CLINICAL INVESTIGATION PLAN

Study Title:	An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution
Study Number:	CTS-5066
Study Device:	Trima Accel® Apheresis system and InterSol Solution
Manufacturer:	Terumo BCT, Inc. 10811 West Collins Avenue Lakewood, CO 80214 USA Phone: (303) 231-4832
Sponsor:	Terumo BCT, Inc. 10811 West Collins Avenue Lakewood, CO 80214 USA Phone: (303) 231-4832
Contact:	Heather Pidcoke, MD, PhD Phone: (303) 231-4832 Email: Heather.Pidcoke@terumobct.com

This study will be conducted according to this Clinical Investigation Plan, 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 14145:2011(E), and other regulatory requirements of the regions where the study is conducted. All essential documents will be archived.

Version/Date: 2.0/10 JUL 2017

Confidentiality Statement

CLINICAL INVESTIGATION PLAN APPROVAL

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AMENDMENT 1 SUMMARY OF CHANGES

Study Title:	An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution	
CIP #:	CTS-5066	
Amendment Version / Date:	Version 2.0/10 JUL 2017	
Replaces CIP Version / Date:	Version 1.0/27 FEB 2017	
Rationale:	This CIP was updated to clarify that participants are not allowed to take aspirin or aspirin containing medications, non steroidal anti inflammatory drugs (NSAIDs), anti-platelet agents, or other drugs affecting platelet viability for the duration of the study. Because the study's primary endpoints relate to platelet survival and recovery, this clarification is necessary to ensure the platelets being evaluated are not exposed to drugs affecting their viability throughout the study. Additionally, this amendment ensures participants are aware that they are not permitted to take these medications, and if they do, they will be discontinued from the study. The inclusion criteria, study procedures, and reason for study procedure discontinuation/termination were updated to better clarify this requirement. Additionally, this CIP amendment addresses a minor typographical error noted by the United States Food and Drug Administration (FDA) in the section of the CIP outlining the number of participants. The CIP incorrectly stated "an approximate 45% screen fail/early termination rate which would allow up to 40 healthy adult participants to be enrolled in this study". Applying a 45% screen fail/early termination rate would result in total enrollment of 44 subjects. This study will only enroll up to 40 healthy adult participants, therefore the approximate screen fail/early termination rate was changed from 45% to 40%. Administrative changes, typographical error corrections, abbreviations 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 10.1 Number of Participants and Selection, and Section 16.1 Sample Size	Assuming an approximate 45% screen fail/early termination rate, up to 40 healthy adult participants will be enrolled in this study to ensure 24 evaluable data points across 2 investigational sites in the United States.	Assuming an approximate **40**% screen fail/early termination rate, up to 40 healthy adult participants will be enrolled in this study to ensure 24 evaluable data points across 2 investigational sites in the United States.
Synopsis and Section 10.2 Inclusion Criteria	Has been added	**8. Participants must agree to refrain from using aspirin or aspirin containing medications, non steroidal anti inflammatory drugs (NSAIDs), anti-platelet agents, or other drugs affecting platelet viability for the duration of the study**

Table 11-1 in Section 11 Study Procedures	Confirm participant is healthy and did not take any exclusionary medications on Apheresis Visit and Infusion Day	Confirm participant is healthy on Apheresis Visit and Infusion Day **Record any medications taken in the 7 days prior to apheresis procedure and through study completion on Apheresis Visit, Infusion Day, and Post-Infusion Days** Confirm participant ~~is healthy and~~ did not take any exclusionary medication[b] on Apheresis Visit, Infusion Day, **and Post-Infusion Days** Record ~~medications~~ **medical interventions** to treat ~~any~~ AEs or SAEs **[b] Exclusionary medication includes aspirin or aspirin containing medications, NSAIDs, anti-platelet agents, or other drugs affecting platelet viability.**
Section 11.2.1 Prior to Apheresis Visit	1. Confirm participant is healthy and did not take any excludable medication if screening visit was prior to apheresis visit	1. Confirm participant is healthy **2. Record any medications taken in the 7 days prior to the Apheresis Visit and during this visit.** **3. Confirm the participant** did not take any excludable medication **(see Section 13)** if screening visit was prior to apheresis visit
Section 11.2.2 Apheresis Procedure; Section 11.4 Infusion Day; Section 11.5.1 Post Infusion Days 6-12 (BEST Days 1-7); Section 11.5.2 Post Infusion Day 16 ± 1 day (BEST Day 11 ± 1 day)	Record medications or medical interventions to treat AEs or SAEs	Record ~~medications or~~ medical interventions to treat AEs or SAEs
Section 11.4 Infusion Day; Section 11.5.1 Post Infusion Days 6-12 (BEST Days 1-7); Section 11.5.2 Study Day 16±1 day (BEST Day 11±1 day)	Has been added	**2. Record any concomitant medications taken since previous visit and during this visit**
Section 11.5.1 Study Days 6-12 (BEST Days 1-7) and Section 11.5.2 Study Day16 ± 1 day (BEST Day 11 ± 1 day)	Has been added	**1. Confirm participant did not take any exclusionary medication since previous visit**
Section 11.5.1 Study Days 6-12 (BEST Days 1-7)	Has been added	**2. Record any concomitant medications taken since previous visit and during these visits**

Section 11.6 Study Procedure Discontinuation/Termination	Has been added	**17. Participant took exclusionary medication (see Section 13)**
Section 13 Concomitant Medications	Only medications administered to treat AEs or SAEs will be recorded in the eCRFs.	**Participants are prohibited from taking aspirin or aspirin containing medications for 7 days prior to the apheresis procedure, and NSAIDs, anti-platelet agents, or other drugs affecting platelet viability for 3 days prior to the apheresis procedure. Once enrolled in the study, participants are prohibited from taking these medications throughout their participation in the study.** **Concomitant medications taken from the 7 days before the apheresis visit until study exit will be recorded in the eCRFs.** **Medical interventions** administered to treat AEs or SAEs will be recorded in the eCRFs.

SYNOPSIS

Sponsor:	Terumo BCT, Inc.
Study Title:	An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution
Study Number:	CTS-5066
Target Population:	Healthy Adult Volunteer Donors
Device Description:	The Trima Accel® Automated Blood Collection system (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 Acid Citrate Dextrose, Formula 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. Terumo BCT's Trima Accel system received United States Food and Drug Administration (FDA) 510(k) clearance for hyperconcentrated platelet collections on 17 December 2012 (BK120049). Fenwal's InterSol® was cleared by the FDA on 09 December 2009 (BN080041), as a platelet additive solution (PAS) for the replacement of 65% plasma in platelet components for use with Amicus™ Separator System.
Intended Use:	The intended use for the Trima Accel system and PAS (InterSol) combination to be evaluated in this investigational study is to use the Trima Accel system to collect platelet concentrates from normal healthy donors and to re-suspend the platelets in 35% plasma and 65% InterSol for storage and subsequent transfusion into patients requiring blood product support.
Study Centers Planned:	2 centers in the United States.
Objective:	The primary objective of this study is to determine the in vivo recovery and survival of radiolabeled platelets collected on the Trima Accel system, diluted in 65% InterSol/35% plasma, and stored for 5 days.
Efficacy Endpoints:	<u>Primary Efficacy Endpoints:</u> The primary endpoint for this study will be recovery and survival as calculated using the COST software. 1. For recovery: Test – 0.66*Control ≥ 0 with a 1 sided 97.5% confidence limit 2. For survival: Test – 0.58*Control ≥ 0 with a 1 sided 97.5% confidence limit
Safety Endpoints:	Safety will be monitored through the collection of adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs) from the start of the apheresis procedure venipuncture until study completion. Products will be destroyed per the site's standard operating procedures (SOPs) after all testing has been completed.

Inclusion Criteria:	1. Age 18 years or older 2. Normal health status as per AABB criteria for healthy donor 3. Able to commit to the study schedule 4. Meets the inclusion criteria defined by the Blood Center for apheresis platelet with PAS collection on the Trima Accel system. These criteria are based on FDA Regulations and AABB standards. Note: Participants who are deferred from volunteer community donations because of travel restrictions, piercings, or tattoos may participate in the study, as products are not transfused 5. Participants of child-bearing potential (either male or female) must agree to use an effective method of contraception during the course of the study 6. Females of childbearing potential must be willing to take a pregnancy test prior to infusion of radiolabeled platelets 7. Has given written informed consent 8. Participant must agree to refrain from using aspirin or aspirin containing medications, non steroidal anti inflammatory drugs (NSAIDs), anti-platelet agents, or other drugs affecting platelet viability for the duration of the study
Exclusion Criteria:	1. Previously received radiation therapy 2. Has been diagnosed with a platelet disorder (ie, platelet dysfunction) 3. Already participated in 4 research studies involving radioisotopes within the contemporaneous calendar-year 4. Pregnant or nursing females 5. Participation currently, or within the last 12 months, in another investigational trial that would potentially interfere with the analysis of this investigation 6. History of known hypersensitivity to indium or chromium 7. Treatment with aspirin or aspirin containing medications within 7 days of apheresis or treatment with NSAIDs, anti-platelet agents or other drugs affecting platelet viability within 3 days of apheresis (eg, ibuprofen or other NSAIDs)
Number of Participants Planned:	Assuming an approximate 40% screen fail/early termination rate, up to 40 healthy adult participants will be enrolled in this study to ensure 24 evaluable data points across 2 investigational sites in the United States.

Study Design:	This is a prospective, open-label, multicenter, controlled study to evaluate in vivo recovery and survival of radiolabeled apheresis platelets collected on the Trima Accel system and stored in 65% InterSol/35% plasma for 5 days. One (1) Test unit will be collected as a hyperconcentrated platelet product. The Test unit will be diluted to a final ratio of 65% InterSol/35% plasma. After collection, the Test unit will be stored at room temperature with agitation for 5 days. On Day 5, study sites will follow the "Platelet Radiolabeling Procedure" published by Biomedical Excellence for Safer Transfusion (BEST) and their SOPs for platelet radiolabeling, infusion, radioactivity sampling, and recovery and survival calculations. Following storage for 5 days, an aliquot of Test platelets will be radiolabeled with either ^{111}In or ^{51}Cr. Similarly an aliquot of freshly prepared platelets derived from a whole blood sample donated on Day 5 (Control) will be tagged with the radiolabel not used in the Test platelets. The identity of the label (^{51}Cr or ^{111}In) used for Test and Control platelets will be randomized. The labeled aliquots will then be infused simultaneously on Day 5 (BEST Day 0) back to the autologous donor. On Study Day 5 (BEST Day 0) samples will be drawn at 0 (pre-infusion) and 2 hours ± 15 minutes post-infusion. Next, 1 sample will be drawn daily (except on weekends) from Study Day 6 through Day 12 (BEST Day 1 − 7) for a total of 5 samples. To conclude, 1 final sample will be drawn on Study Day 15, 16, or 17 (BEST Day 10, 11, or 12). Recovery and survival will be calculated at each site according to the COST software.
Study Duration:	Study participation will be up to 9 visits. Screening may be done within 5 days prior to the apheresis procedure or combined as 1 visit, which includes screening and the apheresis procedure all in 1 day. The entire study is anticipated to last approximately 5 months.
Statistical Methodology:	Primary Endpoints: The primary endpoints of this study are to show that recovery and survival of platelets collected on the Trima Accel system, diluted in 65% InterSol/35% plasma and stored for 5 days meet FDA standards defined by: • For recovery: Test – 0.66*Control ≥ 0 with a 1-sided 97.5% confidence limit • For survival: Test – 0.58*Control ≥ 0 with a 1-sided 97.5% confidence limit Recovery (at 24 hours) is expressed as a percentage of the extrapolated platelet count at time 0. Survival is expressed in hours and is approximated using linear regression. For each endpoint, paired differences within each participant will be used to construct the lower limit of a 1-sided 97.5% confidence intervals. If the lower limit is greater than 0 for both endpoints, the test product will be declared to meet the FDA standard.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

^{111}In	Indium 111
^{51}Cr	Chromium 51
ACD-A	Anticoagulant Citrate Dextrose, Solution A
AE	Adverse Event
BEST	Biomedical Excellence for Safer Transfusion
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
ESC	Extent of Shape Change
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HCO^3	Bicarbonate
Hgb	Hemoglobin
HSR	Hypotonic Shock Response
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
LDH	Lactate Dehydrogenase
LOC	Loss of Consciousness
MedDRA	Medical Dictionary For Regulatory Activities
MOP	Manual of Procedures
mg	Milligram(s)
mL	Milliliter(s)
NSAID	Non-steroidal Anti-inflammatory Drugs
PAS	Platelet Additive Solution
pCO_2	Partial Pressure of Carbon Dioxide

PHI	Protected Health Information
pO_2	Partial Pressure of Oxygen
PVC	Polyvinyl Chloride
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Source Documents
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
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, chemotherapy, and in thrombocytopenic individuals (have low platelet count) as well as those with platelet dysfunctions. The platelets used for platelet transfusions are separated from donor blood through either whole blood collections or advanced apheresis techniques. In the United States, the majority of platelets used for transfusion are routinely collected and stored in 100% donor plasma.

In Europe it is common practice to replace part of the storage plasma with a platelet additive solution (PAS). The rationale behind this is that diluting the plasma with PAS may reduce the risk of deleterious reactions such as allergic reactions because there are fewer cellular mediators present than found in 100% plasma.[1] Substituting PAS for plasma may have other advantages as well. Platelet additive solutions have a more consistent composition than plasma from different donors, can be optimized for longer storage, and allow for a more frugal use of blood components since more plasma can then be used for other applications instead of platelet storage.[2,3]

Platelet additive solutions have 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 InterSol Solution (a PAS-E) as a replacement of 65% plasma in platelet components. A second PAS, Isoplate™ Solution (a PAS-F), has since been cleared by the FDA (March 5, 2015, BN090067/0). In Europe, platelet additive solutions and apheresis devices are approved separately, but in the United States the use of a PAS is linked to the specific apheresis device used to obtain the platelets. The Isoplate Solution is approved for use with the Trima Accel® Automated Blood Collection System (Trima Accel system) and the InterSol Solution (hereon referred to as InterSol) is approved for use with the Amicus™ Separator System (Amicus).

Terumo BCT is pursuing FDA clearance for InterSol in combination with the Trima Accel system in order to provide blood centers with the option to use InterSol as well as Isoplate Solution when collecting platelets to be stored in a PAS.

2 DEVICE DESCRIPTION

2.1 Trima Accel System Device Description

The Trima Accel system is an automated blood component collection system that uses centrifugal force to separate whole blood into platelet, plasma, and red blood cell (RBC)

components. These blood components are either collected into storage bags, or returned to the donor. The Trima Accel system consists of:

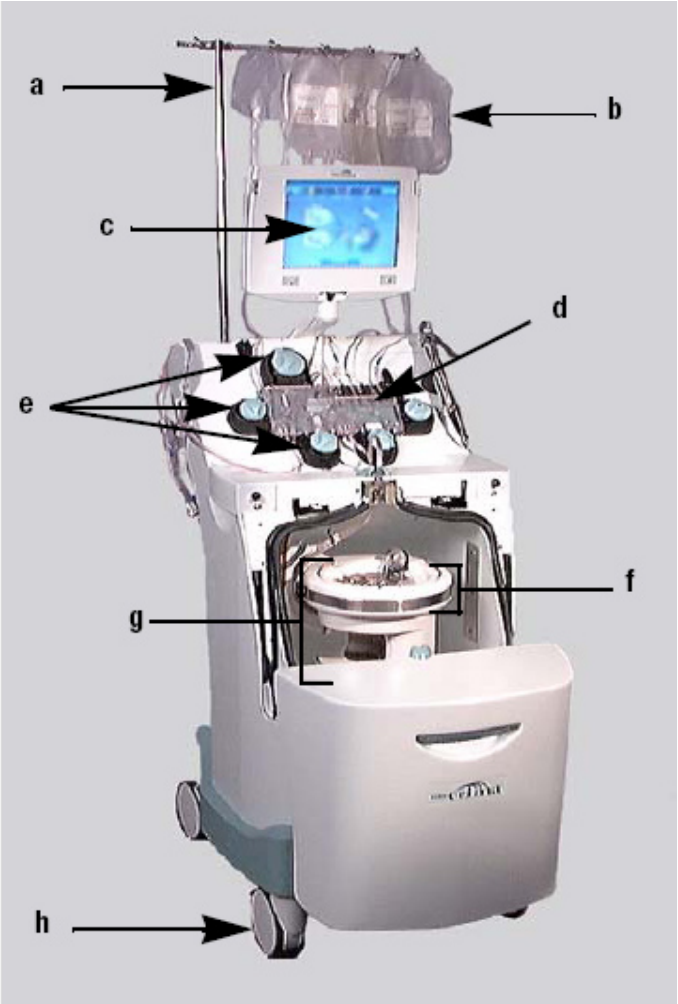
- The Trima Accel machine
- Embedded software
- Disposable tubing sets
- Optional accessories, connected to the system which can include:
    - Accessory storage plasma bag
    - Accessory storage platelet bag
    - Trima Accel seal safe system
    - Trima barcode scanner kit

The products collected depend on the disposable tubing collection set used, the donor specific parameters (donor's total blood volume, hematocrit [HCT] or hemoglobin [Hgb], and platelet count) entered at the time of collection, and the procedure selected. Donor blood type may also be used to limit which blood components are collected.

The current Trima Accel system equipment is approximately 42 inches tall and 21 inches wide, and weighs less than 200 pounds. The Trima Accel system uses disposable tubing sets with a cassette that automatically loads the tubing into the pumps, valves, and sensors. The touch screen display is designed to lead the operator through the setup and operating procedures, and provide detailed messages to assist in troubleshooting the collection procedures.

Figure 2-1 identifies the major components of the Trima Accel system.

Figure 2-1: Components of the Trima Accel System



a. The IV pole is a metal tube with an arm that contains hooks for hanging the product bags. The pole is lowered for transport.
b. The product bags are part of the disposable tubing set. Product bags hold the collected RBCs, platelets, and plasma.
c. The touch-screen display is the screen that is used to monitor and control the blood collection procedure. Throughout the procedure, the display guides the operator from step to step.
d. The cassette is part of the disposable tubing set that snaps into place on the front of the system. The cassette guides the flow of blood and blood products through the system. It also ensures that the tubing is positioned so that the pumps, valves, and sensors are loaded automatically.
e. The 5 pumps are the components that push the blood and products through the system.
f. The filler is designed with a groove in which the channel is loaded. The filler comprises the top portion of the centrifuge.
g. The centrifuge is a rotating device that spins at up to 3,000 rpm, creating a gravitational force to separate the whole blood into its components.
h. The wheels can be locked in position to stabilize the Trima Accel system during a collection procedure or unlocked to easily move the Trima Accel system to a new location.

The Trima Accel system was cleared by FDA for the collection of hyperconcentrated platelets stored in Isoplate (BK120049) on 17 December 2012. There will be no modification to the Trima Accel device for this study and it will be used as described in the Trima Accel Operator's Manual.

The Trima Accel Platelet + Sampler + AutoPAS MultiPlasma, RBC disposable set was cleared by the FDA (BK120049) on 17 December 2012. This disposable set will be used for the collection of hyperconcentrated platelets in this study as described in the Trima Accel Operator's Manual.

2.2 InterSol Solution

InterSol, from Fenwal™, a Fresenius Kabi company, was FDA approved for the storage of hyperconcentrated platelets (BN080041) on 09 December 2009. InterSol is an isotonic solution

designed to replace a proportion of the plasma used in the storage of Amicus derived leukoreduced apheresis platelets under standard blood banking conditions.

The solution contains: sodium acetate as a nutrient, sodium citrate to prevent platelet clumping and activation, sodium phosphate for buffering, and sodium chloride for osmolarity. InterSol 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 normally used.

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

Each 100 mL 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.[4]

3 INTENDED USE STATEMENT

The intended use for the Trima Accel system and PAS (InterSol) combination to be evaluated in this investigational study is to use the Trima Accel system to collect platelet concentrates from normal donors and to re-suspend the platelets in 35% plasma/65% InterSol for storage and subsequent transfusion into patients requiring blood product support.

4 CLINICAL STUDY EXPERIENCE

A randomized, paired, prospective, open-label, multicenter, controlled study was conducted in 2016 to evaluate the in vitro quality of platelets collected on the Trima Accel system and stored for up to 7 days in 65% InterSol/35% plasma (Test) compared to platelets stored in 100% plasma (Control). All the Test products had a pH $\geq$ 6.2 after 5 and 7 days of storage and thus met the FDA acceptance criteria for pH.[5,6]

Secondary endpoint analyses of partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), bicarbonate (HCO_3^-), lactate, glucose, lactate dehydrogenase (LDH), extent of shape change (ESC), hypotonic shock response (HSR), morphology, and P-selectin were performed after storage of the products for 5 and 7 days. Of these secondary endpoints, only ESC, HSR, morphology, and P-selectin had established acceptance criteria. Morphology met the established acceptance criteria but ESC, HSR, and P-selectin values did not. The results from this study of Trima Accel collected platelets stored in InterSol are consistent with results of similar studies evaluating Amicus collected platelets stored in InterSol.[6,7]

5 RATIONALE FOR THE CURRENT STUDY

This is a prospective, open-label, multicenter, controlled study to evaluate the in vivo platelet recovery and survival of hyperconcentrated platelets collected on the Trima Accel system and stored for 5 days in InterSol. In order to promote better standardization among the industry for determining the safety and effectiveness of different platelets products (ie, different collection methods, different processing procedures, and/or different storage conditions), the FDA has issued guidance outlining the appropriate study design for in vivo platelet evaluation.[8] This guidance recommends the radiolabeling of both stored (Test) and fresh (Control) platelets and their autologous reinfusion for the determination of recovery and survival.[8] Using these recommendations, the Biomedical Excellence for Safer Transfusion (BEST) Collaborative generated a platelet radiolabeling protocol that provides a detailed procedure for the generation, infusion, timing of blood draws, and calculations needed to determine the platelet recovery and survival of new platelet products.[9]

Using the BEST Collaborative protocol, this study will determine the recovery and survival of 5 day platelets stored in 65% InterSol/35% plasma. Specifically, a single hyperconcentrated platelet unit will be collected on the Trima Accel system, diluted with 65% InterSol/35% plasma, and stored at room temperature with agitation for 5 days (Test). On Study Day 5, the Test platelets will be radiolabeled with either Indium 111 (^{111}In) or Chromium 51 (^{51}Cr) according to a predetermined randomization scheme and their recovery and survival will be compared to fresh platelets (Control) radiolabeled with the other radioisotope (^{111}In or ^{51}Cr). The recovery and survival of Test platelets will be calculated at each site according to the COST software.

6 OBJECTIVE

The primary objective of this study is to determine the in vivo recovery and survival of radiolabeled platelets collected on the Trima Accel system, diluted in InterSol, and stored for 5 days.

7 EFFICACY ENDPOINTS

7.1 Primary Efficacy Endpoints

The primary endpoint for this study will be the recovery and survival of platelets as calculated using the COST software. Recovery (at 24 hours) is expressed as a percentage of the extrapolated platelet count at time 0. Survival is expressed in hours and is approximated using linear regression.

1. In vivo radiolabeled platelet recovery > 66%
2. In vivo radiolabeled platelet survival > 58%

For each endpoint, paired differences within each participant will be used to construct the lower limit of a 1-sided 97.5% confidence interval. If the lower limit is greater than 0 for both endpoints, the test product will be declared to meet the FDA criteria.

8 SAFETY ENDPOINTS

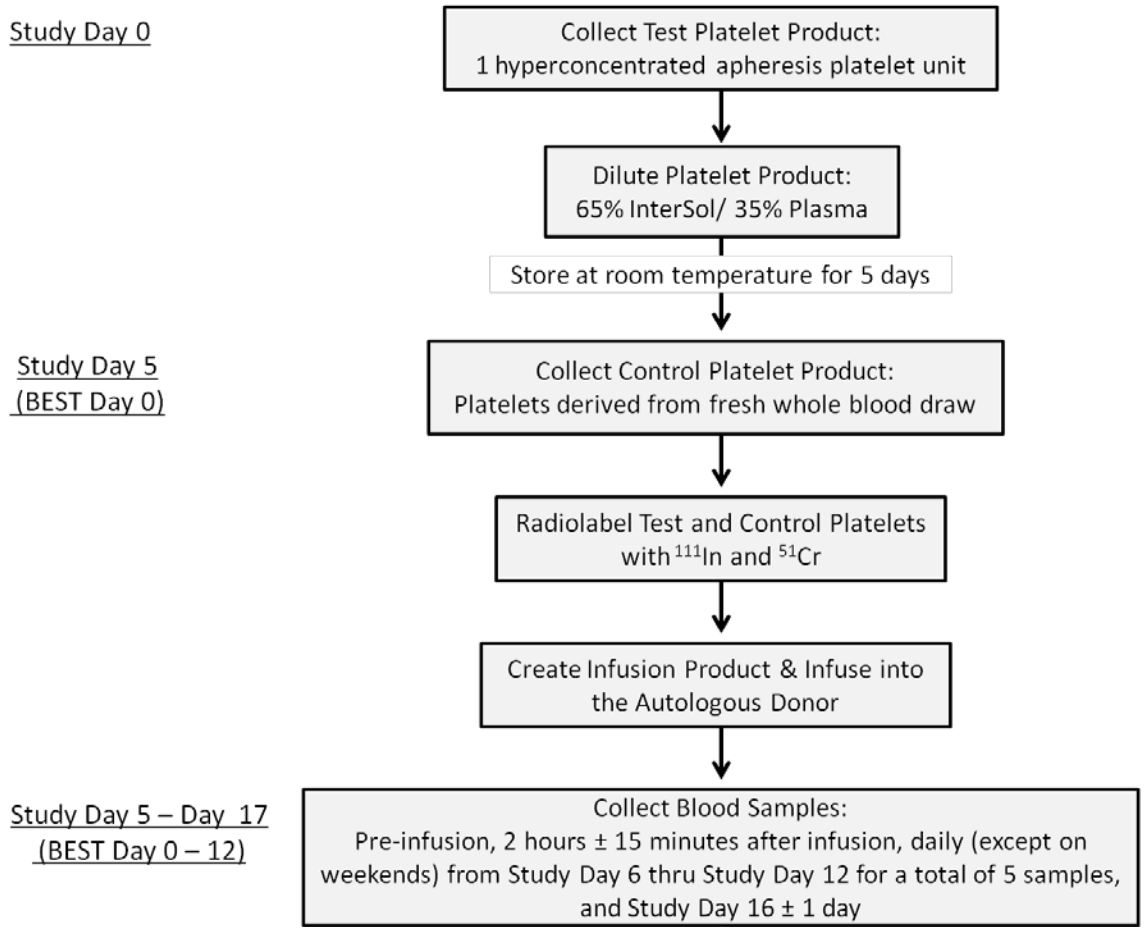
Safety will be monitored through the collection of adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs) from the start of the apheresis procedure venipuncture until study completion.

9 INVESTIGATIONAL PLAN

9.1 Study Design

This is a prospective, open-label, multicenter, controlled study to determine the in vivo recovery and survival of radiolabeled hyperconcentrated platelets collected on the Trima Accel system and stored for 5 days in 65% InterSol/35% plasma. An outline of the full study design is provided in Figure 9-1.

Figure 9-1: Study Design



Up to 40 participants will be enrolled to ensure 24 evaluable collections across 2 investigational sites. An evaluable collection is defined as the participant completing the recovery and survival procedure and neither the participant or the product meeting any of the Clinical Investigation Plan (CIP) analysis exclusion criteria outlined in Section 16.4.

Two (2) sets of platelets will be collected from each participant:

- A Test unit - A hyperconcentrated platelet product collected on the Trima Accel system and diluted to a final ratio of 65% InterSol/35% plasma through the addition of InterSol directly to the platelet bag by the Trima Accel system after collection.
- A Control sample - Fresh platelets prepared from a whole blood sample drawn from the same donor on Study Day 5 in accordance with the BEST Collaborative.

After donation of a Test unit, study participants will return to the site on Study Day 5 to begin the radiolabeled recovery and survival procedure. Test and Control platelets (prepared from a whole blood sample collected that day) will be prepared and radiolabeled with either ^{111}In or ^{51}Cr following the labeling and washing procedures outlined by the BEST Collaborative.[9] The choice of the radioisotope used will be randomly determined for each participant based on a

randomization scheme provided to each site from the Sponsor. After infusion with the radiolabeled Test and Control platelets, blood samples for radioactivity measurements and the calculations to determine platelet recovery and survival will be conducted by the sites as outlined in the BEST Collaborative.[9] Recovery and survival will be calculated at each site according to the COST software.

9.2 Study Duration

Study participation will be up to 9 visits. Screening may be done within 5 days prior to 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, depending on the machine configuration, participant parameters, the quality of the vascular access, and the tolerance of the participant to the Anticoagulant Citrate Dextrose, Solution A (ACD-A).

After the apheresis collection, participants will be asked to return to the site 5 days later for the collection of fresh (Control) platelets and to be infused with an aliquot of the radiolabeled Test and Control platelets. Participants will then return to the site for whole blood sample collections as described in Section 11.

The entire study is anticipated to last approximately 5 months.

10 STUDY POPULATION

10.1 Number of Participants and Selection

Assuming an approximate 40% screen fail/early termination rate, up to 40 healthy adult participants will be enrolled in this study to ensure 24 evaluable data points across 2 investigational 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. Participants will be recruited in a non-coercive manner and recruitment will be irrespective of ethnicity or gender.

10.2 Inclusion Criteria

1. Age 18 years or older
2. Normal health status as per AABB criteria for a healthy donor
3. Able to commit to the study schedule

4. 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: Participants who are deferred from volunteer community donations because of travel restrictions, piercings, or tattoos may participate in the study, as products are not transfused
5. Participants of child-bearing potential (either male or female) must agree to use an effective method of contraception during the course of the study
6. Female of childbearing potential must be willing to take a pregnancy test prior to infusion of radiolabeled platelets
7. Has given written informed consent
8. Participants must agree to refrain from using aspirin or aspirin containing medications, non steroidal anti inflammatory drugs (NSAIDs), anti-platelet agents, or other drugs affecting platelet viability for the duration of the study

10.3 Exclusion Criteria

1. Previously received radiation therapy
2. Has been diagnosed with a platelet disorder (ie, platelet dysfunction)
3. Already participated in 4 research studies involving radioisotopes within the contemporaneous calendar-year
4. Pregnant or nursing females
5. Participation currently, or within the last 12 months, in another investigational trial that would potentially interfere with the analysis of this investigation
6. History of known hypersensitivity to indium or chromium
7. Treatment with aspirin or aspirin containing medications within 7 days of apheresis or treatment with NSAIDs, anti-platelet agents or other drugs affecting platelet viability within 3 days of apheresis (eg, ibuprofen or other NSAIDs)

10.4 Enrollment

A donor is considered to be an enrolled participant following informed consent. It is expected that due to the screening and eligibility requirements, some fraction of participants will not qualify for a platelet donation after consent and some who are enrolled may not complete all of their anticipated procedures. Participants will be considered screen failures if they fail to meet any of the eligibility criteria after signing informed consent. Participants who do not have a complete donation (donor receives rinseback, there was automated addition of PAS, and final platelet product has a platelet yield $\geq 3.0 \times 10^{11}$ and $\leq 5.1 \times 10^{11}$) or do not return for the recovery and survival sample collections per BEST Collaborative will be considered an early termination.

After informed consent has been obtained, participants will receive a unique study identification (USID) number. The USID number will use the following convention: XX-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).

Participants that fail screening criteria on information or laboratory values that are anticipated to change, may be rescreened. Participants that are an early termination or donated a product that meets any of the protocol analysis exclusions (Section 16.4) may rescreen as long as they were not infused with a radiolabeled product and will meet all the inclusion criteria when they return. Participants that are rescreened will be assigned a new USID number.

11 STUDY PROCEDURES

A summary of study procedures is provided in Table 11-1.

Table 11-1: List of Study Procedures

	Screening Visit (Day -5 – Day 0)	**Apheresis Visit** (Day 0)	**Post Collection** (Day 0 – 5)	**Infusion Day** (Study Day 5 or BEST Day 0)	**Post-Infusion Days** (Study Days 6-17 or BEST Days 1-12)[a]
Obtain informed consent	X				
Confirm eligibility	X				
Collect demographics (date of birth, gender, race, ethnic origin), height, and weight	X				
Record relevant medical history	X				
Confirm participant is healthy		X		X	
Record any medications taken in the 7 days prior to apheresis procedure and through study completion		X		X	X
Confirm participant did not take any exclusionary medication[b]		X		X	X
Fingerstick for Hgb or HCT		X			
Conduct apheresis procedure per Trima Accel Operator's Manual		X			
Collect venous whole blood sample from diversion pouch and conduct CBC in duplicate[c]		X			
Update Trima Accel machine with the averaged CBC results		X			
Record serial numbers, lots, and expiry dates of equipment, disposables, and solutions[d]		X			
Record Trima End Run Summary Report details[e]		X			
Conduct CBC on platelet product[f]		X			
Label product[g]			X		
Store at 20°C − 24°C with agitation away from normal blood inventory			X		
Conduct bacterial testing on stored platelet product[h]			X		
Conduct pregnancy test for women of child bearing potential (serum or urine)				X	
Test stored platelet product pH[i]				X	

	Screening Visit (Day -5 – Day 0)	**Apheresis Visit** (Day 0)	**Post Collection** (Day 0 – 5)	**Infusion Day** (Study Day 5 or BEST Day 0)	**Post-Infusion Days** (Study Days 6-17 or BEST Days 1-12)[a]
Collect whole blood sample and generate Control platelets according to BEST				X	
Radiolabel Test and Control platelets according to BEST				X	
Record vital signs[j]				X	
Infuse radiolabeled autologous platelets (Test and Control) according to BEST				X	
Collect 5-10 mL of whole blood into an EDTA tube for radiation counting				X[k]	X
Conduct radiation counting per BEST protocol				X	X
Record AE, SAEs, or UADEs		X		X	X
Record medical interventions to treat AEs or SAEs		X		X	X
Review AEs/SAEs since previous visit, if applicable				X	X
Record device deficiencies		X		X	

[a] Post-infusion visits will occur daily (except on weekends) from Study Day 6 through Study Day 12 (BEST Day 1-7). Additionally, 1 final visit will occur on Study Day 15, 16, or 17 (Best Day 10, 11, or 12).

[b] Exclusionary medication includes aspirin or aspirin containing medications, NSAIDs, anti-platelet agents, or other drugs affecting platelet viability.

[c] After venipuncture, a CBC will be done in duplicate for Hgb or HCT and platelet count. These averaged values will be used to update the Trima Accel machine.

[d] Record Trima Accel machine serial number and lot number and expiration date of the disposable set, ACD-A, PAS adaptor, and InterSol used.

[e] Record end run time, platelet volume, platelet yield, PAS volume added, and Trima flags that result in study discontinuation per Section 11.6.

[f] Confirm platelet yield is $\geq 3.0 \times 10^{11}$ and $\leq 5.1 \times 10^{11}$ total platelets and platelet product concentration is 0.7 to $2.1 \times 10^{6}/\mu L$.

[g] Label “For Investigational Use Only” and with USID number.

[h] Bacterial testing conducted per site standard operating procedures with results confirmed on Study Day 5.

[i] Confirm pH ≥ 6.2.

[j] Vital signs taken prior to preinfusion sample collection and to include blood pressure, heart rate, and temperature.

[k] Blood samples will be drawn pre-infusion and 2 hours ± 15 minutes after infusion.

Abbreviations: AE = adverse event; BEST = Biomedical Excellence for Safer Transfusion Collaboration; CBC = complete blood count; EDTA = ethylenediaminetetraacetic acid; HCT = hematocrit; Hgb = hemoglobin; NSAID = non-steroidal anti inflammatory drug; PAS = platelet additive solution; SAE = serious adverse event; UADE = unanticipated adverse device effect; USID = unique subject identification.

11.1 Screening Visit: Study Days -5 to 0

Screening can be performed within 5 days before the apheresis procedure or combined with the Apheresis Visit.

The following evaluations will be performed:

1. Obtain informed consent prior to initiating any study specific procedures
2. Confirm eligibility
3. Collect demographics (date of birth, gender, race, ethnic origin), height, and weight
4. Record relevant medical history

11.2 Apheresis Visit: Study Day 0

The following procedures will be performed during the apheresis visit.

11.2.1 Prior to Apheresis

1. Confirm participant is healthy
2. Record any medications taken in the 7 days prior to the Apheresis Visit and during this visit
3. Confirm the participant did not take any excludable medication (see Section 13) if screening visit was prior to apheresis visit
4. Finger stick for Hgb or HCT testing

11.2.2 Apheresis Procedure

Apheresis procedures will be run according to the instructions and precautions described in the commercially available Trima Accel Operator's Manual. The procedure selection process (platelet yield, volume, and concentration) will be conducted per the site's standard practice for a single platelet donation.

The following procedures will be performed:

1. Venipuncture
2. Collect venous whole blood sample from the diversion pouch
    a. Conduct a complete blood count (CBC) in duplicate for Hgb or HCT and platelet count
3. Update Trima Accel device with updated averaged platelet count and Hgb or HCT
4. Perform apheresis procedure for a single hyperconcentrated platelet product
5. Record the following:

a. Trima Accel machine serial number and lot number and expiration date of disposable set, ACD-A, PAS adaptor, and InterSol used

b. Trima End Run Summary Report details

   i. End run time, platelet volume, platelet yield, PAS volume added, and Trima flags that result in study discontinuation per Section 11.6

c. AEs, SAEs, and UADEs starting from the time of venipuncture

d. Medical interventions to treat AEs or SAEs

e. Device deficiencies

6. Conduct CBC on collected platelet product to confirm platelet yield and concentration conform to Trima Accel platelet storage bag specifications

   a. Record platelet yield and confirm platelets yield is $\geq 3.0 \times 10^{11}$ and $\leq 5.1 \times 10^{11}$

   b. Record platelet concentration and confirm it is within 0.7 to $2.1 \times 10^{6}/\mu L$

11.3 Post Collection Handling: Study Days 0 - 5

Blood products collected in this study will be labeled 'For Investigational Use Only' and with the USID number and will be stored segregated from the site's normal blood product inventory.

The Test platelet units will be stored at 20ºC − 24ºC with agitation for 5 days. Platelets will be tested for bacterial testing per the site's SOP and all products that are negative will be used. Any product that is positive will be destroyed per the site's SOPs and will not be radiolabeled or infused into the participant.

11.4 Infusion Day: Study Day 5 (BEST Day 0)

Five (5) days after a study participant has donated a Test product, they will return for the donation of fresh Control platelets, reinfusion of Test and Control platelets, and post-infusion sampling. Study Day 5 corresponds to the Infusion Day/Day 0 in BEST.

The following procedures will be conducted:

1. Confirm participant is healthy and did not take any excludable medication
2. Record any concomitant medications taken since previous visit and during this visit
3. Conduct pregnancy test for women of childbearing potential (serum or urine)
4. Test pH of the Test platelet product to confirm product meets FDA specifications (pH ≥ 6.2)
5. Review AEs/SAEs since previous visit, if applicable
6. Collect a whole blood sample per BEST procedures for the production of Control platelets

7. Radiolabel Test and Control platelets according to BEST

When the combined injectate is ready for infusion, the following procedures will take place:

1. Record vital signs (blood pressure, heart rate, temperature) prior to preinfusion sample collection
2. Infuse radiolabeled autologous combined Test and Control platelets into participant's vein per BEST procedure
3. Collect a 5-10 mL sample into an EDTA tube for pre- and post-infusion testing using the opposite arm as for the infusion
    a. Prior to infusion
    b. 2 hours ± 15 minutes post-infusion
4. Record AEs, SAEs, or UADEs
5. Record medical interventions used to treat AEs or SAEs
6. Record device deficiencies
7. Conduct radiation counting per BEST protocol

11.5 Post-Infusion Days

11.5.1 Study Days 6-12 (BEST Days 1-7)

The participant will return to the investigation site daily (except on weekends) between Study Day 6 and Study Day 12 (BEST Day 1 through Day 7). A total of 5 samples are required to be collected in this 7 day period in order for the participant's data to be evaluable for primary endpoint analysis, per BEST.

The participant procedures at each of these visits are as follows:

1. Confirm participant did not take any exclusionary medication since previous visit (see Section 13)
2. Record any concomitant medications taken since previous visit and during these visits
3. Collect a 5-10 mL sample into an EDTA tube to measure radioactivity
4. Conduct radiation counting per BEST protocol
5. Record AEs, SAEs or UADEs experienced since previous visit and during visit
6. Record medical interventions to treat AEs or SAEs

11.5.2 Study Day 16 ± 1 day (BEST Day 11 ± 1 day)

The participant will return to the investigation site for 1 final sample on Study Day 15, 16, or 17 which corresponds to BEST Day 10, 11, or 12.

The participant procedures at each of these visits are as follows:

1. Confirm participant did not take any exclusionary medication since previous visit (see Section 13)
2. Record any concomitant medications taken since previous visit and during this visit
3. Collect a 5-10 mL sample into an EDTA tube to measure radioactivity
4. Record AEs, SAEs, or UADEs experienced since previous visit and during visit
5. Record medical interventions to treat AEs or SAEs

11.6 Study Procedure Discontinuation/Termination

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

Reasons for study termination may include:

1. Development of an AE that interferes with the participant's continued participation
2. Participant refuses further treatment and/or follow-up and withdraws consent
3. Device deficiency or protocol deviation that ends the apheresis procedure early
4. Inability to collect a complete platelet unit
5. Procedure that produces a product quality Trima flag that results in the Test platelet product having insufficient yield, insufficient leukoreduction, or insufficient additive solution delivery
6. Incomplete or incorrect post-collection processing due to equipment failure or malfunction (eg, under-delivery of PAS due to unrecoverable system failure or malfunctioning sterile barrier filter)
7. Solution other than InterSol added to platelets prior to storage
8. The collected platelet product falls outside of the Trima Accel platelet product storage boundaries:
    a. $< 3.0 \times 10^{11}$ or $> 5.1 \times 10^{11}$ total platelets
    b. Platelet product concentrations outside of 0.7 to $2.1 \times 10^{6}/\mu L$
9. Product damaged during storage
10. Positive pregnancy test
11. Positive bacterial test
12. pH of Test product < 6.2
13. Investigator decision

14. Sponsor decision
15. Participant is lost to follow-up or does not complete at least 5 of the post-infusion blood sampling for recovery and survival calculations
16. Participant death
17. Participant took exclusionary medication (see Section 13)

11.7 Stopping Rules

There are no pre-specified stopping rules for this study. The Sponsor may stop the study for any reason.

12 LABORATORY TESTS

12.1 Clinical Laboratory Tests

The clinical laboratory tests for the participant's finger stick, the CBC (run in duplicate) for the Trima Accel update, and the pregnancy test on childbearing females prior to infusion of radiolabeled platelets will be analyzed locally at each study site. Copies of the current laboratory certifications and normal ranges will be provided to the Sponsor prior to start of the study and upon every renewal throughout the duration of the study.

12.2 Test Product Laboratory Test

The Test platelet product will have a CBC conducted on Day 0 per Section 11.2.2, bacterial contamination testing conducted between Study Day 0 and Study Day 5 per site's SOPs per Section 11.3, and pH testing conducted on Day 5 per Section 11.4.

12.3 Platelet Radiolabeling Procedures

Radiolabeling of Test and Control platelets, the subsequent testing of participant blood samples for the primary endpoint analysis, and the calculations to determine the platelet recovery and survival will be conducted locally at each study site as outlined by the BEST collaborative in 2006 [9]. The recovery and survival of platelets will be calculated at each site according to the COST software.

All platelet products will be destroyed per the site's SOPs after the final sample is taken.

13 CONCOMITANT MEDICATIONS

Participants are prohibited from taking aspirin or aspirin containing medications for 7 days prior to the apheresis procedure, and NSAIDs, anti-platelet agents, or other drugs affecting platelet

viability for 3 days prior to the apheresis procedure. Once enrolled in the study, participants are prohibited from taking these medications throughout their participation in the study.

Concomitant medications taken from the 7 days before the apheresis visit until study exit will be recorded in the eCRFs.

Medical interventions administered to treat AEs or SAEs will be recorded in the eCRFs.

14 ADVERSE EVENTS/EFFECTS

14.1 Anticipated Risks

14.1.1 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 14-1.

Table 14-1: 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[10-12]	Apprehension	Presyncope[a]	Faint[b]			
At puncture site[11-14]		Hematoma		Nerve irritation	Arterial puncture	
		Pain		Infection		
Distant of puncture site[11,12,14]		Discomfort			Skin allergy	Phlebitis
					Neuropathic pain	DVT

Abbreviations: DVT = deep vein 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.

14.1.2 Apheresis Complications in Healthy Donors

Donor reactions are mostly transient self-limited events and in very rare exceptions a donor may experience long-term morbidity or sustain permanent impairment.[11,14] 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.[11-14] 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]

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 14 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.[11,13-15] Mild citrate reactions are very common with apheresis procedures, while vasovagal reactions are substantially lower compared to whole blood donation.[12-14] 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 14-2 are general apheresis risks and are not specific to the Trima Accel system.

Table 14-2: 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[13,14,16,17]	Paresthesia	Nausea	Vomiting	Tetany	Arrhythmia	Cardiac arrest
		Lightheadedness	Cramps	Seizure		
		Metallic taste	Spasms			
			Chills			
Vasovagal Reactions[a 12-14,17]		Presyncope[b]	Vomiting	Convulsion	LOC with trauma injury	
		Weakness	Hypotension	Seizure		
			Syncope	Bradycardia		
Other Notable Events[12-14,17]						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.

14.1.3 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, the Sponsor has no knowledge that any such event has occurred with the Trima Accel system to date.

14.1.4 Potential Risks of Infusion of Radiolabeled Platelets

The amount of radiation exposure received by the participant is low and is not considered to be a health hazard.[18] However, women who are pregnant or who are nursing will be excluded from the study, as the risks of radiation exposure to a fetus or infant are unknown. All enrolled women will have a pregnancy test performed before the re-infusion of the radiolabeled platelets as an added precaution. Any participant with a positive pregnancy test will be withdrawn from the study.

14.2 Risk Mitigation

To minimize risks of participant 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 Participant Protection, and Clinical Investigation Plan (CIP) training to include device and procedure training.

2. Ensuring that participants who are enrolled meet all eligibility criteria, including minimum Hgb or HCT and platelet limits for donation. The apheresis devices are programmed to allow collection of products only from participants who will meet projected HCT/Hgb and platelet standards at the completion of the collection. These limitations are for the safety of participants and apply to this CIP.

3. If the Investigator deems appropriate, stopping the procedure if a moderate or severe AE occurs. The participant 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. Case report forms will be uploaded to the electronic data capture (EDC) with only participant and product number as participant identifiers, to ensure confidentiality.

5. Participants will be questioned concerning adverse experiences throughout the apheresis procedure. Participants will also be visually monitored for signs of distress during blood

donations. Suspected adverse reactions will be treated according to study sites' SOPs and documented on the SD and eCRFs.

14.3 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a clinical investigation participant, 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.

14.4 Adverse Event Recording

Adverse events that occur after the start of the apheresis procedure venipuncture until study completion will be recorded on the AE eCRF.

14.5 Adverse Event Reporting

14.5.1 Severity

This study will utilize the Common Terminology Criteria for Adverse Events [CTCAE] Scale, Version 4.03 for AE grading.[19] 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.

14.5.2 Relationship

The Investigator 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 participant'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 participant'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 participant'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.

14.6 Adverse Event Follow-up

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

14.7 Serious Adverse Events and Unanticipated Adverse Device Effect

14.7.1 Definition

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

Serious AEs are defined (21 CFR 312.32 and ISO 14145:2011 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 participant, 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 an SAE.

Per 21 CFR 812.3 an 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 Operator's Manual, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

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

14.7.2 SAE/UADE Reporting

Any SAE/UADE that occurs after the start of the apheresis procedure venipuncture 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 the Sponsor within 24 hours of knowledge of the event to:

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

The Sponsor 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 eCRF. Follow-up SAE/UADE reports need to be submitted to the Sponsor as soon as additional information regarding the event becomes available.

The Sponsor 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

14.8 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.

The Sponsors is responsible for reporting all deviations into the EDC. Clinical Investigation Plan deviations that may affect the scientific soundness of the study or affect the rights, safety, or welfare of study participants, must be reported to the Sponsor and the IRB as per the IRB's standard reporting procedure.

14.9 Medical Monitoring

It is the responsibility of the Investigator to oversee the safety of the study at his/her site. A Data Safety Monitoring Board will not be involved in this study because it involves healthy participants undergoing a commonly practiced research evaluation procedure and no investigational product will be transfused.

The Sponsor will monitor the safety of the study participants from the venipuncture for the apheresis procedure and until conclusion of their participation in the study.

15 STUDY DEVICE

15.1 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.

15.2 Device Accountability

15.2.1 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.

15.2.2 Storage

The Trima Accel device, the InterSol, and the 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.

15.2.3 Accountability

The Trima Accel device, disposables, InterSol, and software will be provided by the Sponsor for use in this study. The Trima Accel disposables, software, and InterSol are FDA cleared and marketed in the United States; however platelets collected on the Trima Accel system and stored in InterSol is not, therefore the site must take appropriate measures to ensure it is properly stored away from approved inventory.

16 STATISTICAL PLAN

16.1 Sample Size

Assuming an approximate 40% screen fail/early termination rate, up to 40 healthy adult participants will be enrolled in this study to ensure 24 evaluable data points across 2 investigational 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. Participants will be recruited in a non-coercive manner and recruitment will be irrespective of ethnicity or gender.

16.2 Outcome Measures

This study will determine the recovery and survival of hyperconcentrated platelets collected on the Trima Accel system and stored for 5 days in 65% InterSol/35% plasma. The recovery and survival of Test platelets will be compared to fresh Control platelets.

16.2.1 Primary Endpoint

The acceptance criterion for the recovery (%) of platelets is the demonstration of non-inferiority by the rejection of the Null Hypothesis (H0) defined by the following hypotheses:

Null Hypothesis	H_0: $\mu_d \leq 0$	where $\mu_{d=}\mu_T$-0.66*μ_C
Alternate Hypothesis	H_1: $\mu_d > 0$	

Let $\Delta Xi = (X_{Ti}\text{-}0.66*X_{Ci})$ be a difference if recovery for patient *i*. The sample mean and standard deviations of these observed differences will be used to construct the lower limit of a 1-sided 97.5% confidence interval for μ_d assuming a t-distribution with n-1 degrees of freedom. If the lower limit of the confidence interval is greater than 0, the null hypothesis will be rejected in

favor of the alternative hypothesis suggesting the Test product meets the FDA acceptance criteria for platelet recovery.

The acceptance criterion for the survival (hours) of platelets is the demonstration of non-inferiority by the rejection of the null hypothesis (H0) defined by the following hypotheses:

Null Hypothesis	H_0: $\mu_d \leq 0$	where $\mu_{d=}\mu_T$-0.58*μ_C
Alternate Hypothesis	H_1: $\mu_d > 0$	

Let $\Delta Xi = (X_{Ti}$-0.58*$X_{Ci})$ be a difference in survival for patient *i*. The sample mean and standard deviations of these observed differences will be used to construct the lower limit of a 1-sided 97.5% confidence interval for μd assuming a t-distribution with n-1 degrees of freedom. If the lower limit of the confidence interval is greater than 0, the null hypothesis will be rejected in favor of the alternative hypothesis suggesting the Test product meets the FDA acceptance criteria for platelet survival.

16.2.2 Safety Measures

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

16.3 Analysis Population

The safety population will include all participants enrolled in this trial who undergo any study related apheresis procedure.

The Full Analysis Set (FAS) will consist of all completed procedures/products where the corresponding Test and Control values for the primary endpoint are valid. If any of the criteria outlined in Section 16.4 are met, the product will not be included in the FAS. The FAS will be used to examine the primary endpoints.

16.4 CIP Analysis Exclusions

Data points may be excluded from analysis in the following situations:

1. Primary endpoint laboratory samples are lost or not available
2. Failure of the site to follow post-collection handling procedures for endpoint assays

17 STUDY MANAGEMENT

17.1 Investigator Responsibilities

17.1.1 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.

17.1.2 Institutional Review Board

The IRB or other committee functioning in a similar capacity will review and approve the CIP and any CIP 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 the Sponsor before any participant is enrolled into this study.

17.1.3 Informed Consent

The Investigator is responsible for preparing the written IC document for this study. The Sponsor 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 participant participation in this study, the Investigator must obtain written IRB approval for the CIP and the ICF. The approved consent form will clearly reflect the IRB approval date.

Once the participant's initial eligibility has been determined, the Investigator or person designated by the Investigator, who has been trained on the CIP, will explain the nature and scope of the study, potential risks and benefits of participation, answer questions for the participant and ask the participant to participate in the study. The study will be explained to the study participant in lay terms, in their native language in a quiet, non-disruptive setting. Potential participants 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 participant 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 participant agrees to participate, the participant has read the ICF, and has had all of their questions answered, then the ICF must be signed and personally dated by the participant and the person completing the consent process. A copy of the signed and dated ICF will be provided to the study participant.

All participants 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 participant discontinuing or terminating from the study must be recorded on the eCRF.

17.1.4 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.

17.1.5 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.

17.2 Sponsor Responsibilities

17.2.1 Amendments to the CIP

Any amendment to the CIP, as deemed appropriate by the Sponsor, will be implemented as the study progresses. Amendments will be submitted to the FDA and IRB for written approval, before implementation.

17.2.2 General Responsibilities

As per International Organization for Standardization (ISO) 14145 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 and government authorities as well as annual reports as required.

17.3 Joint Investigator-Sponsor Responsibilities

17.3.1 Training

The Sponsor will train applicable study team members as to the device, CIP, 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.

17.4 Collecting and Recording Data

The Investigators will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by the Sponsor 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.

17.4.1 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.

17.4.2 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 clinical research associate will verify the EDC data with the participant'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 participant must be completed in a timely manner.

17.5 CIP Compliance

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

17.6 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, the Sponsor may terminate the study at any time upon immediate notice for any reason, including but not limited to, the Sponsor's belief that termination is necessary for the safety of participants or failure to meet the primary endpoints.

17.7 Publication Policy

The Sponsor 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 the Sponsor for timely review in accordance with the terms of the CTA between the Investigator, the Institution, and the Sponsor. The Sponsor 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.

18 REFERENCES

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Appendix 1 Investigator Signature

Study Title: An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution

Study Number CTS-5066

Version/Date: 2.0 / 10 JUL 2017

I have read the Clinical Investigation Plan (CIP), including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study in compliance with the CIP, GCP, 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 CIP and access to all information provided by Terumo BCT. I will discuss this material with them to ensure that they are fully informed about the study.

Principal Investigator Name (Printed)	Signature

Date

Appendix 2 BEST Collaborative Platelet Radiolabeling Procedure