P-selectin expression [CD62P], and morphology scoring) was robust in InterSol solution stored platelets and was comparable to control platelets stored in plasma.

5 CLINICAL TRIAL EXPERIENCE

The software modifications being proposed in Trima Accel Version 7.0 software have been studied alone and in combination from clinical donations from healthy donors. Software changes made to previously released software versions were tested to determine if the additional Version 7.0 software modifications resulted in improved leukoreduction, maintained platelet yield, and decreased procedure time.

5.1 Hyperconcentrated Platelet Leukoreduction Improvements

Changes to the platelet collection algorithm were tested in blood donations from healthy volunteers to determine if software modifications resulted in improvements to the platelet leukoreduction in hyperconcentrated platelet products. In hyperconcentrated platelet products, the modified platelet collection algorithm alone showed an overall system performance of 100% of products containing $< 5.0 \times 10^6$ WBCs per transfusable dose and 99.9% of hyperconcentrated products contain $< 1.1 \times 10^6$ WBCs per transfusable dose per log normal regression analysis. When this modification was assessed with additional Version 7.0 enhancements (n = 24), all of the hyperconcentrated products contained $< 5.0 \times 10^6$ WBCs per transfusable dose.

5.2 Platelet Yield and Procedure Time Improvements

The Trima Version 7.0 software has been modified to improve the overall platelet collection procedure time by modifications to the disposable set priming procedure and the LRS chamber purge process. Changes to the prime procedure alone (n = 52), resulted in a product volume accuracy ± 6% and when tested with other Version 7.0 enhancements (n = 40) platelet concentrations in the plasma product averaged 5×10^3 cells/uL.

The venous access monitor has been modified to adjust the draw flow rate in response to venous access alerts (autoflow). A clinical assessment of the autoflow algorithm paired with the arm cuff (n = 30) resulted in the average operator intervention per procedure being 0.433 ± 0.935. An additional study was conducted with the autoflow paired with the Version 7.0 software modifications and showed an average operator intervention rate of 0.50 ± 0.88 per procedure. These modifications are a significant improvement over the United States average of access related events (approximately 5 per procedure as determined by Terumo BCT historical data).

The LRS chamber purge modifications resulted in 3-5 minutes of time advantage over the current Trima Accel collection for each algorithm respectively. There is an even greater time savings advantage for runs where 1 or more purges are saved due to LRS chamber purge changes. The time savings due to PIR software modifications are dependent on the donor size and precount on the day of donation and therefore may differ per donation.

6 RATIONALE FOR THE CURRENT STUDY

The study is designed to evaluate changes to the Trima Accel software (Version 7.0) to ensure they meet the FDA acceptance criteria for leukoreduction[9,10] ($< 5.0 \times 10^6$ WBC per transfusable unit) and results in platelet yields $\geq 3.0 \times 10^{11}$ for singles, $\geq 6.2 \times 10^{11}$ for doubles and $\geq 9.3 \times 10^{11}$ for triples.

The operating range for the system flow rates, anti-coagulant ratios, storage conditions, and centrifugal forces are the same as the currently FDA cleared Trima Accel system. There are no

changes to the environment or storage conditions for platelets therefore no platelet quality data will be evaluated. Additionally, no products will be transfused from this study.

The Trima Accel system Version 7.0 software is intended to consolidate multiple enhanced software versions with the additional value of creating improvements relevant globally. This effort will yield a software release with several new enhancements targeted at improving productivity, leukoreduction and WBC flagging, reducing procedure time, reducing venous access alarms, and improving the user and donor experience.

7 ENDPOINTS

7.1 Primary Endpoint

The proportion of platelet units with an acceptable residual WBC level. Acceptable WBC levels for single, double, and triple platelet products are presented in Table 7-1.

Table 7-1: Primary Endpoint Acceptance Criteria

Parameter	Measured	Acceptance Criteria
Residual WBC Count – Single Unit	Flow cytometry; BD Leukocount™ 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.

7.2 Secondary Endpoint

The proportion of platelet units with an acceptable platelet yield. Acceptable platelet yield for single, double and triple platelet products are presented in Table 7-2.

Table 7-2: 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.

7.3 Safety Measures

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

8 INVESTIGATIONAL PLAN

8.1 Study Design

This is a prospective, open-label, multi-center controlled study to evaluate the leukoreduction of platelets stored in PAS collected on the Trima Accel system with Version 7.0 software enhancements. Up to 450 healthy adult subjects will be enrolled in this study to ensure 93 single, 93 double, and 93 triple platelet product evaluable data points. Evaluable is defined as a completed platelet product that does not meet any of the protocol analysis exclusion criteria (Section 15.4).

The additional subjects account for screen failures, incomplete procedures, and protocol analysis exclusions.

Concurrent plasma will be collected from qualifying subjects to exercise the platelet/plasma product combination. Of the 93 evaluable procedures required for each type (singles, doubles, and triples) at least 25% of collections will include concurrent plasma collection. The Trima Accel system calculates subject eligibility for blood product combinations based on platelet count, hemoglobin or hematocrit, and total blood volume (TBV) of the subject.

Red blood cells will not be collected in this study; platelets will be collected in 65% InterSol PAS and 35% plasma. The Trima Accel system collects RBCs after platelets and plasma, therefore there is no effect of RBC collections on the platelet collections due to platelet collection software modifications. Similarly, there is no effect of the platelet collections on subsequent RBC collections.

8.2 Study Duration

Study participation will be up to 30 days and will consist of 1 or 2 visits. Screening may be done within 30 days of the apheresis procedure or combined as 1 visit, which includes screening and the apheresis procedure all in 1 day. The apheresis procedure can last from 25 to 150 minutes, dependent upon the product to be collected, machine configuration, subject parameters, the quality of the vascular access, and the tolerance of the subject to the ACD-A anticoagulant.

The entire study should be completed in approximately 16 months.

9 STUDY POPULATION

9.1 Number of Subjects and Selection

Up to 450 healthy volunteer donors will be enrolled in this study in at least 2 and up to 8 investigative sites in the United States.

Donors will be selected from the community donor and/or research pool and will be representative of the healthy adult volunteer population. The subjects who participate in this research will have no direct benefit. Subjects will be recruited in a non-coercive manner and recruitment will be irrespective of ethnicity or gender.

9.2 Inclusion Criteria

1. Age 18 years or older.
2. Meets the inclusion criteria defined by the Blood Center for an apheresis platelet with PAS collection on the Trima Accel system. These criteria are based on FDA Regulations and AABB standards. Note: Subjects who are deferred from volunteer community donations because of travel restrictions, piercings, or tattoos may participate in the study, as products are not transfused.
3. Has given written informed consent.

9.3 Exclusion Criteria

1. Has previously donated an evaluable platelet product in this study (CTS-5059).

9.4 Enrollment

A donor is considered to be an enrolled subject following informed consent. It is expected that due to the screening and eligibility requirements, some fraction of subjects will not qualify for a platelet/plasma donation after consent and some who are enrolled may not complete their anticipated procedures. Subjects will be considered screen failures if they fail to meet any of the eligibility criteria, and subjects who do not complete their anticipated procedure (after venipuncture) will be considered as a study procedure discontinuation/termination.

After informed consent has been obtained, subjects will receive a unique study identification (USID) number. The USID number will use the following convention: 59XX-YYY, where XX is the pre-assigned site number and -YYY will be a sequential number starting with 001. The USID number will be recorded on the electronic Case Report Form (eCRF).

Subjects that fail screening criteria on information or laboratory values that are anticipated to change, may be rescreened. Subjects that have incomplete procedures or donated a product that meets any of the protocol analysis exclusions (Section 15.4) may rescreen if they meet all

inclusion criteria when they return. Subjects that are rescreened will be assigned a new USID number.

10 STUDY PROCEDURES

10.1 Screening (Days -30 to 1)

Screening can be performed within 30 days before the apheresis procedure or combined with the Day 1 Apheresis Visit.

The following evaluations will be performed:

1. Informed consent will be obtained prior to initiating any study specific procedures.
2. Eligibility will be confirmed.
3. Demographics (age, gender, ethnic origin), height, weight, and donor identification number will be collected.
4. Venipuncture will be conducted for hemoglobin or hematocrit and platelet count on subjects who are new to the Site or who do not have recent and/or historical hemoglobin and/or platelet count measurements.
5. Record any AEs and SAEs.

10.2 Day of Apheresis (Day 1)

10.2.1 Prior to Apheresis

1. Finger stick for hemoglobin or hematocrit testing.

10.2.2 Apheresis Procedure

Plateletpheresis will be per site standard practice and per applicable FDA guidelines such as the "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods, December 2007" and the "Guidance for Industry: Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion, September 2012".[9,10]

Apheresis procedures will be run according to the instructions and precautions described in the Version 6.0 Trima Accel Operator's Manual and the Version 7.0 user change summary.

The following procedures will be performed:

1. Venipuncture.
2. Collect venous whole blood sample.
    a. Complete blood count (hemoglobin or hematocrit and platelet count).
3. Update Trima Accel device with updated platelet count and hemoglobin or hematocrit.

4. Perform apheresis procedure.
5. Record the following:
    a. Type of cuff used.
    b. Trima procedure details.
    c. AEs, SAEs and UADEs.
    d. Medical interventions to treat AEs, if applicable.
    e. Device deficiencies.

This will conclude the subject's participation.

10.2.3 Data from Collected Platelet and Plasma Products

1. Platelet Product
    a. Dilution factor.
    b. Residual WBC count.
    c. Complete blood count test (platelet count).
    d. Product weight.
2. Plasma Product
    a. Residual WBC count.
    b. Complete blood count tests (platelet count and RBC count).
    c. Product weight.

10.3 Study Procedure Discontinuation/Termination

All subjects are free to withdraw from participation in this study at any time, for any reason, specified and unspecified, and without prejudice. The reason for the subject discontinuing study treatment or terminating from the study will be recorded on the Source Documents (SD) and eCRF.

Reasons for study termination include:

1. Development of an AE that interferes with the subject's continued participation.
2. Subject refuses further treatment and/or follow-up and withdraws consent.
3. After receiving platelet count based on the venous sample, a subject qualifies for a study procedure which has already reached its target enrollment (ie, testing indicates the subject qualifies for single platelet donation; however, 93 subjects have already completed the single platelet product donation).

4. Investigator decision.
5. Sponsor decision.
6. Subject is lost to follow-up.
7. Subject death.

11 LABORATORY TESTS

Laboratory tests will be analyzed locally at each study site. Copies of the current laboratory certifications and normal ranges will be provided to Terumo BCT prior to start of the study and upon every renewal throughout the duration of the study.

12 CONCOMITANT MEDICATIONS

Medications administered to treat AEs will be recorded on the site source documents and eCRFs.

13 ADVERSE EVENTS/EFFECTS

13.1 Anticipated Risks

13.1.1 Potential Apheresis Related Risks

Donor reactions are mostly transient self-limited events, and in very rare exceptions a donor may experience long-term morbidity or sustain permanent impairment.[11,12] Small hematomas, presyncopal episodes, and citrate reactions account for the majority of complications in automated collection procedures, and younger or first-time donors are more likely to experience complications.[12-14] Although rare (< 5 out of 10,000 apheresis donations), almost 40% of reactions requiring medical care outside the donation premises are venipuncture related, including large hematoma, and possible nerve irritation.[14]

13.1.2 Venipuncture Related

The risks associated with venipuncture for blood sampling or intravenous (IV) access include apprehension, pain, discomfort, venospasm, fainting, bruising, infiltration at the venipuncture site, clotting in the IV tubing, and/or administrative errors. Occurrence rates of venipuncture AEs are summarized in Table 13-1.

Table 13-1: Venipuncture Adverse Event Frequency

Location	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very rare < 1/10,000	Not known Sporadic case reports
General[11,13-15]	Apprehension	Presyncope[a]	Faint[b]			
At puncture site[11,13,14,17]		Hematoma		Nerve irritation	Arterial puncture	
		Pain		Infection		
Distant of puncture site[11,13,14,16]		Discomfort			Skin allergy	Phlebitis
					Neuropathic pain	DVT

Abbreviations: DVT = deep venous thrombosis
[a] Presyncope includes symptoms such as pallor, lightheadedness, dizziness, nausea, diaphoresis.
[b] Faint defined as a brief loss of consciousness, usually less than 30 seconds.

13.1.3 Apheresis Complications in Healthy Donors

Apheresis donation is reasonably safe and the majority of complications are mild in nature. While definitions on severity differ in the literature, commonly used parameters to assess severity are the necessity for outside medical care, recovery time, and potential life-threatening consequences. Mild reactions consist of signs and symptoms with a normal recovery time (within 15 min). Moderate reactions usually require medical care and/or have a prolonged recovery time (within 30 min), and severe reactions comprise life-threatening risks and/or recovery time goes beyond 30 min.[17-19] Mild citrate reactions are very common with apheresis procedures, while vasovagal reactions are substantially lower compared to whole blood donation.[14,17] Some donor reactions that have been previously reported for automated collection procedures are anxiety, chills, digit and/or facial paresthesia, fever, headache, hematoma, hyperventilation, hypotension, light-headedness, nausea and vomiting, fainting, unpleasant taste sensations, urticaria, and allergic reactions. Adverse reactions listed in Table 13-2 are general apheresis risks and are not specific to the Trima Accel system.

Table 13-2: Apheresis Adverse Event Frequency

Event type	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very rare < 1/10,000	Not known Sporadic case reports
Citrate Reactions[13,14,17,20]	Paresthesia	Nausea	Vomiting	Tetany	Arrhythmia	Cardiac arrest
		Lightheadedness	Cramps	Seizure		
		Metallic taste	Spasms			
			Chills			
Vasovagal Reactions[a 14,17]		Presyncope[b]	Vomiting	Convulsion	LOC with trauma injury	
		Weakness	Hypotension	Seizure		
			Syncope	Bradycardia		
Other Notable Events[13,14,17,21]						Respiratory distress
						Circulatory collapse
						Anaphylactic reaction
						Hemolysis
						Air emboli
						Death

Abbreviations: LOC = loss of consciousness

[a] Some events might be contributed to accidental (due to disposable/equipment failure causing additional blood loss) hypovolemia instead of a vasovagal reaction.

[b] Presyncope includes symptoms such as pallor, lightheadedness, dizziness, nausea, diaphoresis.

13.1.4 Apheresis Risks with the Trima Accel System

Trima Accel disposable tubing sets are sterilized with ethylene oxide which may cause anaphylactic reactions. Though cases of allergic reactions to ethylene oxide are reported in literature, Terumo BCT has no knowledge that any such event has occurred with the Trima Accel system to date.

13.2 Risk Mitigation

To minimize risks of subject injury, the following general procedures are to be followed:

1. Ensuring that all Investigators are properly qualified and meet pre-specified criteria for Investigator selection and that they and their study teams successfully complete the following training: Site specific training, Human Subject Protection, and Clinical Investigation Plan (CIP) training to include device and procedure training.

2. Ensuring that subjects who are enrolled meet all eligibility criteria, including minimum hemoglobin or hematocrit and platelet limits for donation. The apheresis devices are

programmed to allow collection of products only from subjects who will meet projected hematocrit and platelet standards at the completion of the collection. These limitations are for the safety of subjects and apply to this protocol.

3. Stopping the procedure if moderate or severe AEs occur. The subject can also request that the procedure be stopped at any time.

4. With the collection of protected health information (PHI) associated with this research study, there is a small risk of violation of privacy and loss of confidentiality. The apheresis collections will be documented on the Study Site's SD. Electronic CRFs will be uploaded to the electronic data capture (EDC) with only subject and product number as subject identifiers, to ensure confidentiality.

5. Subjects will be questioned concerning adverse experiences throughout the procedure. Subjects will also be visually monitored for signs of distress during blood donation. Suspected adverse reactions will be treated according to study sites' SOPs and documented on the SD and eCRFs.

13.3 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medical device, whether or not considered related to the medical device and/or procedure. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the medical device and/or procedure.

13.4 Adverse Event Recording

Adverse events that occur after signing the informed consent form (ICF) will be recorded on the AE eCRF.

13.5 Adverse Event Reporting

13.5.1 Severity

This study will utilize the Common Terminology Criteria for Adverse Events [CTCAE] Scale, Version 4.03 for AE grading.[22] The CTCAE includes a grading (severity) scale for each AE term. Grades were developed using the following guidelines:

Grade 0 – No AE or within normal limits.

Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 – Moderate; minimal, local or noninvasive intervention indicated.

Grade 3 – Severe; medically significant but not immediately life threatening.

Grade 4 – Life threatening.

Grade 5 – Fatal.

13.5.2 Relationship

The Principal Investigator (PI) at each site will be asked to document his/her opinion of the relationship of the event to the device and/or procedure(s) as follows:

Not Related:

The event is clearly related to factors other than the study device and/or procedure(s), such as the subject's clinical state.

Possibly Related:

The event follows a reasonable temporal sequence from the time of study treatment administration/ procedure, and/or follows a known response pattern to study device/procedure(s) but could have been produced by other factors, such as the subject's clinical state or other therapeutic interventions.

Probably Related:

The event follows a reasonable temporal sequence from the time of study device/procedure(s) and cannot be reasonable explained by other factors, such as the subject's clinical state or therapeutic interventions.

Definitely Related:

The event follows a reasonable temporal sequence from the time of study device/procedure(s), and follows a known response pattern, and cannot be reasonably explained by other factors. In addition, the event occurs immediately following study procedure(s), and/or improves on stopping the study procedure, and/or reappears on resumption of study procedure(s).

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

13.6 Adverse Event Follow-up

All treatment-related AEs must be followed in accordance with the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (e.g., US Code of Federal Regulations [CFR] 812). The expected AE of mild hematoma (bruise) and/or mild infiltration are not followed to resolution.

13.7 Serious Adverse Events and Unanticipated Adverse Device Effect

13.7.1 Definition

In the interest of subject care and to allow Terumo BCT to fulfill all regulatory requirements, any SAE and/or UADE, regardless of causal relationship to study treatment/procedure(s), must be reported to Terumo BCT within 24 hours of knowledge of the event.

SAEs are defined (21 CFR 312.32 and ISO 14155:2011 Sec. 3.37) as those AEs which meet any of the following criteria:

- Results in death
- Led to serious deterioration in the health of the subject, that either resulted in
- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function, or
- Inpatient or prolonged hospitalization, or
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition or a planned procedure, without serious deterioration in health, is not considered a serious adverse event.

Unanticipated adverse device effect (UADE): per 21 CFR 812.3 a UADE is defined as 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 CIP and/or Trima Accel operators manual, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

NOTE: Anticipated adverse device effects are effects, which by nature, incidence, severity or outcome have been identified in the CIP and/or Trima Accel operators manual.

13.7.2 SAE/UADE Reporting

Any AE/SAE/UADE that occurs after signing the ICF until study completion/termination must be reported. Follow-up (regardless of relationship to the study treatment/procedure[s]) must be reported and an AE/SAE/UADE Form must be submitted to Terumo BCT within 24 hours of knowledge of the event to:

Terumo BCT
Email: ClinicalAffairs@TerumoBCT.com
Fax: (303) 876-9146

Terumo may request additional information from the Investigator to ensure the timely completion of accurate safety reports.

Additionally the SAE/UADE must be entered on the AE page(s) of the CRF. Follow-up SAE/UADE reports need to be submitted to Terumo BCT as soon as additional information regarding the event becomes available.

Terumo BCT will be responsible for reporting SAE/UADEs to the regulatory authorities in accordance with applicable regulatory reporting guidelines. The Investigator is responsible for submitting SAE/UADEs to his/her Institutional Review Board (IRB) as required by local policy.

Exclusions to SAE/UADE Reporting Requirements

The following are not considered SAEs/UADEs:

- Planned hospitalization.
- Anticipated day-to-day fluctuations of pre-existing condition(s) present or detected at the start of the study that do not worsen.

13.8 Clinical Investigation Plan Deviations

A CIP deviation is defined as any event where the Investigator or site personnel deviate from the study CIP or study procedures for any reason.

All CIP deviations will be reported to the Sponsor. Protocol deviations that may affect the scientific soundness of the study or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and the IRB as per the IRB's standard reporting procedure.

13.9 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study at his/her site. There will not be a Data Safety Monitoring Board for this study because it involves healthy subjects undergoing a commonly practiced research evaluation procedure.

Terumo BCT will monitor the safety of the study subjects on an ongoing basis.

14 STUDY DEVICE

14.1 Device Deficiencies

All device deficiencies involving any device component must be reported within 24 hours upon knowledge to the Sponsor utilizing the Device Deficiency Report Form. Every attempt should be made by the Site to save or collect the defective device, and if appropriate, the packaging, for return to the Sponsor. A qualified company representative will investigate and determine root cause and corrective actions as applicable, and directives will be provided to the site if warranted.

14.2 Device Accountability

14.2.1 Receipt of Study Device

The contents should be examined upon receipt to ensure packaging and labeling is intact and the devices have not been damaged. Any damage should be immediately reported to the Sponsor.

14.2.2 Storage

The device and disposables should be stored in a dry place at room temperature. Proper care should be taken to ensure that the study inventory will not be damaged.

14.2.3 Accountability

The Trima Accel device, disposables, arm cuff, InterSol solution, and software will be provided by Terumo BCT for use in this study. The Trima Accel disposables and InterSol solution are FDA cleared and marketed in the United States.

15 STATISTICAL PLAN

The following section summarizes the statistical methods that will be used in the analysis of the clinical data from this active-controlled trial. Continuous variables will be described using means, medians, and measures of dispersion including standard deviation and ranges with categorical variables will be summarized with frequencies and percentages.

15.1 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. [9] With 93 platelet products being collected, 16 failures or fewer is required to show that the proportion of platelet units with an acceptable platelet yield is at least 75% with 95% confidence.

15.2 Outcome Measures

15.2.1 Primary Endpoint

The primary endpoint for this study is the proportion of platelet units with an acceptable residual WBC level. Counts and percentages of success rates and the lower one-sided 95% exact binomial confidence intervals will be calculated separately for success rates of single, double, and triple platelet products. If 0 or 1 failure is observed, then the confidence interval will suggest that the true success rate is at least 95% with 95% confidence for the given platelet product. This approach will be applied independently to single, double, and triple platelet products.

15.2.2 Secondary Endpoint

The secondary endpoint of platelet yield will be summarized for single, double, and triple platelet products. Separately for single, double, and triple platelet products, the lower one-sided 95% exact binomial confidence intervals will be calculated for the proportion of platelet units with an acceptable platelet yield. If 16 or fewer failures are observed, then the confidence interval will suggest that the true success rate is at least 75% with 95% confidence for the given platelet product.

15.2.3 Safety Measures

Adverse events will be summarized by the medical dictionary for regulatory activities (MedDRA Version 18.1 or later). Tables will describe the frequency and percentage of all AEs, SAEs, and UADEs reported by subjects in the safety population. Presentations will summarize AEs by maximum reported severity and relationship to device and procedure. AEs leading to study or procedure discontinuation will also be tabulated.

15.3 Analysis Populations

The safety population will include of all subjects enrolled in this trial for whom at least 1 apheresis procedure is initiated. The Full Analysis Set (FAS) will be defined separately for single, double, and triple platelet products. The FAS for a given platelet product will consist of the first 93 collections that do not meet any of the protocol exclusion criteria described in Section 15.4. The FAS will be used to examine the primary and secondary endpoints.

15.4 Protocol Analysis Exclusions

Data points will be excluded from 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 (ie 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 that affects the primary or secondary endpoint 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 collection or 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. Solution other than InterSol added to platelets prior to storage.

    g. Results of endpoint assays are not available.

16 STUDY MANAGEMENT

16.1 Investigator Responsibilities

16.1.1 Investigator Agreement

Each Investigator will provide the Sponsor a copy of his/her current curriculum vitae and a signed Investigator Agreement, prior to initiation of the study.

16.1.2 Institutional Review Board

The IRB or other committee functioning in a similar capacity will review and approve the protocol and any protocol amendments, initial and revised informed consent (IC) documents, and recruitment materials, if applicable. After approval by the IRB, documentation of approval and the approved IC document will be sent to Terumo BCT before any subject is enrolled into this study.

16.1.3 Informed Consent

The Investigator is responsible for preparing the written IC document for this study. Terumo BCT will provide the Investigator an IC template. The Investigator may rearrange or reword the contents of the template, or may add other elements or language, provided the meaning and content are not changed or deleted.

Prior to subject participation in this study, the Investigator must obtain written IRB approval for the protocol and the ICF. The approved consent form will clearly reflect the IRB approval date.

Once the subject's initial eligibility has been determined, the Investigator or person designated by the Investigator, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, answer questions for the subject and ask the subject to participate in the study. The study will be explained to the study subject in lay terms, in their native language in a quiet, non-disruptive setting. Potential subjects will be given as much time and privacy as necessary to review the informed consent prior to agreeing to participate in the study. Additionally, if the subject desires, they can take a copy of the consent with them so that they can discuss potential participation with others outside the study team. If the subject agrees to participate, the subject has read the ICF, and has had all of their questions answered, then the ICF must be signed and personally dated by the subject and the person completing the consent process. A copy of the signed and dated ICF will be provided to the study subject.

All subjects are free to withdraw from participation in this study at any time, for any reason(s), specified or unspecified, and without prejudice. The reason(s) for the subject discontinuing or terminating from the study must be recorded on the eCRF.

16.1.4 Study Files and Record Retention

Investigational sites will maintain all records pertaining to this study for a minimum of 2 years following pre-market approval or 2 years after the study is discontinued. The sponsor will notify investigational sites of the discontinuation. Prior to discarding any study-related records, all clinical sites must contact the sponsor for direction.

16.1.5 Regulatory Compliance

Sites are responsible for meeting all applicable FDA regulations (eg, 21 CFR 600-680 and 21 CFR 800) and AABB standards. Sites will be responsible for staying current on new standards and meeting any new regulations which may be implemented during the course of this study.

16.2 Sponsor Responsibilities

16.2.1 Amendments to the Clinical Investigation Plan

Any amendment to the protocol, as deemed appropriate by Terumo BCT, will be implemented as the study progresses. Amendments will be submitted to the IRB for written approval, before implementation.

16.2.2 General Responsibilities

As per ISO 14155 Section 8 and 21 CFR 812, Terumo BCT is responsible for selecting qualified Investigators and providing them with the information they need to conduct the investigation properly, ensuring quality study conduct and proper monitoring of the investigation, ensuring required approvals are obtained and that significant new information about an investigation is promptly reported to reviewing IRB/EC and government authorities as well as annual reports as required.

16.3 Joint Investigator-Sponsor Responsibilities

16.3.1 Training

The Sponsor will train applicable study team members as to the device, protocol, and study procedures and will provide updated information as it becomes available during the course of the study, if applicable. The Investigator is responsible for ensuring that additional site personnel that were not trained by the Sponsor receive applicable documents and training.

16.4 Collecting and Recording Data

The Investigators will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by Terumo BCT access to all study data at any time. Such data shall also be secured in order to prevent loss of data.

All required data for this study will be recorded from the source documentation onto standardized eCRFs.

16.4.1 Source Documents

Source data is all information, original records of clinical observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of that trial. Source data are contained in source documents. Examples of these original documents and data records include Blood Center records, evaluation checklists, and laboratory results.

16.4.2 Case Report Forms

The study eCRF via EDC is the primary data collection instrument for the study. All data must be recorded in English. Any missing data must be explained.

Completed eCRFs will be reviewed and signed by the Investigator. The CRA will verify the EDC data with the subject's source data, evaluate the data for accuracy, consistency, and completeness, and will ensure that all forms with missing data and/or errors are ultimately addressed. Accurate and complete eCRFs for a subject must be completed in a timely manner.

16.5 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol

16.6 Termination of the Study

For reasonable cause, either the Investigator or the Sponsor may terminate the Investigator's participation in this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement (CTA). In addition, Terumo BCT may terminate the study at any time upon immediate notice for any reason, including but not limited to, Terumo BCTs' belief that termination is necessary for the safety of subjects or failure to meet the primary endpoints.

16.7 Publication Policy

Terumo BCT recognizes the importance of communication of medical study data, and encourages the publication of such data in reputable scientific journals and the presentation of such data at scientific seminars and conferences. Any proposed publication or presentation of the data generated from the study must be provided to Terumo BCT for timely review in accordance with the terms of the CTA between the Investigator, the Institution, and Terumo BCT. Terumo BCT shall not, in its scientific publications or promotional material, quote from publications by Investigators without full acknowledgment of the source. As this will be a multi-site study, all

Investigators agree not to publish individual site data. All study data will be published as 1 or more manuscripts based on the accumulated data from all study sites.

17 REFERENCES

1. Jaben EA, Gandhi MJ. The post-platelet 100,000 count: Effects of platelet collection and future. Journal of clinical apheresis 2011;26(1):53-5.
2. Ness PM, Campbell-Lee SA. Single donor versus pooled random donor platelet concentrates. Current opinion in hematology 2001;8(6):392-6.
3. Akahoshi M, Takanashi M, Masuda M, et al. A case of transfusion-associated graft-versus-host disease not prevented by white cell-reduction filters. Transfusion. 1992;32(2):169-172.
4. Hayashi H, Nishiuchi T, Tamura H, Takeda K. Transfusion-associated graft-versus-host disease caused by leukocyte-filtered stored blood. Anesthesiology. 1993;79(6):1419-1421.
5. Alhumaidan H, Sweeney J. Current status of additive solutions for platelets. J Clin Apher 2012;27(2):93-8.
6. Holme S, Heaton WAL, Whitley P. Platelet Storage Lesions in Second Generation Containers: Correlation with in vivo Behavior with Storage up to 14 Days. Vox Sanguinis 1990;59(1):12-8.
7. Slichter SJ, Corson J, Jones MK, Christoffel T, Pellham E, Bailey SL, Bolgiano D. Exploratory studies of extended storage of apheresis platelets in a platelet additive solution (PAS). Blood 2014;123(2):271-80.
8. American Association for Blood Banks. Donor Services Training Manual. September 2012.
9. Center for Biologics Evaluation and Research. Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods. December 2007.
10. Center for Biologics Evaluation and Research. Guidance for Industry: Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion. September 2012.
11. Sorensen BS, Johnsen SP, Jorgensen J. Complications related to blood donation: a population-based study. Vox sanguinis. Feb 2008;94(2):132-137.
12. Gavillet M, Tissot JD, Canellini G. Blood donation associated risks: data from a Swiss regional haemovigilance program. Transfusion medicine. Aug 2013;23(4):269-271.
13. Danic B, Lefort C. Effets indésirables donneurs et leur prise en charge. Transfusion Clinique et Biologique. Dec 2010;17(5–6):301-305.
14. Eder AF, Dy BA, Kennedy JM, et al. The American Red Cross donor hemovigilance program: complications of blood donation reported in 2006. Transfusion. Sep 2008;48(9):1809-1819.
15. Deacon B, Abramowitz J. Fear of needles and vasovagal reactions among phlebotomy patients. Journal of anxiety disorders. 2006;20(7):946-960.

16. Sorensen BS, Jorgensen J, Jensen TS, Finnerup NB. Pain following blood donation: a questionnaire study of long-term morbidity (LTM) in blood donors. Vox sanguinis. Mar 31 2015.

17. McLeod BC, Price TH, Owen H, et al. Frequency of immediate adverse effects associated with apheresis donation. Transfusion. Oct 1998;38(10):938-943.

18. Wiltbank TB, Giordano GF. The safety profile of automated collections: an analysis of more than 1 million collections. Transfusion. Jun 2007;47(6):1002-1005.

19. Shehata N, Kusano R, Hannach B, Hume H. Reaction rates in allogeneic donors. Transfusion medicine. Oct 2004;14(5):327-333.

20. Makar YF, Butler MO, Cockersole GM, Gabra G, Serevitch JM. National audit of citrate toxicity in plateletpheresis donors. Transfusion medicine. Jun 2002;12(3):187-191.

21. Nakajima K. Donor complications and donor care. ISBT Science Series. 2009;4(n2):411-417.

22. Health, U.S.D.o. and S. Human, *Common terminology criteria for adverse events (CTCAE)*. 2012.

18 INVESTIGATOR SIGNATURE

Study Title:	Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in Platelet Additive Solution
Study Number:	CTS-5059
Version/Date:	Version 4.0/22 NOV 2016

I have read the clinical investigation plan, including all appendices, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will conduct this study in compliance with the clinical investigation plan, Good Clinical Practices, and all applicable regulations. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the clinical investigation plan and grant access to all information provided by Terumo BCT. I will discuss this material with all study personnel under my supervision to ensure that they are fully informed about the study.

Investigator Name (printed)	Signature
Date	