

## CLINICAL INVESTIGATION PLAN

**Study Title:** In Vivo 24-Hour Recovery Study of Leukoreduced RBCs Collected on the Trima Accel System Using Non-DEHP Disposable Sets and Stored for 42 Days

**Study Number:** CTS-5091

**Study Device:** Trima Accel System

**Legal Manufacturer:** Terumo BCT, Inc.  
10811 West Collins Avenue; Lakewood, CO 80215; USA  
Phone: +1 (877) 339-4228

**Sponsor:** Terumo BCT, Inc.  
10811 West Collins Avenue; Lakewood, CO 80215; USA  
Phone: +1 (877) 339-4228

**Sponsor Contact:** Janet Johnson, RAC  
Vice President, Global Regulatory, Clinical Affairs & Labeling  
Phone: +1 (720) 668-1021  
Email: Janet.Johnson@terumobct.com

**Principal Investigator:** Multisite

**Funded By:** Terumo BCT, Inc.

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Revision:  
Date:

Revision B  
*See last signature date*





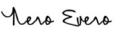





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## CLINICAL INVESTIGATION PLAN APPROVAL

Name:	Caroline Raasch Alquist, MD, PhD, F(ACHI)		
Title:	Principal Investigator, Hoxworth Blood Center / University of Cincinnati		
	<div><div>Signed by:</div><div></div><div><div>Signer Name: Caroline Raasch Alquist Signing Reason: I approve this document Signing Time: 8/15/2024   9:27:52 AM EDT</div></div><div>55E855A2FDA14511BCE4BC0F6692AB83</div></div>		
Signature:	_____	Date:	8/15/2024
Name:	Bethany L. Brown, PhD		
Title:	Principal Investigator, American Red Cross		
	<div><div>Signed by:</div><div></div><div><div>Signer Name: Bethany Brown Signing Reason: I approve this document Signing Time: 8/15/2024   5:44:00 AM PDT</div></div><div>D71A36A382BC4ADD84246415A1FEAAEA</div></div>		
Signature:	_____	Date:	8/15/2024
Name:	Janet Johnson, RAC		
Title:	Vice President, Global Regulatory, Clinical Affairs & Labeling		
	<div><div>Signed by:</div><div></div><div><div>Signer Name: Janet Johnson Signing Reason: I approve this document Signing Time: 8/15/2024   7:17:46 AM MDT</div></div><div>4C9B29F2CDE24250A1F8A9E8B48EC90F</div></div>		
Signature:	_____	Date:	8/15/2024
Name:	Rebecca Sedjo, PhD, MSPH		
Title:	Clinical Development Manager, Global Clinical Affairs		
	<div><div>Signed by:</div><div></div><div><div>Signer Name: Rebecca Sedjo Signing Reason: I approve this document Signing Time: 8/15/2024   7:40:45 AM MDT</div></div><div>692492C189904E0FBD63616DBC3FC2B4</div></div>		
Signature:	_____	Date:	8/15/2024

Name: Title:	Emily Mason, MSCS Sr. Clinical Scientist, Global Clinical Affairs		
<div><div>Signed by:</div><div></div><div><div>Signer Name: Emily Mason Signing Reason: I am the author of this document Signing Time: 8/14/2024   9:15:31 PM MDT 434FFEEA2CEA460BAE90BD7044932C24</div></div></div>			
Signature:		Date:	8/14/2024
Name: Title:	Jack Rhodes, BS Senior Manager, Global Clinical Affairs		
<div><div>Signed by:</div><div></div><div><div>Signer Name: Jack Rhodes Signing Reason: I approve this document Signing Time: 8/14/2024   10:03:15 PM MDT 3BC40A2306EC41428DB19E059837B6D9</div></div></div>			
Signature:		Date:	8/14/2024
Name: Title:	Nero Evero, MS Clinical Trial Manager, Global Clinical Affairs		
<div><div>Signed by:</div><div></div><div><div>Signer Name: Nero Evero Signing Reason: I approve this document Signing Time: 8/14/2024   9:12:40 PM MDT B968B87D731E423AA4292C7BDF81FD2B</div></div></div>			
Signature:		Date:	8/14/2024
Name: Title:	Joel Kniep, MD Global Medical Safety Physician, Global Medical Safety		
<div><div>Signed by:</div><div></div><div><div>Signer Name: Joel Kniep Signing Reason: I approve this document Signing Time: 8/15/2024   8:37:38 AM MDT 6D812CD218DB417A996E83CD87A7360B</div></div></div>			
Signature:		Date:	8/15/2024
Name: Title:	Richard Cook, PhD Consultant Statistician, Lifetime Scientific, Inc.		
<div><div>Signed by:</div><div></div><div><div>Signer Name: Richard Cook Signing Reason: I approve this document Signing Time: 8/14/2024   8:32:38 PM PDT E996A47EF631418D9528260AC5040B58</div></div></div>			
Signature:		Date:	8/14/2024

## DOCUMENT REVISION HISTORY

<b>Study Title:</b>	In Vivo 24-Hour Recovery Study of Leukoreduced RBCs Collected on the Trima Accel System Using Non-DEHP Disposable Sets and Stored for 42 Days	
<b>Study Number:</b>	CTS-5091	
<b>CIP Amendment Revision:</b>	Revision B	
<b>Replaces CIP Revision:</b>	Revision A	
<b>Rationale:</b>	<p>This revision history captures updates from Revision A to the current Revision B.</p> <p>A summary of updates includes:</p> <ul style="list-style-type: none"> <li>• Specification that research-grade chromium will be used in the radiolabeling process if Good Manufacturing Practice (GMP) chromium is unavailable, to include aseptic preparation steps per site SOPs (eg, syringe filtration and endotoxin testing).</li> <li>• Updating study procedures and statistical analysis to accommodate using either both the single-label (using chromium-51 [<sup>51</sup>Cr] only) and dual-label (using <sup>51</sup>Cr and technetium-99m [<sup>99m</sup>Tc]) radiolabeling methods or the single-label method only to address the potential for unavailability of <sup>99m</sup>Tc labeling kits at one or both study sites. The dual-label method will only be pursued if <sup>99m</sup>Tc labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event <sup>99m</sup>Tc labeling kits are expected to be unavailable, the dual-label method will not be pursued and only the single-label method will be conducted.</li> <li>• Completion of CTS-5090 clinical trial data.</li> </ul> <p>Changes are indicated in bold. Administrative changes, section renumbering, typographical error corrections, and minor wording changes made for clarification purposes are not reflected in the table below.</p>	
<b>Section(s)</b>	<b>Used to Read:</b>	<b>Now Reads:</b>
Section 6 – Clinical Trial Experience	<p>Each of the Trima Accel system's collection protocols has been extensively studied in Terumo BCT sponsored clinical trials. Terumo BCT has sponsored 13 clinical trial investigations (2 RBC, 9 platelets and 1 plasma, 1 non-DEHP) assessing the safety and efficacy of the system. A summary of each trial is provided in Table 6-1. Results from these studies have shown that the Trima Accel system can safely collect RBCs, platelets, and plasma alone and in combination, and the products collected meet both the FDA and EDQM requirements for transfusion.</p> <p>The most relevant data for the current investigation is CTS-5090, the in vitro study and precursor for this trial.</p>	<p>Each of the Trima Accel system's collection protocols has been extensively studied in Terumo BCT sponsored clinical trials. Terumo BCT has sponsored 13 clinical trial investigations (2 RBC, 9 platelets and 1 plasma, 1 non-DEHP) assessing the safety and efficacy of the system. A summary of each trial is provided in Table 6-1. Results from these studies have shown that the Trima Accel system can safely collect RBCs, platelets, and plasma, alone and in combination, that meet both the FDA and EDQM requirements for transfusion.</p> <p><b>The most relevant data for the current investigation (CTS-5091) is the AutoRBC (ie, LR-RBC) arm of CTS-5090, the in vitro study and precursor for this trial. This</b></p>

	<p>The Sponsor is conducting this in vitro study to determine if RBCs, platelets, and plasma collected on the Trima Accel system into investigational non-DEHP disposable sets meet established standards for a transfusable blood product. Although the study is still ongoing, analyses have been conducted on 59 LR-RBC units from participants who underwent a Trima Accel AutoRBC collection procedure with AS-3 as the additive solution and stored in investigational non-DEHP disposable sets for up to 42 days due to timing for starting the current in vivo study. The mean total Day 0 residual white blood cell (rWBC) content was <math>0.13 \times 10^6</math> cells <math>\pm 0.12 \times 10^6</math> cells, Day 0 RBC Filtration Recovery was <math>93.61\% \pm 4.25\%</math>, Day 35 Hemolysis was <math>0.19\% \pm 0.08\%</math>, and Day 42 Hemolysis was <math>0.21\% \pm 0.11\%</math>. A 95/95 binomial approach was utilized to evaluate whether the LR-RBC units met the primary endpoint of Day 0 rWBC content (<math>&lt; 5.0 \times 10^6</math> cells) and RBC filtration recovery (<math>\geq 85\%</math>) along with both Day 35 and Day 42 hemolysis (<math>\leq 1.0\%</math>). Based on <math>n=59</math>, 58 (98.3%) procedures met the 3-part FDA criteria with a one-sided 95% lower confidence limit of 92.21% which does not meet the 95/95 binomial approach. One unit did not meet the RBC filtration recovery criteria (value was 82.5%). An extensive evaluation of the cause of this failure has been conducted (see Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091). The most probable cause of the unit not meeting the 85% filter recovery endpoint was an overestimated fingerstick hematocrit value at donor qualification, which was imputed into the Trima Accel at the start of the procedure. It was asserted by the Sponsor that the failure was not due to the system or investigational non-DEHP disposable set since Trima Accel and the filter did not change, and that the system was operating as</p>	<p><b>data was provided in the Response to FDA Request for Info: IDE29212/11 dated 30 May 2024.</b> The Sponsor <b>conducted</b> this in vitro study to determine if <b>LR-RBCs</b> collected on the Trima Accel system into investigational non-DEHP disposable sets meet established standards for a transfusable blood product. <b>Analyses were conducted on 61 LR-RBC units</b> from participants who underwent a Trima Accel AutoRBC collection procedure with AS-3 as the additive solution and stored in investigational non-DEHP disposable sets for up to 42 days. <b>The mean total Day 0 residual white blood cell (rWBC) content was <math>0.13 \times 10^6</math> cells <math>\pm 0.12 \times 10^6</math> cells, Day 0 RBC Filtration Recovery was <math>93.44\% \pm 4.28\%</math>, Day 35 Hemolysis was <math>0.19\% \pm 0.08\%</math>, and Day 42 Hemolysis was <math>0.21\% \pm 0.11\%</math>.</b> A 95/95 binomial approach was utilized to evaluate whether the LR-RBC units met the primary endpoint of Day 0 rWBC content (<math>&lt; 5.0 \times 10^6</math> cells) and RBC filtration recovery (<math>\geq 85\%</math>) along with both Day 35 and Day 42 hemolysis (<math>\leq 1.0\%</math>). <b>Based on <math>n=61</math>, 60 (98.4%) procedures met the 3-part FDA criteria with a one-sided 95% lower confidence limit of 92.46% which does not meet the 95/95 binomial approach.</b> One unit did not meet the RBC filtration recovery criteria (value was 82.5%). An extensive evaluation of the cause of this failure has been conducted (Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091; <b>submitted to FDA under IDE 29212/S011, Page 211 of 241</b>). The most likely reason the unit did not meet the 85% filter recovery endpoint was an overestimated fingerstick hematocrit value during donor qualification, which was entered into the Trima Accel at the start of the procedure. The Sponsor asserted that this failure was not due to the Trima Accel system or the investigational non-DEHP disposable set, as neither the system nor the filter underwent any</p>
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	expected. Nevertheless, even with the filter recovery <85%, the unit still met all transfusable dose requirements. There were no serious PEAEs, severe PEAEs, serious device-related PEAEs, or UADEs.	changes, and the system was operating as expected. Despite the filter recovery being below 85%, the unit still met all requirements for a transfusable dose. Additionally, there were no serious PEAEs, severe PEAEs, serious device-related PEAEs, or UADEs reported.
Table 6-1: Summary of Trima Accel Clinical Trials  (Sample Size for CTS-5090 Collection of Blood Products Acquired by the Trima Accel System into Non-DEHP Disposable Tubing Sets for Laboratory Evaluations)	n=59 evaluable AutoRBC products	n=61 evaluable AutoRBC products
Table 6-1: Summary of Trima Accel Clinical Trials  (Findings/Conclusions for CTS-5090 Collection of Blood Products Acquired by the Trima Accel System into Non-DEHP Disposable Tubing Sets for Laboratory Evaluations)	The Sponsor is conducting this in vitro study to determine if RBCs, platelets, and plasma collected on the Trima Accel system into investigational non-DEHP disposable sets meet established standards for a transfusable blood product. Although the study is still ongoing, analyses have been conducted on 59 LR-RBC units from participants who underwent a Trima Accel AutoRBC collection procedure with AS-3 as the additive solution and stored in investigational non-DEHP disposable sets for up to 42 days due to timing for starting the current in vivo study. The mean total Day 0 residual white blood cell (rWBC) content was $0.13 \times 10^6$ cells $\pm 0.12 \times 10^6$ cells, Day 0 RBC Filtration Recovery was $93.61\% \pm 4.25\%$ , Day 35 Hemolysis was $0.19\% \pm 0.08\%$ , and Day 42 Hemolysis was $0.21\% \pm 0.11\%$ . A 95/95 binomial approach was utilized to evaluate whether the LR-RBC units met the primary endpoint of Day 0 rWBC content ( $< 5.0 \times 10^6$ cells) and RBC filtration recovery ( $\geq 85\%$ ) along with both Day 35 and Day 42 hemolysis ( $\leq 1.0\%$ ). Based on n=59, 58 (98.3%) procedures met the 3-part FDA criteria with a one-sided 95% lower	The Sponsor <b>conducted</b> this in vitro study to determine if <b>LR-RBCs</b> collected on the Trima Accel system into investigational non-DEHP disposable sets meet established standards for a transfusable blood product. Analyses were conducted on <b>61</b> LR-RBC units from participants who underwent a Trima Accel AutoRBC collection procedure with AS-3 as the additive solution and stored in investigational non-DEHP disposable sets for up to 42 days. <b>The mean total Day 0 residual white blood cell (rWBC) content was <math>0.13 \times 10^6</math> cells <math>\pm 0.12 \times 10^6</math> cells, Day 0 RBC Filtration Recovery was <math>93.44\% \pm 4.28\%</math>, Day 35 Hemolysis was <math>0.19\% \pm 0.08\%</math>, and Day 42 Hemolysis was <math>0.21\% \pm 0.11\%</math>. A 95/95 binomial approach was utilized to evaluate whether the LR-RBC units met the primary endpoint of Day 0 rWBC content (<math>&lt; 5.0 \times 10^6</math> cells) and RBC filtration recovery (<math>\geq 85\%</math>) along with both Day 35 and Day 42 hemolysis (<math>\leq 1.0\%</math>). Based on n=61, 60 (98.4%) procedures met the 3-part FDA criteria with a one-sided 95% lower confidence limit of 92.46% which does not meet the 95/95 binomial approach. One unit did not meet the RBC filtration</b>

	<p>confidence limit of 92.21% which does not meet the 95/95 binomial approach. One unit did not meet the RBC filtration recovery criteria (value was 82.5%). An extensive evaluation of the cause of this failure has been conducted (see Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091). The most probable cause of the unit not meeting the 85% filter recovery endpoint was an overestimated fingerstick hematocrit value at donor qualification, which was imputed into the Trima Accel at the start of the procedure. It was asserted by the Sponsor that the failure was not due to the system or investigational non-DEHP disposable set since Trima Accel and the filter did not change, and that the system was operating as expected. Nevertheless, even with the filter recovery &lt;85%, the unit still met all transfusable dose requirements. There were no serious PEAEs, severe PEAEs, serious device-related PEAEs, or UADEs.</p>	<p>recovery criteria (value was 82.5%). An extensive evaluation of the cause of this failure has been conducted (Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091; <b>submitted to FDA under IDE 29212/S011, Page 211 of 241</b>). The most likely reason the unit did not meet the 85% filter recovery endpoint was an overestimated fingerstick hematocrit value during donor qualification, which was entered into the Trima Accel at the start of the procedure. The Sponsor asserted that this failure was not due to the Trima Accel system or the investigational non-DEHP disposable set, as neither the system nor the filter underwent any changes, and the system was operating as expected. Despite the filter recovery being below 85%, the unit still met all requirements for a transfusable dose. Additionally, there were no serious PEAEs, severe PEAEs, serious device-related PEAEs, or UADEs reported.</p>
Section 9.1 – Primary Endpoint	<p>The primary endpoint is the 24-hour in vivo RBC recovery after 42 days of refrigerated storage. The single label method for 24-hour RBC recovery uses Nadler's method<sup>9</sup> to estimate a participant's blood volume by accounting for their gender, height, and weight. However, since the single label method for 24-hour in vivo RBC recovery is not always accurate for some healthy donor populations with higher ranges of body weight and body mass index, the double label method using chromium-51 (<sup>51</sup>Cr) and technetium-99m (<sup>99m</sup>Tc) will be employed. The double label method uses a direct determination of the blood volume of the participant through the co-infusion of autologous, freshly collected <sup>99m</sup>Tc-labeled RBCs.<sup>10-15</sup></p>	<p>The primary endpoint is the 24-hour in vivo RBC recovery after 42 days of refrigerated storage, <b>determined using the single-label (using <sup>51</sup>Cr only) and dual-label (using <sup>51</sup>Cr and <sup>99m</sup>Tc, if possible, dependent upon availability of <sup>99m</sup>Tc labeling kits at both study sites) radiolabeling methods.</b> The single label method for 24-hour RBC recovery uses Nadler's method<sup>9</sup> to estimate a participant's blood volume by accounting for their gender, height, and weight. The dual-label method uses a direct determination of the blood volume of the participant through the co-infusion of autologous, freshly collected <sup>99m</sup>Tc-labeled RBCs.<sup>10-15</sup></p>
Section 10.1 – Study Design	<p>This is a prospective, open-label, multicenter study designed to demonstrate that LR-RBCs collected on the Trima Accel system with the investigational non-DEHP disposable tubing sets with</p>	<p>This is a prospective, open-label, multicenter study designed to demonstrate that LR-RBCs collected on the Trima Accel system with the investigational non-DEHP disposable tubing sets with</p>

	<p>integrated AS-3 delivery meet the FDA criteria for 24-hour recovery after refrigerated storage for 42 days.<sup>8</sup> Healthy adult volunteers will undergo an AutoRBC collection procedure with AS-3 as the additive solution according to the Trima Accel Operator's Manual and site standard operating procedures (SOPs). After processing, complete blood count (CBC), product volume, spun hematocrit, and hemolysis will be measured per site procedures. The LR-RBC units will be stored at 2-6°C for 42 days away from the transfusion inventory, with bacterial testing occurring during the storage period per site SOPs. After 42 days of refrigerated storage, the LR-RBCs will be tested for CBC, spun hematocrit, hemolysis, along with a visual quality check and confirmation of a negative bacterial screen per site SOPs. An autologous aliquot of stored LR-RBCs and fresh RBCs will be radiolabeled with <sup>51</sup>Cr and <sup>99m</sup>Tc, respectively, and reinfused to the participant. For RBC recovery testing, blood samples will be collected at baseline and approximately 5, 7.5, 10, 12.5, 15, 20, 30 minutes, and 24 hours post reinfusion. Participants will be monitored for AEs throughout their participation in the study. All procedures related to collection, processing, storage, labeling, reinfusion, and sampling will follow the site's common standardized procedures and SOPs. The procedures for radiolabeling of RBCs to evaluate RBC recovery are based and adapted from methods recommended by International Committee of Standardization in Haematology (ICSH) Recommended Methods for Radioisotope Red-Cell Survival Studies and previously published literature by Moroff and colleagues.<sup>11,16</sup> The method of calculating the blood volume with <sup>99m</sup>Tc is based on the ICSH Recommended Methods for Measurement of Red-Cell And Plasma Volume.<sup>17</sup></p>	<p>integrated AS-3 delivery meet the FDA criteria for 24-hour recovery after refrigerated storage for 42 days.<sup>8</sup> Healthy adult volunteers will undergo an AutoRBC collection procedure with AS-3 as the additive solution according to the Trima Accel Operator's Manual and site standard operating procedures (SOPs). After processing, complete blood count (CBC), product volume, spun hematocrit, and hemolysis will be measured per site procedures. The LR-RBC units will be stored at 2-6°C for 42 days away from the transfusion inventory, with bacterial testing occurring during the storage period per site SOPs. After 42 days of refrigerated storage, the LR-RBCs will be tested for CBC, spun hematocrit, hemolysis, along with a visual quality check and confirmation of a negative bacterial screen per site SOPs. <b>Both the single-label and dual-label radiolabeling methods can be used to determine the primary endpoint, 24-hour RBC recovery. For both single- and dual-label methods, an autologous aliquot of stored LR-RBCs will be radiolabeled with either Good Manufacturing Practice (GMP) <sup>51</sup>Cr or qualified research-grade <sup>51</sup>Cr, dependent upon the source of <sup>51</sup>Cr available to study sites. If research-grade <sup>51</sup>Cr is used, aseptic preparation steps will be conducted per site SOPs to qualify research-grade <sup>51</sup>Cr, which may include but is not limited to syringe filtration and endotoxin testing. The dual-label method requires an additional autologous aliquot of fresh RBCs to be labeled with GMP <sup>99m</sup>Tc, dependent upon the availability of <sup>99m</sup>Tc labeling kits at the study sites. The labeled RBCs will be reinfused to the participant. The dual-label method will only be pursued if <sup>99m</sup>Tc labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event <sup>99m</sup>Tc labeling kits are expected to be</b></p>
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		<p><b>unavailable, the dual-label method will not be pursued and only the single-label method will be conducted.</b> For RBC recovery testing, blood samples will be collected at baseline and approximately 5, 7.5, 10, 12.5, 15, 20, 30 minutes, and 24 hours post reinfusion. Participants will be monitored for AEs throughout their participation in the study. All <b>radiolabeling</b> procedures, <b>including aseptic preparation steps (if applicable)</b>, labeling, reinfusion, and sampling, will follow the site's common standardized procedures and SOPs. The procedures for radiolabeling of RBCs to evaluate RBC recovery are based and adapted from methods recommended by International Committee of Standardization in Haematology (ICSH) Recommended Methods for Radioisotope Red-Cell Survival Studies and previously published literature by Moroff and colleagues.<sup>11,16</sup> The method of calculating the blood volume with <sup>99m</sup>Tc is based on the ICSH Recommended Methods for Measurement of Red-Cell and Plasma Volume.<sup>17</sup></p>
Section 12.5.3 – Following LR-RBC Collection	<ol style="list-style-type: none"> <li>1. Record the following procedure summary information: <ol style="list-style-type: none"> <li>a. Total AC used (mL)</li> <li>b. AC to donor (mL)</li> <li>c. End of run time (hh:mm)</li> <li>d. Duration of run (min)</li> <li>e. Post HCT (%)</li> <li>f. Blood volume processed (mL)</li> <li>g. Solution addition start time (hh:mm)</li> <li>h. Packed RBC residual loss (mL)</li> <li>i. Draw flow rate (mL/min)</li> <li>j. Plasma residual loss (mL)</li> <li>k. RBC product: label as leukoreduced? (yes/no)</li> <li>l. If no, reason(s)</li> <li>m. RBC product values: <ol style="list-style-type: none"> <li>n. Total volume of product (mL)</li> <li>o. Volume of AC in RBC (mL)</li> <li>p. Volume of additive solution (mL)</li> </ol> </li> <li>q. Product flags (if applicable)</li> <li>r. Alarms (if applicable)</li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1. Record the following procedure summary information: <ol style="list-style-type: none"> <li>a. Total AC used (mL)</li> <li>b. AC to donor (mL)</li> <li>c. End of run time (hh:mm)</li> <li>d. Duration of run (min)</li> <li>e. Post HCT (%)</li> <li>f. Blood volume processed (mL)</li> <li>g. Solution addition start time (hh:mm)</li> <li>h. Packed RBC residual loss (mL)</li> <li>i. Draw flow rate (mL/min)</li> <li>j. Plasma residual loss (mL)</li> <li>k. RBC product: label as leukoreduced? (yes/no)</li> <li>l. If no, reason(s)</li> <li>m. RBC product values: <ol style="list-style-type: none"> <li>n. Total volume of product (mL)</li> <li>o. Volume of AC in RBC (mL)</li> <li>p. Volume of additive solution (mL)</li> </ol> </li> <li>q. Product flags (if applicable)</li> <li>r. Alarms (if applicable)</li> </ol> </li> </ol>

	<p>2. To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs on the day of reinfusion (Day 42), the site must follow their standard labeling and handling process intended to eliminate errors in linking LR-RBC units with the correct study participant.</p> <p>3. The following assessments will be conducted on the LR-RBC products from the collections. Any product that does not meet the product quality criteria will be destroyed and the participant will be withdrawn from the study.</p> <ol style="list-style-type: none"> <li>CBC</li> <li>Product volume</li> <li>Plasma free hemoglobin (used along with CBC to quantify hemolysis)</li> <li>Spun hematocrit</li> </ol> <p>4. The LR-RBC product will then be stored for 42 days at 2-6°C away from the transfusion inventory.</p> <p>5. Bacterial testing of the LR-RBC units will be done according to site SOPs during storage.</p> <p>6. Record AEs, DDs, and PDs.</p>	<p>2. To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs on the day of reinfusion (Day 42), the site must follow their standard labeling and handling process intended to eliminate errors in linking LR-RBC units with the correct study participant.</p> <p>3. The following assessments will be conducted on the LR-RBC products from the collections.</p> <ol style="list-style-type: none"> <li>CBC</li> <li>Product volume</li> <li>Plasma free hemoglobin (used along with CBC <b>hemoglobin and spun hematocrit</b> to quantify hemolysis)</li> <li>Spun hematocrit</li> </ol> <p>4. The LR-RBC product will then be stored for 42 days at 2-6°C away from the transfusion inventory. <b>Temperature monitoring and handling of excursions will be done per site SOPs.</b></p> <p>5. Bacterial testing of the LR-RBC units will be done according to site SOPs during storage.</p> <p>6. Record AEs, DDs, and PDs.</p>
Section 12.6 – Reinfusion of Radiolabeled RBCs (Day 42 Visit)	The procedures during this visit will follow the site’s procedures for labeling, reinfusion, sampling and RBC recovery/mass determination.	The <b>radiolabeling</b> procedures, <b>including aseptic preparation steps for research-grade <sup>51</sup>Cr (if applicable)</b> , during this visit will follow the site’s procedures for labeling, reinfusion, sampling, and RBC recovery/mass determination.
Section 12.6.1.1 – Collection of Sample for Baseline Assessment and Fresh Sample for Radiolabeling (if Applicable)	Two blood samples are required to be collected prior to reinfusion. One sample will be collected for baseline assessment to be used in the calculation of 24-hour RBC recovery (%). Additionally, an aliquot of fresh blood will be taken from the participant and processed for RBC isolation. The freshly collected and prepared RBCs will be radiolabeled with <sup>99m</sup> Tc. The arm used for the blood draws and time of blood draws will be recorded.	<b>Fresh</b> blood samples are required to be collected prior to reinfusion. A sample will be collected for baseline assessment to be used in the calculation of 24-hour RBC recovery (%). Additionally, <b>if applicable (see Section 10.1)</b> , an aliquot of fresh blood <b>may</b> be taken from the participant and processed for RBC isolation. The freshly collected and prepared RBCs will be radiolabeled with <sup>99m</sup> Tc. The arm used for the blood draw(s) and time of blood draw(s) will be recorded.
Section 12.6.1.2 - Radiolabeling	To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs on the day of reinfusion (Day 42), the site must follow their standard labeling and handling process intended to	To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs on the day of reinfusion (Day 42), the site must follow their standard labeling and handling process intended to

	<p>eliminate errors in linking LR-RBC units with the correct study participant. Qualified RBCs will be radiolabeled with <math>^{51}\text{Cr}</math> (LR-RBC) and <math>^{99\text{m}}\text{Tc}</math> (fresh blood) and then reinfused back into the original participant. Radiolabeling will be done per site procedures and SOPs.</p>	<p>eliminate errors in linking LR-RBC units with the correct study participant. Qualified RBCs will be radiolabeled with <math>^{51}\text{Cr}</math> (LR-RBC) and <math>^{99\text{m}}\text{Tc}</math> (fresh blood), <b>if applicable</b>, and then reinfused back into the original participant. Radiolabeling will be done per site procedures and SOPs, <b>including aseptic preparation steps for research-grade <math>^{51}\text{Cr}</math> use (if applicable; see Section 10.1). If an issue is identified per the aseptic preparation steps, the <math>^{51}\text{Cr}</math> radiolabeled RBC will not undergo autologous radiolabeled reinfusion and will be destroyed per site SOPs, and the participant will be withdrawn from the study.</b></p>
<p>Section 12.7 – 24-Hour Post Reinfusion Blood Draw (Day 43 Visit)</p>	<p>The final study visit, the Day 43 visit, will occur 43 days after the LR-RBC collection. The visit will follow site SOPs for determining 24-hour recovery. The following procedures will be conducted:</p> <ol style="list-style-type: none"> <li>1. Record changes in health status (including AEs) and medications since last visit (if applicable)</li> <li>2. A blood sample (6-10 mL) will be drawn <math>24 \pm 4</math> hours post reinfusion and the following information will be recorded on the site's post-reinfusion worksheet: <ol style="list-style-type: none"> <li>a. Date and time of the blood draw</li> <li>b. Arm used for the blood draw (which will be the opposite arm than was used for reinfusion)</li> <li>c. Complete the worksheet for cpm readings from blood sample taken in duplicate or as many samples as required per site SOPs, net cpm, and corrected cpm recorded on the worksheet for cpm readings from blood sample.</li> <li>d. Hemoglobin or hematocrit of the blood sample</li> <li>e. 24-hour RBC recovery (%)</li> </ol> </li> <li>3. Collect vital signs (pulse rate, blood pressure, temperature).</li> <li>4. Record AEs and PDs (if applicable)</li> </ol> <p>The Day 43 Visit will conclude the</p>	<p>The final study visit, the Day 43 visit, will occur 43 days after the LR-RBC collection. The visit will follow site SOPs for determining 24-hour recovery. The following procedures will be conducted:</p> <ol style="list-style-type: none"> <li>1. Record changes in health status (including AEs) and medications since last visit (if applicable)</li> <li>2. A blood sample (6-10 mL) will be drawn <math>24 \pm 4</math> hours post reinfusion and the following information will be recorded on the site's post-reinfusion worksheet: <ol style="list-style-type: none"> <li>a. Date and time of the blood draw</li> <li>b. Complete the worksheet(s) for cpm readings from blood sample taken in duplicate or as many samples as required per site SOPs, net cpm, and corrected cpm recorded on the worksheet for cpm readings from blood sample.</li> <li>c. Hemoglobin or hematocrit of the blood sample</li> <li>d. 24-hour RBC recovery(<b>ies</b>) (%)</li> </ol> </li> <li>3. Collect vital signs (pulse rate, blood pressure, temperature).</li> <li>4. Record AEs and PDs (if applicable)</li> </ol> <p>The Day 43 Visit will conclude the participant's involvement in the study.</p>

	<p>participant's involvement in the study.</p> <p>The primary endpoint, 24-hour RBC recovery, will be calculated from the data of this visit and that of the Day 42 Visit according to the site's standardized in vivo RBC recovery procedure.</p>	<p>The primary endpoint, 24-hour RBC recovery, <b>determined using the single-label and dual-label (if possible) methods</b> will be calculated from the data of this visit and that of the Day 42 Visit according to the site's standardized in vivo RBC recovery procedure.</p>
Section 12.9.2 – Participant Withdrawal	<p>Participants will be considered withdrawals if following screening they are found unsuitable for continued participation or they do not otherwise complete the study procedures, as applicable. All participants are free to withdraw from participation at any time, for any reason, specified and unspecified, and without prejudice. The reason for participant withdrawal will be recorded as described in Section 19.5. Reasons for the participant's withdrawal may include but are not limited to:</p> <ol style="list-style-type: none"> <li>1. Development of an AE that interferes with the participant's continued participation</li> <li>2. Participant refuses further participation and/or follow-up and withdraws consent</li> <li>3. Investigator decision</li> <li>4. Sponsor decision</li> <li>5. Participant is lost to follow-up</li> <li>6. Participant death</li> <li>7. Circumstances beyond one's control (eg, natural disasters, power outages)</li> <li>8. Issues that do not result in an AE but interfere with the participant's continued participation</li> <li>9. Other (eg, positive pregnancy test, positive viral screen, positive bacterial test, failed visual assessment, failed hemolysis testing, or other explanation required)</li> </ol>	<p>Participants will be considered withdrawals if following screening they are found unsuitable for continued participation or they do not otherwise complete the study procedures, as applicable. All participants are free to withdraw from participation at any time, for any reason, specified and unspecified, and without prejudice. The reason for participant withdrawal will be recorded as described in Section 19.5. Reasons for the participant's withdrawal may include but are not limited to:</p> <ol style="list-style-type: none"> <li>1. Development of an AE that interferes with the participant's continued participation</li> <li>2. Participant refuses further participation and/or follow-up and withdraws consent</li> <li>3. Investigator decision</li> <li>4. Sponsor decision</li> <li>5. Participant is lost to follow-up</li> <li>6. Participant death</li> <li>7. Circumstances beyond one's control (eg, natural disasters, power outages)</li> <li>8. Issues that do not result in an AE but interfere with the participant's continued participation</li> <li>9. Other (eg, positive pregnancy test, positive viral screen, positive bacterial test, <b>positive endotoxin sample test</b>, failed visual assessment, failed hemolysis testing, <b>radiolabeling procedure issues including aseptic preparation of research-grade <sup>51</sup>Cr per site SOPs [if applicable]</b>, or other specified reason)</li> </ol>
Section 15.1.5 – Risk of Autologous Radiolabeled Red	<p>Since participants will be reinfused with a small amount of their own radiolabeled RBCs, the risk of a</p>	<p>Since participants will be reinfused with a small amount of their own radiolabeled RBCs, the risk of a</p>

Blood Cell Reinfusion	<p>transfusion reaction is minimal; however, in very rare cases, a reaction may occur, causing severe illness or death.</p> <p>The amount of radiation exposure from the radioisotopes, <math>^{51}\text{Cr}</math> and <math>^{99\text{m}}\text{Tc}</math>, used in this study and received by the participant is limited to reduce participant radiation exposure and is not considered to be harmful.<sup>15</sup></p> <p>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 of childbearing potential will have a pregnancy test performed prior to LR-RBC collection and prior to reinfusion as an added precaution. Any participant with a positive pregnancy test will not be given radiolabeled RBCs and will be withdrawn from the study.</p> <p>Additionally, participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study. The participant can discuss options for birth control with research staff.</p>	<p>transfusion reaction is minimal; however, in very rare cases, a reaction may occur, causing severe illness or death.</p> <p>The radiation exposure from <math>^{51}\text{Cr}</math> and <math>^{99\text{m}}\text{Tc}</math>, <b>if used</b>, received by the participant during this study is limited to reduce participant exposure and is not considered to be harmful.<sup>15</sup> 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 of childbearing potential will have a pregnancy test performed prior to LR-RBC collection and prior to reinfusion as an added precaution. Any participant with a positive pregnancy test will not be given radiolabeled RBCs and will be withdrawn from the study.</p> <p>Additionally, participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study. The participant can discuss options for birth control with research staff.</p> <p><b>Research-grade <math>^{51}\text{Cr}</math> may be used in this study, dependent upon the availability of GMP <math>^{51}\text{Cr}</math> at study sites. Since GMP <math>^{51}\text{Cr}</math> includes a sterilization step which is not included for research-grade <math>^{51}\text{Cr}</math>, an added sterility risk has been identified for research-grade <math>^{51}\text{Cr}</math>. To mitigate this risk, study sites will aseptically prepare research-grade <math>^{51}\text{Cr}</math> (such as by performing syringe filtration and endotoxin testing) according to their SOPs prior to reinfusion of radiolabeled RBCs.</b></p>
Section 15.1.6 – Bacterial Growth	<p>There is a possibility of bacterial overgrowth if bacteria have inadvertently entered the blood bag collection system. Samples of the stored LR-RBCs will be cultured using standard laboratory methods. The results from this testing will be available prior to the reinfusion of RBCs. Any participant with positive results will not be reinfused with their RBCs.</p>	<p>There is a possibility of bacterial overgrowth if bacteria have inadvertently entered the <b>RBC storage bag or materials used to prepare RBCs for reinfusion</b>. Samples of the stored LR-RBCs will be cultured using standard laboratory methods. The results from this testing will be available prior to the reinfusion of RBCs. Any participant with positive results will not be reinfused with their RBCs.</p>

<p>Section 15.2 – Risk Mitigation</p>	<p>To minimize risks of participant injury, the following general procedures are to be followed:</p> <ul style="list-style-type: none"> <li>• 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 protocol/CIP training to include device and procedure training.</li> <li>• Ensuring that enrolled participants meet all eligibility criteria.</li> <li>• Following the Operator’s Manual for the Trima Accel system and the package insert for the Trima Accel disposable tubing set, site SOPs, and any training provided by the Sponsor for apheresis procedures.</li> <li>• Following all package inserts associated with RBC collection, site SOPs, site procedures, and/or any training provided by the Sponsor for collection procedures.</li> <li>• Ensuring universal precautions are used for handling all study blood products in accordance with site SOPs.</li> <li>• Stopping the procedure if any of the more moderate or severe AEs occur, as defined by site SOPs. The participant can also request that the procedure be stopped at any time.</li> <li>• Ensuring that all participants meet the AABB and FDA recommendations for blood donation pertaining to the limits on the frequency of donation and the total amount of blood product that can be donated annually.</li> <li>• Ensuring that all participants meet the minimum hematocrit limits for donation, as defined by AABB. The apheresis devices are programmed such that they only allow collection of products from participants who will meet projected hematocrit standards at</li> </ul>	<p>To minimize risks of participant injury, the following general procedures are to be followed:</p> <ul style="list-style-type: none"> <li>• 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 protocol/CIP training to include device and procedure training.</li> <li>• Ensuring that enrolled participants meet all eligibility criteria.</li> <li>• Following the Operator’s Manual for the Trima Accel system and the package insert for the Trima Accel disposable tubing set, site SOPs, and any training provided by the Sponsor for apheresis procedures.</li> <li>• Following all package inserts associated with RBC collection, site SOPs, site procedures, and/or any training provided by the Sponsor for collection procedures.</li> <li>• Ensuring universal precautions are used for handling all study blood products in accordance with site SOPs.</li> <li>• Stopping the procedure if any of the more moderate or severe AEs occur, as defined by site SOPs. The participant can also request that the procedure be stopped at any time.</li> <li>• Ensuring that all participants meet the AABB and FDA recommendations for blood donation pertaining to the limits on the frequency of donation and the total amount of blood product that can be donated annually.</li> <li>• Ensuring that all participants meet the minimum hematocrit limits for donation, as defined by AABB. The apheresis devices are programmed such that they only allow collection of products from participants who will meet projected hematocrit standards at the completion of the collection.</li> </ul>
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	<p>the completion of the collection. These limitations are for the safety of blood donors and apply to this protocol.</p> <ul style="list-style-type: none"> <li>Ensuring the privacy and confidentiality of all research participants. 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 eCRFs. To ensure confidentiality, the eCRFs will be de-identified and any products sent to the Sponsor will only have the Donor ID, USID, and product numbers listed as participant identifiers.</li> <li>Ensuring participant safety throughout the procedures. Participants will be questioned concerning adverse experiences throughout the procedures. Participants will also be visually monitored for signs of distress during blood donation and reinfusion. Suspected adverse reactions will be treated according to site's SOPs and documented in the eCRFs.</li> <li>Participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study</li> <li>Female participants of childbearing potential must agree to take pregnancy tests prior to the apheresis procedure and prior to reinfusion of radiolabeled RBCs</li> </ul>	<p>These limitations are for the safety of blood donors and apply to this protocol.</p> <ul style="list-style-type: none"> <li>Ensuring the privacy and confidentiality of all research participants. 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 eCRFs. To ensure confidentiality, the eCRFs will be de-identified and any products sent to the Sponsor will only have the Donor ID, USID, and product numbers listed as participant identifiers.</li> <li>Ensuring participant safety throughout the procedures. Participants will be questioned concerning adverse experiences throughout the procedures. Participants will also be visually monitored for signs of distress during blood donation and reinfusion. Suspected adverse reactions will be treated according to site's SOPs and documented in the eCRFs.</li> <li>Participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study</li> <li>Female participants of childbearing potential must agree to take pregnancy tests prior to the apheresis procedure and prior to reinfusion of radiolabeled RBCs</li> <li><b>If research-grade <sup>51</sup>Cr is used in this study, study sites will perform aseptic preparation steps (eg, syringe filtration and endotoxin testing) according to their SOPs to mitigate sterility risks prior to reinfusion of radiolabeled RBCs</b></li> </ul>
Section 17.2.2 – Storage	The Trima Accel device and the investigational disposables should be stored in a dry place at room temperature (15.5°C [60°F] to	The Trima Accel device and the investigational disposables <b>will be stored according to the Operator's Manual and IFU</b> . Proper care

	27.7°C [82°F]). Proper care should be taken to ensure that the study inventory will not be damaged.	should be taken to ensure that the study inventory will not be damaged.
Section 18.3.1 – Primary Endpoint Analysis	<p>The analysis of the primary endpoint will be conducted using the EAS, defined in Section 18.4.3. In vivo RBC viability has been assessed for decades using radiolabeled autologous RBCs to assess the proportion of RBCs remaining in the circulation 24 hours after autologous reinfusion (24-hr RBC recovery). Radiolabeling methods and reporting of recovery have been standardized, allowing comparison of data between studies. Calculation of the proportion of RBCs surviving at 24-hr post reinfusion requires that RBC mass be accurately measured. This can be performed by extrapolating the early disappearance of cells to the midpoint of the reinfusion. Additional analyses may be performed on estimates of RBC recovery using RBC mass derived from <sup>99m</sup>Tc radiolabeling. RBC recovery 24 hours after reinfusion will be reported using the method recommended by Moroff et al.<sup>11</sup> The <sup>51</sup>Cr value at time = 0 (T zero, T0) is obtained by doing a regression analysis of the values obtained for <sup>51</sup>Cr labeled samples drawn at different timepoints post reinfusion. The T0 is used to calculate the percent recovery at 24 hours. The calculated T0 may be falsely low if the labeled RBCs are removed by the reticulo-endothelial (RE) system in large numbers prior to the first blood being drawn at 5 minutes post injection. This would result in a falsely higher 24-hour recovery. Recovery at 24 hours will be calculated using the following equation:<sup>11</sup></p> $\% \text{ recovery} = (\text{Adjusted RBC cpm at 24 hours} / \text{Adjusted RBC cpm at time 0}) \times 100$ <p>Radiolabeled samples will be drawn at different timepoints post reinfusion. The counts will be adjusted for background counts and corrected for loss of label (elution)</p>	<p>The analysis of the primary endpoint will be conducted using the EAS, defined in Section 18.4.3. In vivo RBC viability has been assessed for decades using radiolabeled autologous RBCs to assess the proportion of RBCs remaining in the circulation 24 hours after autologous reinfusion (24-hr RBC recovery). Radiolabeling methods and reporting of recovery have been standardized, allowing comparison of data between studies. Calculation of the proportion of RBCs surviving at 24-hr post reinfusion requires that RBC mass be accurately estimated. This can be performed by extrapolating the early disappearance of cells to the midpoint of the reinfusion.</p> <p><b>Calculation of the primary endpoint may be done using both the single-label and dual-label (if possible) method, dependent upon the availability of <sup>99m</sup>Tc labeling kits at both study sites. The dual-label method will only be conducted with data reported if <sup>99m</sup>Tc labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event <sup>99m</sup>Tc labeling kits are expected to be unavailable, the dual-label method will not be pursued and only the single-label method will be conducted with data reported. If complete data are collected for both the single-label and dual-label methods, analysis will be conducted to evaluate the 24-hour RBC recovery primary endpoint and reported for each method. If there is discordance in the results between the two methods, the dual-label method will take precedence.</b></p> <p>RBC recovery 24 hours after reinfusion will be reported using the method recommended by Moroff et al.<sup>11</sup> The <sup>51</sup>Cr value at time = 0 (T zero, T0) is obtained by doing a regression analysis of the values</p>

	<p>over time.<sup>10</sup></p> <p>The primary endpoint of RBC percent recovery at 24 hours post reinfusion will be used to assess each of the three criteria specified by FDA.<sup>8</sup> To assess the criteria associated with the percentage of samples with at least a 75% recovery, a success or failure for each observed value will be determined. RBC recovery of at least 75% will be deemed a success, and failure otherwise. A one-sided confidence interval for the proportion of successes will be determined using an exact 95% confidence interval. If the one-sided 95% lower confidence limit is greater than 70% the study will have met its primary endpoint in regards to this criterion, which will be met if no more than 3 failures occur (ie, samples with less than 75% recovery).</p> <p>Summary statistics and one-sided confidence intervals will be presented to assess the actual RBC recovery values and to evaluate the remaining criteria specified by FDA.</p> <p>Additional analyses will be performed on estimates of RBC recovery using RBC mass derived from <sup>99m</sup>Tc radiolabeling.</p>	<p>obtained for <sup>51</sup>Cr labeled samples drawn at different timepoints post reinfusion. The T0 is used to calculate the percent recovery at 24 hours. The calculated T0 may be falsely low if the labeled RBCs are removed by the reticulo-endothelial (RE) system in large numbers prior to the first blood being drawn at 5 minutes post injection. This would result in a falsely higher 24-hour recovery. Recovery at 24 hours will be calculated using the following equation:<sup>11</sup></p> $\% \text{ recovery} = (\text{Adjusted RBC cpm at 24 hours} / \text{Adjusted RBC cpm at time 0}) \times 100$ <p>Radiolabeled samples will be drawn at different timepoints post reinfusion. The counts will be adjusted for background counts and corrected for loss of label (elution) over time.<sup>10</sup></p> <p>The primary endpoint of RBC percent recovery at 24 hours post reinfusion will be assessed against the three FDA-specified criteria.<sup>8</sup> <b>To evaluate the criterion related to the percentage of samples with at least a 75% recovery, each observed value will be categorized as a success (recovery ≥ 75%) or failure (recovery &lt; 75%). A one-sided 95% confidence interval for the proportion of successes will be calculated using an exact method. The study will meet this primary endpoint criterion if the lower confidence limit exceeds 70% (equivalent to no more than 3 failures).</b></p> <p>Summary statistics and one-sided confidence intervals will be presented to assess the actual RBC recovery values and to evaluate the remaining criteria specified by FDA.</p>
Section 18.4.3 – Evaluable Analysis Set	<p>The Evaluable Analysis Set (EAS) will consist of the first 24 to 26 evaluable participants in the SS. An evaluable participant is defined as a participant who completes all study visits per the CIP with a valid 24-hour recovery endpoint without having met any of the protocol analysis exclusion criteria described in Section 18.5. Participants will</p>	<p>The Evaluable Analysis Set (EAS) will consist of the first 24 to 26 evaluable participants in the SS. An evaluable participant is defined as a participant who completes all study visits per the CIP with valid 24-hour recovery endpoint(s) <b>for the single-label and dual-label (if used) methods</b> without having met any of the protocol analysis exclusion</p>

	<p>only be included in the EAS once. The EAS is used in the analysis of the primary endpoint. The analysis of the primary endpoint in the EAS will be based on all recorded data. While the criteria outlined in the CIP allow for up to 26 participants, the final analysis will be based on all participants meeting the EAS. Within the EAS, all attempts will be made to obtain complete recovery data from all participants for the analysis of the primary endpoint.</p>	<p>criteria described in Section 18.5. Participants will only be included in the EAS once. The EAS is used in the analysis of the primary endpoint. The analysis of the primary endpoint in the EAS will be based on all recorded data. While the criteria outlined in the CIP allow for up to 26 participants, the final analysis will be based on all participants meeting the EAS. Within the EAS, all attempts will be made to obtain complete recovery data from all participants for the analysis of the primary endpoint.</p>
Section 18.5 – Protocol Analysis Exclusions	<p>There may be situations wherein the data will be considered non-evaluable and will not be included in the EAS. Data will be excluded from the EAS in the following situations:</p> <ol style="list-style-type: none"> <li>Inability to complete the procedure and/or study due to: <ol style="list-style-type: none"> <li>Participant issues (eg, inadequate access, reaction, needle abort)</li> <li>Participant lost to follow-up or withdrawn from study</li> <li>Equipment failure or malfunction (eg, filter plugs)</li> <li>Compromised product sterility (eg, open weld, bag puncture)</li> <li>Unanticipated processing failure</li> <li>Decision to stop procedure by participant, Investigator, site staff or operator</li> </ol> </li> <li>Incomplete post-collection processing <ol style="list-style-type: none"> <li>Equipment failure or malfunction (eg, unrecoverable system failure)</li> <li>Product damaged during storage</li> </ol> </li> <li>Protocol deviations (PDs) that affect the primary endpoint due to: <ol style="list-style-type: none"> <li>Failure to follow collection procedures outlined in the device Operator’s Manual, IFU (Package Insert), CIP, MOP(s), and site SOPs</li> </ol> </li> <li>Product non-reinfusable due to: <ol style="list-style-type: none"> <li>Product not available</li> <li>Product does not pass quality check for reinfusion (eg,</li> </ol> </li> </ol>	<p>There may be situations wherein the data will be considered non-evaluable and will not be included in the EAS. Data will be excluded from the EAS in the following situations:</p> <ol style="list-style-type: none"> <li>Inability to complete the procedure and/or study due to: <ol style="list-style-type: none"> <li>Participant issues (eg, inadequate access, reaction, needle abort)</li> <li>Participant lost to follow-up or withdrawn from study</li> <li>Equipment failure or malfunction (eg, filter plugs)</li> <li>Compromised product sterility (eg, open weld, bag puncture)</li> <li>Unanticipated processing failure</li> <li>Decision to stop procedure by participant, Investigator, site staff or operator</li> </ol> </li> <li>Incomplete post-collection processing <ol style="list-style-type: none"> <li>Equipment failure or malfunction (eg, unrecoverable system failure)</li> <li>Product damaged during storage</li> </ol> </li> <li>Protocol deviations (PDs) that affect the primary endpoint due to: <ol style="list-style-type: none"> <li>Failure to follow collection procedures outlined in the device Operator’s Manual, IFU (Package Insert), CIP, MOP(s), and site SOPs</li> </ol> </li> <li>Product non-reinfusable due to: <ol style="list-style-type: none"> <li>Product not available</li> <li>Product does not pass quality check for reinfusion (eg,</li> </ol> </li> </ol>

	visual inspection, hemolysis, bacterial growth, target radiolabel)	<b>positive viral screen</b> , visual inspection, hemolysis, bacterial growth, <b>radiolabeling procedure issues to include aseptic preparation of research-grade <sup>51</sup>Cr per site SOPs [if applicable] or failed endotoxin testing [if applicable]</b> )
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## SYNOPSIS

<b>Sponsor:</b>	Terumo BCT, Inc.
<b>Study Title:</b>	In Vivo 24-Hour Recovery Study of Leukoreduced RBCs Collected on the Trima Accel System Using Non-DEHP Disposable Sets and Stored for 42 Days
<b>Study Number:</b>	CTS-5091
<b>Device Description:</b>	<p>The Trima Accel system is an automated blood component apheresis 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, Solution A (ACD-A), as the anticoagulant (AC). There are four major components of the Trima Accel system: Equipment, Embedded Software, Disposable Tubing Sets, and Optional Accessories.</p> <p>The Trima Accel Equipment, Embedded Software, and Optional Accessories (if applicable) are commercially available and are not under test in this investigation. They will be used in this study according to the released Operator's Manual and Instructions for Use (IFU). The Disposable Tubing Sets are under test in this investigation as described below.</p> <p>The approved single-use disposables are manufactured using di(2-ethylhexyl) phthalate (DEHP). Recently, Annex XIV of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), also called the REACH authorization list, was amended to include DEHP on the list of substances that cannot be marketed or used after a given 'sunset date' in manufactured products. As the existing Trima Accel disposables contain DEHP, the Sponsor has developed investigational, non-DEHP plastics to replace all DEHP plasticized disposables to comply with the REACH regulation (ie, &lt; 0.1% weight for weight [w/w] DEHP).</p>
<b>Intended Use:</b>	<p>The Trima Accel system is an automated blood cell separator intended for use in collecting blood components for later transfusion into patients. (NOTE: blood products will not be transfused to recipient patients in this study but will be autologously reinfused to healthy adult volunteers.) Depending on the disposable tubing set used, the Trima Accel system has been cleared to collect:</p> <ul style="list-style-type: none"> <li>• Double ACD-A/Additive Solution Formula 3 (AS-3) RBCs (leukocytes reduced or not leukoreduced)</li> </ul> <p>Or the following products alone or in combination:</p> <ul style="list-style-type: none"> <li>• ACD-A/AS-3 RBCs</li> <li>• ACD-A/AS-3 RBCs, Leukocytes Reduced utilizing an integrated filter (TLR gravity drain filter or Auto RBC filter)</li> <li>• Platelets Pheresis, Leukocytes Reduced (single, double, or triple units)</li> <li>• Platelets Pheresis, Leukocytes Reduced, Platelet Additive Solution (Isoplate or InterSol) (single, double, or triple units)</li> <li>• Plasma for Fresh Frozen Plasma and Fresh Frozen Plasma, Leukocytes Reduced</li> <li>• Plasma for Plasma Frozen Within 24 Hours After Phlebotomy (PF24) and Plasma Frozen Within 24 Hours After Phlebotomy, Leukocytes Reduced</li> <li>• Plasma for Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy (PF24RT24) and Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy, Leukocytes Reduced</li> <li>• Source Plasma</li> </ul>
<b>Objectives:</b>	The primary objective of this study is to demonstrate that leukoreduced (LR) RBCs collected on the Trima Accel system using investigational non-DEHP disposable tubing sets with AS-3 meet the United States (US) Food and Drug Administration (FDA) criteria for 24-hour in vivo recovery after refrigerated storage in non-DEHP

	storage bags for 42 days. <sup>1</sup> NOTE: blood products will not be transfused to recipient patients in this study but will be autologously reinfused to healthy adult volunteers.
<b>Efficacy Endpoint:</b>	<p><u>Primary Endpoint:</u></p> <p>The primary endpoint is the 24-hour in vivo RBC recovery after 42 days of refrigerated storage, determined using the single-label (using <sup>51</sup>Cr only) and dual-label (using <sup>51</sup>Cr and <sup>99m</sup>Tc, if possible, dependent upon availability of <sup>99m</sup>Tc labeling kits at both study sites) radiolabeling methods.</p>
<b>Safety Endpoints:</b>	Safety will be monitored through collection of adverse events (AEs), serious AEs (SAEs), and unanticipated adverse device effects (UADEs).
<b>Study Design:</b>	<p>This is a prospective, open-label, multicenter study designed to demonstrate that LR-RBCs collected on the Trima Accel system with the investigational non-DEHP disposable tubing sets with integrated AS-3 delivery meet the FDA criteria for 24-hour recovery after refrigerated storage for 42 days.<sup>1</sup> Healthy adult volunteers will undergo an AutoRBC collection procedure with AS-3 as the additive solution according to the Trima Accel Operator's Manual and site standard operating procedures (SOPs). After processing, complete blood count (CBC), product volume, spun hematocrit, and hemolysis will be measured per site procedures. The LR-RBC units will be stored at 2-6°C for 42 days away from the transfusion inventory, with bacterial testing occurring during the storage period per site SOPs.</p> <p>After 42 days of refrigerated storage, the LR-RBCs will be tested for CBC, spun hematocrit, hemolysis, along with a visual quality check and confirmation of a negative bacterial screen per site SOPs. Both the single-label and dual-label radiolabeling methods can be used to determine the primary endpoint, 24-hour RBC recovery. For both single- and dual-label methods, an autologous aliquot of stored LR-RBCs will be radiolabeled with either Good Manufacturing Practice (GMP) <sup>51</sup>Cr or qualified research-grade <sup>51</sup>Cr, dependent upon the source of <sup>51</sup>Cr available to study sites. If research-grade <sup>51</sup>Cr is used, aseptic preparation steps will be conducted per site SOPs to qualify research-grade <sup>51</sup>Cr, which may include but is not limited to syringe filtration and endotoxin testing. The dual-label method requires an additional autologous aliquot of fresh RBCs to be labeled with GMP <sup>99m</sup>Tc, dependent upon the availability of <sup>99m</sup>Tc labeling kits at the study sites. The labeled RBCs will be reinfused to the participant. The dual-label method will only be pursued if <sup>99m</sup>Tc labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event <sup>99m</sup>Tc labeling kits are expected to be unavailable, the dual-label method will not be pursued and only the single-label method will be conducted. For RBC recovery testing, blood samples will be collected at baseline and approximately 5, 7.5, 10, 12.5, 15, 20, 30 minutes, and 24 hours post reinfusion. Participants will be monitored for AEs throughout their participation in the study.</p> <p>All radiolabeling procedures, including aseptic preparation steps (if applicable), labeling, reinfusion, and sampling, will follow the site's common standardized procedures and SOPs. The procedures for radiolabeling of RBCs to evaluate RBC recovery are based and adapted from methods recommended by International Committee of Standardization in Haematology (ICSH) Recommended Methods for Radioisotope Red-Cell Survival Studies and previously published literature by Moroff and colleagues.<sup>2,3</sup> The method of calculating the blood volume with <sup>99m</sup>Tc is based on the ICSH Recommended Methods for Measurement of Red-Cell and Plasma Volume.<sup>4</sup></p>
<b>Study Sites Planned:</b>	2 sites in the US
<b>Study Duration:</b>	<p>Up to 58 days (44 days + up to 14 days for screening) per participant. Up to 4 study visits per participant.</p> <p>The total study duration will be approximately 8 months.</p> <p>A healthy adult volunteer is considered an enrolled participant upon giving informed</p>

	consent for study participation; this timepoint represents the beginning of a participant's involvement in the study. A participant's involvement in the study will conclude upon participant screen failure, participant withdrawal, following completion of the Day 43 visit, or upon follow-up and stabilization/resolution of AEs, as applicable. A healthy adult volunteer can enroll more than once in the study but can only complete the study once with data included in the Evaluable Analysis Set (EAS).
<b>Target Population:</b>	Healthy adult volunteers
<b>Number of Participants Planned:</b>	At least 24 and up to 26 evaluable participants (up to 50 enrolled).
<b>Inclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1. Given written informed consent</li> <li>2. Age 18 years or older</li> <li>3. Normal health status as per AABB criteria for healthy donor</li> <li>4. Able to commit to the study schedule</li> <li>5. Meets the inclusion criteria defined by site SOPs for automated blood component collection systems or whole blood donation. These criteria are based on AABB standards and FDA regulations. <ol style="list-style-type: none"> <li>a. Note: Participants who are deferred from volunteer community donations due to certain restrictions may participate in the study, as products are not used for allogeneic transfusion; however, sites may or may not implement this depending on their standard procedures.</li> </ol> </li> <li>6. Participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study</li> <li>7. Female participants of childbearing potential must agree to take pregnancy tests prior to the apheresis procedure and prior to reinfusion of radiolabeled LR-RBCs</li> <li>8. Participants must agree to report AEs throughout their participation in the study</li> </ol>
<b>Exclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1. Currently pregnant or nursing females</li> <li>2. Serum ferritin &lt;12 ng/mL</li> <li>3. Has previously completed this study with data included in the EAS</li> <li>4. Participation currently, or within the past 30 days, in another investigational trial that would potentially interfere with the analysis of this investigation (eg, pharmaceutical trial)</li> <li>5. As determined by the Investigator <ol style="list-style-type: none"> <li>a. Has been diagnosed with a blood disorder(s) affecting RBC characteristics (eg, Glucose 6 Phosphate Dehydrogenase [G6PD] Deficiency)</li> <li>b. Reported history of RBC autoantibodies/autoimmune hemolytic anemia, RBC alloantibodies</li> <li>c. Clinically significant acute or chronic disease</li> <li>d. Reported history of hypersensitivity to technetium or chromium</li> <li>e. Other unspecified reason that, in the opinion of the Investigator, makes the healthy adult volunteer unsuitable for enrollment</li> </ol> </li> <li>6. Treatment with any medication as specified in site deferral list (based on AABB medication deferral list for apheresis donors)</li> <li>7. Previously transfused/reinfused with RBCs within the last 120 days</li> </ol>

<p><b>Statistical Methodology:</b></p>	<p><u>Sample Size:</u></p> <p>The sample size is based on the US FDA's 3-part RBC recovery criteria shown below (ie, primary endpoint). The derivation of the sample size was based on the level of precision attained with at least 24 and up to 26 participants relative to the first criterion.</p> <p>Estimates were prepared based on the 1st criterion with at least 24 participants, examining the one-sided confidence interval for the proportion of successes using the Clopper-Pearson exact method for a 95% confidence interval. If the observed proportion of treatment successes is 21/24 (87.50%) or higher, the one-sided lower 95% binomial confidence interval will exceed 70% (lower confidence limit = 70.77%) and the study will be deemed to have met its primary endpoint. If a participant does not return for reinfusion of radiolabeled RBCs and/or 24-hour recovery sampling, an additional participant must be enrolled to replace the missing sample. This additional participant will then require sample storage for 42 days. To avoid this type of potential delay, up to 2 additional participants will be enrolled so the final sample size will be at least 24 and up to 26 participants. Three (3) or fewer failures will meet the 1st FDA criterion with 24 to 26 participants. Comparison of the statistical scenarios between sample sizes of n=24 and n=26 demonstrates that the planned statistical method will not be impacted across this sample size range (ie, 3 failures would result in the one-sided lower 95% binomial confidence interval exceeding 70% [lower confidence limit = 70.77% for n=24 and 72.81% for n=26]).</p> <p>In order to reach the total target number of evaluable participants, additional participants will be enrolled to replace those for whom the primary endpoints are not evaluable (as determined using study protocol analysis exclusion criteria, Section 18.5). It is anticipated that up to 50 healthy adult volunteers may need to be enrolled to accrue at least 24 and up to 26 evaluable participants for the primary endpoint analysis. All participants, regardless of the availability of their endpoint data, will be included in evaluations of in vitro data (where samples are available) and in evaluations of AEs.</p> <p><u>Primary Endpoint:</u></p> <p>Calculation of the primary endpoint may be done using both the single-label and dual-label (if possible) method, dependent upon the availability of <sup>99m</sup>Tc labeling kits at both study sites. The dual-label method will only be conducted with data reported if <sup>99m</sup>Tc labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event <sup>99m</sup>Tc labeling kits are expected to be unavailable, the dual-label method will not be pursued and only the single-label method will be conducted with data reported. If complete data are collected for both the single-label and dual-label methods, analysis will be conducted to evaluate the 24-hour RBC recovery primary endpoint and reported for each method. If there is discordance in the results between the two methods, the dual-label method will take precedence.</p> <p>Based on US FDA criteria for in vivo RBC quality,<sup>1</sup> the following criteria will be used to assess the primary endpoint:</p> <ul style="list-style-type: none"> <li>• A one-sided lower confidence limit for the proportion of RBC components with 24-hour RBC in vivo recovery &gt;75% is 70%*,</li> <li>• *Allows for low recoveries (&lt;75%) in up to 3 out of 24 to 26 participants</li> <li>• A sample mean of in vivo 24-hour RBC percent recovery ≥ 75%, and</li> <li>• A sample standard deviation of in vivo 24-hour RBC percent recovery ≤ 9%.</li> </ul> <p>If all 3 criteria are met, the Trima Accel system with the investigational non-DEHP disposable tubing sets will be deemed to have met the pre-established criteria for 24-hour in vivo RBC recovery.</p>
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	<u>Safety:</u> The tabulation of AEs will be based on the reported incidence by system organ class and preferred term and summarized using counts and percentages.
<b>References:</b>	<ol style="list-style-type: none"><li>1. Vostal J. Presentation: FDA Evaluation of Red Cell Products. US Food and Drug Administration, Laboratory of Cellular Hematology, OBRR, CBER, FDA. 2016.</li><li>2. Moroff G, Sohmer PR, Button LN. Proposed standardization of methods for determining the 24-hour survival of stored red cells. Transfusion. 1984;24(2):109-114.</li><li>3. Recommended method for radioisotope red-cell survival studies. International Committee for Standardization in Haematology. Br J Haematol. 1980;45(4):659-666.</li><li>4. Recommended methods for measurement of red-cell and plasma volume: International Committee for Standardization in Haematology. J Nucl Med. 1980;21(8):793-800.</li></ol>

## TABLE OF CONTENTS

<b>SYNOPSIS .....</b>	<b>20</b>
<b>1 STATEMENT OF COMPLIANCE .....</b>	<b>32</b>
<b>2 INTRODUCTION.....</b>	<b>32</b>
2.1 Background .....	32
<b>3 DEVICE DESCRIPTION .....</b>	<b>33</b>
3.1 Equipment and Embedded Software.....	34
3.2 Investigational Disposable Tubing Sets .....	35
<b>4 INTENDED USE STATEMENT.....</b>	<b>36</b>
<b>5 NONCLINICAL STUDIES.....</b>	<b>38</b>
5.1 Product Volume Accuracy .....	39
5.2 Plasma Free Hemoglobin .....	39
<b>6 CLINICAL TRIAL EXPERIENCE.....</b>	<b>40</b>
<b>7 RATIONALE FOR THE CURRENT STUDY .....</b>	<b>51</b>
<b>8 OBJECTIVES .....</b>	<b>51</b>
8.1 Primary Objective .....	51
<b>9 ENDPOINTS .....</b>	<b>52</b>
9.1 Primary Endpoint .....	52
9.2 Safety Endpoints .....	52
<b>10 INVESTIGATIONAL PLAN .....</b>	<b>52</b>
10.1 Study Design .....	52
10.2 Study Duration .....	53
<b>11 STUDY POPULATION .....</b>	<b>54</b>
11.1 Number of Participants and Selection.....	54
11.2 Inclusion Criteria .....	55
11.3 Exclusion Criteria .....	55
11.4 Recruitment and Pre-Screening .....	56
<b>12 STUDY PROCEDURES .....</b>	<b>56</b>
12.1 Informed Consent Process .....	56
12.2 Participant Enrollment .....	57
12.3 Schedule of Procedures .....	57
12.4 Enrollment and Initial Eligibility Assessment (Days -14 to 0 Visit) .....	61

12.5	Eligibility Confirmation and LR-RBC Collection via the Trima Accel System (Day 0 Visit) .....	61
12.5.1	Prior to LR-RBC Collection .....	61
12.5.2	LR-RBC Collection .....	62
12.5.3	Following LR-RBC Collection .....	62
12.6	Reinfusion of Radiolabeled RBCs (Day 42 Visit) .....	63
12.6.1	Prior to Reinfusion of Radiolabeled RBCs .....	64
12.6.2	Reinfusion of Radioabeled RBCs .....	65
12.6.3	Following Reinfusion of Radiolabeled RBCs .....	65
12.7	24-Hour Post Reinfusion Blood Draw (Day 43 Visit) .....	66
12.8	Long-Term Follow-Up .....	66
12.9	Participant Disposition .....	67
12.9.1	Participant Screen Failure .....	67
12.9.2	Participant Withdrawal .....	67
12.9.3	Participant Study Completion .....	67
<b>13</b>	<b>LABORATORY TESTS .....</b>	<b>68</b>
<b>14</b>	<b>CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES .....</b>	<b>71</b>
<b>15</b>	<b>ADVERSE EVENTS/EFFECTS .....</b>	<b>71</b>
15.1	Anticipated Risks .....	71
15.1.1	Venipuncture Related Risks .....	71
15.1.2	Apheresis Related Risks .....	71
15.1.3	Trima Accel System Related Risks .....	72
15.1.4	Investigational Non-DEHP Material .....	74
15.1.5	Risk of Autologous Radiolabeled Red Blood Cell Reinfusion .....	74
15.1.6	Bacterial Growth .....	75
15.2	Risk Mitigation .....	75
15.3	Potential Benefits .....	76
15.4	Adverse Event/Effect Definitions .....	76
15.4.1	Adverse Event .....	76
15.4.2	Procedure-Emergent Adverse Event .....	77
15.4.3	Serious Adverse Event .....	77
15.4.4	Adverse Device Effect .....	77
15.4.5	Unanticipated Adverse Device Effect .....	78

15.5	Adverse Event Recording .....	78
15.6	Adverse Event Classification .....	79
15.6.1	Severity .....	79
15.6.2	Relatedness .....	79
15.7	Adverse Event Follow-up .....	80
15.8	Serious Adverse Event Reporting Requirements.....	80
15.8.1	Reporting Requirements for SAEs and UADEs .....	80
15.9	Medical Monitoring .....	81
<b>16</b>	<b>DATA MONITORING COMMITTEE .....</b>	<b>81</b>
<b>17</b>	<b>STUDY DEVICE .....</b>	<b>81</b>
17.1	Device Deficiencies .....	81
17.2	Device Accountability .....	82
17.2.1	Receipt of Study Device .....	82
17.2.2	Storage .....	82
17.2.3	Accountability.....	82
<b>18</b>	<b>STATISTICAL PLAN.....</b>	<b>83</b>
18.1	General Considerations for Data Analysis.....	83
18.2	Sample Size Rationale .....	83
18.3	Endpoint Analyses .....	85
18.3.1	Primary Endpoint Analysis .....	85
18.3.2	Safety Endpoints Analysis .....	86
18.4	Analysis Populations.....	86
18.4.1	Enrolled Set.....	86
18.4.2	Safety Set .....	86
18.4.3	Evaluable Analysis Set .....	86
18.5	Protocol Analysis Exclusions .....	87
18.6	Missing, Unused, and/or Spurious Data .....	87
18.7	Interim Analysis.....	87
<b>19</b>	<b>STUDY MANAGEMENT.....</b>	<b>88</b>
19.1	Ethics.....	88
19.2	Investigator Responsibilities.....	88
19.2.1	Investigator Agreement.....	88

19.2.2	Institutional Review Board/Ethics Committee .....	88
19.2.3	Informed Consent.....	88
19.2.4	Study Files and Record Retention.....	88
19.3	Sponsor Responsibilities .....	89
19.3.1	General Responsibilities .....	89
19.3.2	Amendments to the Clinical Investigation Plan.....	89
19.4	Joint Investigator-Sponsor Responsibilities.....	89
19.4.1	Access to Information for Monitoring and Auditing .....	89
19.4.2	Training.....	89
19.5	Collecting and Recording Data.....	89
19.5.1	Source Documents .....	90
19.5.2	Electronic Case Report Forms .....	90
19.5.3	Data Queries.....	90
19.6	Clinical Investigation Plan Compliance.....	90
19.6.1	Protocol Deviations.....	90
19.7	Suspension or Termination of the Study.....	91
19.8	Publication Policy .....	91
<b>20</b>	<b>REFERENCES.....</b>	<b>93</b>
<b>21</b>	<b>INVESTIGATOR SIGNATURE.....</b>	<b>95</b>

## LIST OF TABLES

Table 5-1:	List of Biological Risk Assessments (per ISO 10993) Reports and Conclusions.....	38
Table 5-2:	Product Volume Accuracy Testing .....	39
Table 5-3:	Verification Results for Plasma Free Hemoglobin .....	40
Table 6-1:	Summary of Trima Accel Clinical Trials.....	42
Table 12-1:	Schedule of Procedures.....	58
Table 13-1:	In Vitro Tests .....	69
Table 15-1:	Venipuncture Adverse Event Frequency .....	71
Table 15-2:	Apheresis Adverse Event Frequency .....	72
Table 15-3:	Summary of Adverse Events in Manufacturer Sponsored Clinical Investigations .....	73
Table 18-1:	Statistical Scenarios Estimation of LR-RBC Evaluation Sample Size.....	84

## LIST OF FIGURES

Figure 3-1: Major Components of the Trima Accel System .....	35
Figure 10-1: Participant Study Flow.....	54

## LIST OF APPENDICES

Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091	
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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
<sup>51</sup> Cr	chromium-51
<sup>99m</sup> Tc	technetium-99m
AABB	Association for the Advancement of Blood & Biotherapies
ABO/Rh	blood type
AC	anticoagulant
ACD-A	Anticoagulant Citrate Dextrose Solution, Solution A
ADE	adverse device effect
AE	adverse event
AS-3	Additive Solution Formula 3
CBC	complete blood count
CE	Conformité Européenne
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
cpm	counts per minute
CTA	Clinical Trial Agreement
DEHP	di(2-ethylhexyl) phthalate
DIN	Donation Identification Number
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
eCRF	Electronic Case Report Form
EAS	Evaluable Analysis Set
EDC	Electronic Data Capture
EDQM	European Directorate for the Quality of Medicines and Healthcare
ES	Enrolled Set
EU	European Union
EU MDR	European Union Medical Device Regulation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICSH	International Committee of Standardization in Haematology
IFU	Instructions For Use
IP	investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	intravenous
LOC	loss of consciousness

<b>Abbreviation</b>	<b>Definition</b>
LR	leukoreduced/leukoreduction
MCV	mean corpuscular volume
MOP	Manual of Procedures
PD	protocol deviation
PEAE	procedure-emergent adverse event
PHI	Protected Health Information
PVC	polyvinyl chloride
RBC	red blood cell
RE	reticulo-endothelial
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
rWBC	residual white blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOP	Standard Operating Procedure
SOW	Statement of Work
SS	Safety Set
TMF	Trial Master File
UADE	unanticipated adverse device effect
US	United States
w/w	weight for weight

## **1 STATEMENT OF COMPLIANCE**

This study will be conducted according to this Clinical Investigation Plan (CIP), Good Clinical Practice (GCP) as described in the International Council for Harmonisation (ICH) Guidance for Industry E6(R2), and, as applicable, United States (US) Code of Federal Regulations (CFR) concerning clinical studies (45 CFR Part 46; 21 CFR Parts 50, 56, 312 and 812), International Organization for Standardization (ISO) 14155:2020, European Union Medical Device Regulation (EU MDR) 2017/745, and other regulatory requirements of the region(s) where the study is conducted. The study will not begin until the required approvals or favorable opinions from the Institutional Review Board (IRB) and/or Ethics Committee (EC) and regulatory authority have been obtained, as applicable. As directed, any additional requirements imposed by the IRB/EC or regulatory authority will be followed. Any applicable information required per above regulations that is not contained in this CIP may be submitted in separate documentation and will be attached to the CIP as an appendix. All essential documents will be archived together in the Trial Master File (TMF).

## **2 INTRODUCTION**

### **2.1 Background**

Blood transfusion is a life-saving therapy that has neither an alternative nor an equivalent. Blood transfusions have been widely used in medical practice since the early 20th century and is the most common procedure during hospital stays in the US.<sup>1,2</sup> Blood transfusions are often used as a treatment option for accident victims, organ and marrow transplant recipients, cancer and heart surgery patients, and people with blood-related diseases (eg, sickle cell anemia, leukemia, hemophilia).<sup>3</sup> In the clinical setting, there is typically a component specific trigger (ie, platelet count <50,000) that prompts clinicians to objectively assess the need for a transfusion.<sup>3</sup> Often, patients only need the transfusion of a specific component (ie, red blood cells [RBCs] for sickle cell anemia or platelets for bleeding disorders); therefore, the collection and transfusion of specific blood components can provide clinicians a valuable tool for the specific treatment of a patient.

Automated whole blood collection and processing via apheresis systems is a valuable tool that blood collection and donation centers can use to meet the clinical demand for blood components such as RBCs, platelets, and plasma, while helping to ensure donor safety.<sup>4</sup> Clinical practice guidelines have been published by international and national bodies to inform the best practices for collecting and transfusing blood products/units. In the US, the Food and Drug Administration (FDA) and Association for the Advancement of Blood & Biotherapies (AABB) have established guidelines and best practices for the collection and transfusion of blood products.<sup>5,6</sup>

The Trima Accel system, manufactured by Terumo BCT, Inc., (hereafter referred to as the Sponsor), is an automated blood component collection system that uses continuous-flow

centrifugal force to separate whole blood into RBCs, platelets, and plasma. During the collection procedure, anticoagulant (AC) and whole blood are mixed at a manifold near the needle site. The inlet pump draws the blood and AC mixture into the Trima Accel system, where the mixture enters the channel. As the whole blood is separated within the channel, pumps remove the platelets and plasma. The pressure created from the blood being continuously pumped into the centrifuge pushes RBCs out of the channel. Depending on the selected procedure, RBCs, plasma, and platelets are either collected in the product bags or routed to the return reservoir to be returned to the donor.

The Trima Accel system received US FDA clearance in 2002 (BK010046) and has been Conformité Européenne (CE) marked in Europe since 2001. The Trima Accel software Version 7 (BK170157) received FDA clearance on 04 April 2018. The Trima Accel Software Version 7.0.4. was assessed in accordance with the FDA regulations and guidance documents for when to file a 510(k) for a product change and it was deemed that a new 510(k) submission was not required; therefore, a letter to file was written and entered into file on 18 April 2022.

The current approved disposables are manufactured with materials containing di(2-ethylhexyl) phthalate (DEHP). Recently the Annex XIV of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), also called the REACH authorization list, was amended to include DEHP on the list of substances that cannot be placed on the market or used after a given 'sunset date.' As the existing Trima Accel disposables contain DEHP, the Sponsor has developed investigational non-DEHP plastics to replace all DEHP plasticized polyvinyl chloride (PVC) in the existing Trima Accel disposables to comply with the REACH regulation (ie, < 0.1% weight for weight [w/w] DEHP).

The primary objective of this study is to demonstrate that leukoreduced (LR) RBCs collected on the Trima Accel system using investigational non-DEHP disposable tubing sets with AS-3 meet the US FDA criteria for 24-hour recovery after refrigerated storage in non-DEHP storage bags for 42 days.<sup>8</sup> NOTE: blood products will not be transfused to recipient patients in this study but will be autologously reinfused to healthy adult volunteers.

### **3 DEVICE DESCRIPTION**

The Trima Accel system is an automated blood component collection system that uses continuous-flow centrifugal force to separate whole blood into RBCs, platelets, and plasma. The Trima Accel system uses Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A), as a standalone AC.

The Trima Accel system operates by withdrawing whole blood from the donor and mixing it with ACD-A in the disposable tubing set. The blood is mixed with ACD-A and is then pumped into a channel (a plastic conduit that sits in a specially designed groove in the centrifuge filler), and it is spun at high speed in the centrifuge, separating the blood into its components. Combinations of

RBCs, platelets, and plasma are either collected into storage bags or returned to the donor. If additive solution delivery is required to collected components for storage, it is accomplished post donor disconnect from the device.

Fluid flow through the Trima Accel system is controlled by variable speed peristaltic pumps. The fluid path is dependent on the disposable tubing set used and the procedure selected. The blood and blood components do not come into direct contact with the reusable equipment in the Trima Accel system.

There are four major components of the Trima Accel system:

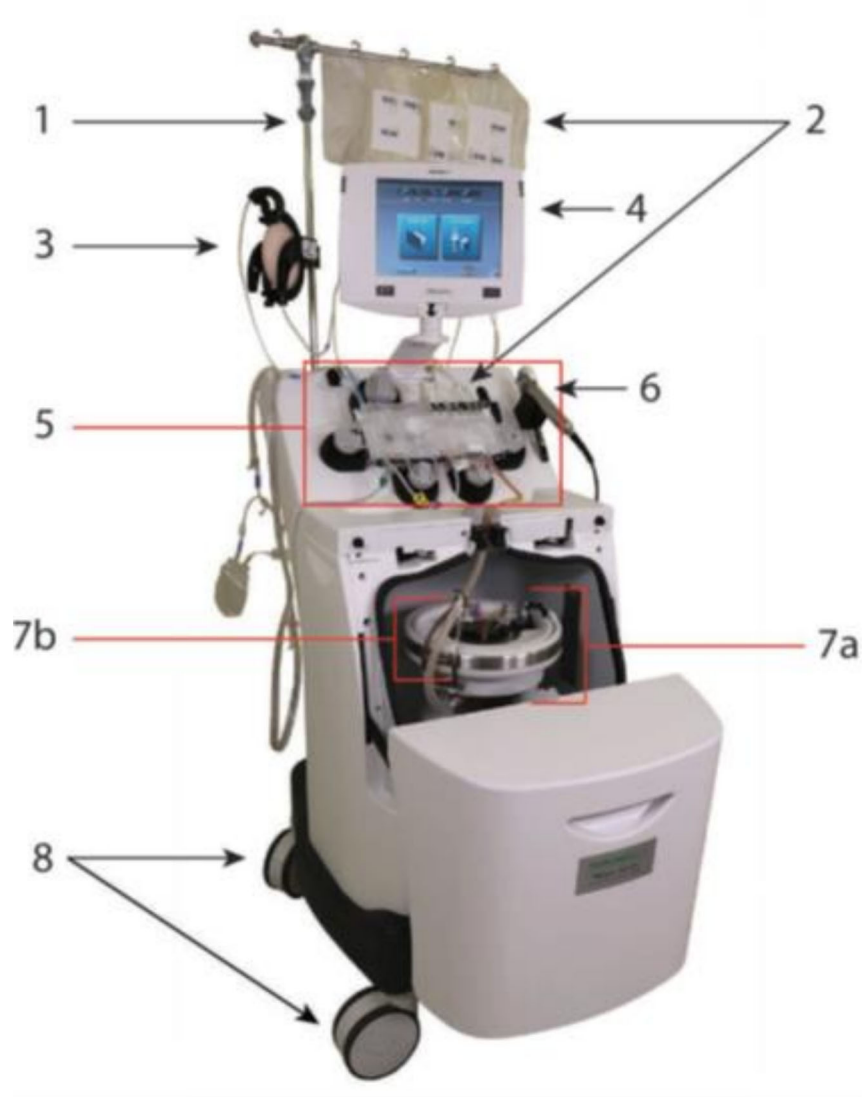
- Equipment
- Embedded Software
- Disposable Tubing Sets
- Optional Accessories

The Trima Accel Equipment, Embedded Software, and Optional Accessories (if applicable) are commercially available in the United States and are not under test in this investigation. They will be used in this study according to the released Operator's Manual and Instructions for Use (IFU). The Disposable Tubing Sets are under test in this investigation as described in Section 3.2. Additional details pertaining to each of the major components are presented in the following sections.

### **3.1 Equipment and Embedded Software**

The Trima Accel system includes an automated blood cell separator control unit that includes pumps, valves, sensors, a centrifuge, and embedded software. The system provides the functions necessary to monitor and control the extracorporeal circuit during apheresis collection procedures. The equipment components of the Trima Accel system are reusable, non-invasive, and considered active medical devices. The components in the Trima Accel system equipment are described in the Operator's Manual and shown in Figure 3-1.

**Figure 3-1: Major Components of the Trima Accel System**



The Trima Accel system Equipment contains the following components (1): Intravenous (IV) bag pole; (2) Disposable tubing set; (3) RBC filter bracket (optional); (4) Display panel; (5) Front panel; (6) Seal Safe mobile cutter/sealer; (7a) Centrifuge (7b) Filler; and (8) Wheels.

### **3.2 Investigational Disposable Tubing Sets**

The final blood products produced by the Trima Accel system during each collection are determined by the disposable tubing set used, donor-specific features (total blood volume, hematocrit, and platelet count) entered at the time of collection, and the procedure selected. The procedure selected for each collection is chosen by the operator from a list of prespecified options displayed by the Trima Accel system, which factors in combinations of collection procedures programmed by the blood center, the blood type of the donor compared to clinical

needs, and donor eligibility criteria. The types of blood products that can be collected are provided in Section 4.

Current FDA cleared and CE marked versions of the Trima Accel disposable set consist of medical grade PVC and Additive Solution Formula 3 (AS-3) as the stand-alone RBC additive solution. The PVC used in these disposables contains DEHP as the plasticizer which allows the plastic in the disposable set to be flexible. DEHP is present in both the blood contact and the non-blood contact sub-components of these disposables.

To meet the new EU regulations, an alternative plasticized PVC material, which does not contain DEHP, has been incorporated as a new material into the manufacturing of investigational Trima Accel disposable tubing sets. The investigational non-DEHP Trima Accel disposable is a hybrid plasticizer system in which the primary RBC bag, plasma bag, platelet bag vinyl, and flexible tubing is comprised of PVC plasticized with the following, or a combination thereof, di(2-ethylhexyl) terephthalate (DEHT), tris(2-ethylhexyl) trimellitate (TOTM), citrate, or Proprietary.

The tubing sets are sterile, non-pyrogenic, functionally closed systems that are used to route whole blood to the channel in the centrifuge and to route the separated components to the product bags and return reservoir. While there are variations in the tubing sets, there are two base configurations for the cassette and tubing sets; either platelet-capable or RBC/plasma-capable sets.

The investigational disposable blood bag set used in this study will be labeled with stickers noting 'CAUTION-Investigational Device. Limited by Federal (or US) law for Investigational use'.

## **4 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. (NOTE: blood products will not be transfused to recipient patients in this study but will be autologously reinfused to healthy adult volunteers.) Depending on the disposable tubing set used, the Trima Accel system has been cleared to collect:

- Double ACD-A/AS-3 RBCs (leukocytes reduced or not leukoreduced)

Or the following products alone or in combination:

- ACD-A/AS-3 RBCs
- ACD-A/AS-3 RBCs, Leukocytes Reduced utilizing an integrated filter (TLR gravity drain filter or Auto RBC filter)
- Platelets Pheresis, Leukocytes Reduced (single, double, or triple units)

- Platelets Pheresis, Leukocytes Reduced, Platelet Additive Solution (Isoplate or InterSol) (single, double, or triple units)
- Plasma for Fresh Frozen Plasma and Fresh Frozen Plasma, Leukocytes Reduced
- Plasma for Plasma Frozen Within 24 Hours After Phlebotomy (PF24) and Plasma Frozen Within 24 Hours After Phlebotomy, Leukocytes Reduced
- Plasma for Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy (PF24RT24) and Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy, Leukocytes Reduced
- Source Plasma

Storage of RBCs collected on the Trima Accel system:

- Adequate studies have not been performed to evaluate the effect of gamma irradiation or freezing on the quality of ACD-A/AS-3 RBC products collected with gravity drain leukoreduction (LR) process (TLR filter) on the Trima Accel system.
- Studies have not been performed to support gamma irradiation or freezing of ACD-A/AS-3 RBCs collected with an integrated in-line RBC LR filter(s) (Auto RBC filter) on the Trima Accel system.

Storage of Platelets collected on the Trima Accel system

- Platelets Pheresis may be manufactured from products that do not meet leukocyte reduction product standards. Platelets Pheresis, Leukocytes Reduced, Platelet Additive Solution (Isoplate or InterSol) may be further processed (eg, irradiated, divided). Platelets Pheresis, Platelet Additive Solution (Isoplate or InterSol) may not be manufactured from products that do not meet leukocyte reduction product standards.
- The storage conditions of the Trima Platelet bag (ELP bag) have been verified for storage up to 7 days post-collection in 100% Plasma and up to 5 days in Isoplate (PAS-F) or InterSol (PAS-C) solutions.
- Additionally, for storage up to 7 days, every product must be tested with a bacterial detection device cleared by FDA and labeled as a "safety measure."
- The Trima Blood Component Sampling Assembly, which is either integrated into the disposable tubing sets or available as an accessory for sterile connection, is intended to allow aseptic removal of a sample from the platelet bag for subsequent bacterial or other applicable testing. The Sampling Assembly does not have contact with blood fluids that are reinfused to a donor or patient.

#### Storage of Plasma Collected on the Trima Accel system

- Fresh Frozen Plasma and Fresh Frozen Plasma, Leukocyte Reduced must be prepared and placed in a freezer at  $-18^{\circ}\text{C}$  or colder within 8 hours of phlebotomy.
- Plasma Frozen Within 24 Hours After Phlebotomy (PF24) and Plasma Frozen Within 24 Hours After Phlebotomy, Leukocytes Reduced must be stored at  $1^{\circ}\text{C}$  to  $6^{\circ}\text{C}$  within 8 hours of phlebotomy and placed in a freezer at  $-18^{\circ}\text{C}$  or colder within 24 hours of phlebotomy and is indicated for replacement of non-labile clotting factors. This product is not equivalent to Fresh Frozen Plasma.
- Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy (PF24RT24) and Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy, Leukocyte Reduced can be stored at room temperature for up to 24 hours after phlebotomy. Product must be placed in a freezer at  $-18^{\circ}\text{C}$  or colder within 24 hours of phlebotomy and is indicated for replacement of non-labile clotting factors. This product is not equivalent to Fresh Frozen Plasma.

Rx only.

## 5 NONCLINICAL STUDIES

Nonclinical studies to assess the investigational non-DEHP disposables are ongoing. A biological risk assessment of the representative non-DEHP Trima Accel Set was performed based on the requirements of the current ISO 10993-1:2018, ISO 14971:2019, 2020 FDA Biocompatibility Guidance, and European Medical Device: 2020/561 Regulation, ISO 21726, and ICH has been performed. Summary results of this testing is provided in Table 5-1.

**Table 5-1: List of Biological Risk Assessments (per ISO 10993) Reports and Conclusions**

Test	Conclusion
Acute Systemic Toxicity Report	Each test article extract met the requirements of the study.
Complement Report	The test article was not considered to be a potential activator of the complement system.
Cytotoxicity Report	The test article extract showed no evidence of causing cell lysis or toxicity.
Cytotoxicity Report-Aged Set	In this assay, the test article did not induce cytotoxicity.
Extractable Report	All system suitability criteria were met for all analytical systems.
Genotoxicity Report Ames	The PEG and saline test article extracts were considered to be nonmutagenic against test strains.
Genotoxicity Report Mouse Lymphoma Assay	The test article was not mutagenic.
Hemolysis Report	The test article in direct contact with blood was slightly hemolytic, and the test article extract was non-hemolytic.
Material Mediated Pyrogenicity Report	The test article met the requirements for the absence of pyrogens.

Test	Conclusion
Partial Thromboplastin Time Report	The test article met the requirements of the test.
Platelet Leukocyte Count Report	The test article passed.
Sensitization Report	The test article was not considered a sensitizer in the guinea pig maximization test.

Additionally, studies have been conducted to establish the safety and performance of the investigational non-DEHP disposable. These studies (outlined below) have found the non-aged (T = 0) investigational non-DEHP sets do not have any significant impact to donor safety parameters using the worst-case blood processing conditions.

## 5.1 Product Volume Accuracy

Per verification testing, the investigational non-DEHP disposable sets meet the acceptance criteria for product volume accuracy for Auto-PAS platelet, platelet, AutoRBC, RBC, plasma, and plasma with plasma rinseback with 95% confidence and 95% reliability (Table 5-2).

**Table 5-2: Product Volume Accuracy Testing**

Product	Average (% Error)	St Dev (% Error)	UCL (% Error)	LCL (% Error)	Requirement (% Error)
Auto-PAS Platelet	-4.75%	1.72%	0.34%	-9.84%	± 10%
Platelet	4.30%	1.38%	8.06%	0.54%	± 10%
AutoRBC	6.69%	1.31%	10.62%	3.31%	± 15%
RBC	1.37%	2.32%	6.8%	-4.08%	± 10%
Plasma	-0.43%	1.62%	3.4%	-4.25%	± 10%
Plasma with Plasma Rinseback	4.15%	0.77%	6.2%	2.04%	± 10%

## 5.2 Plasma Free Hemoglobin

As shown in Table 5-3, plasma free hemoglobin concentration met the pre-determined acceptance criteria of a change in concentration of < 50 mg/dL over the course of the procedure with 95% confidence and 95% reliability.

**Table 5-3: Verification Results for Plasma Free Hemoglobin**

	Control (DEHP)			Test (Non-DEHP)		
	Pre	Post	Delta	Pre	Post	Delta
Average	1.83	8.51	6.68	1.46	7.85	6.39
Standard Deviation	0.81	1.33	1.10	0.26	1.80	1.69
95% Upper Confidence Limit	2.58	9.74	7.70	1.70	9.52	7.96

Overall, pre-clinical verification testing showed no evidence indicating the removal of DEHP substantially impacts processed blood that is returned to the donor.

## 6 CLINICAL TRIAL EXPERIENCE

Each of the Trima Accel system's collection protocols has been extensively studied in Terumo BCT sponsored clinical trials. Terumo BCT has sponsored 13 clinical trial investigations (2 RBC, 9 platelets and 1 plasma, 1 non-DEHP) assessing the safety and efficacy of the system. A summary of each trial is provided in Table 6-1. Results from these studies have shown that the Trima Accel system can safely collect RBCs, platelets, and plasma alone and in combination, that meet both the FDA and EDQM requirements for transfusion.

The most relevant data for the current investigation (CTS-5091) is the AutoRBC (ie, LR-RBC) arm of CTS-5090, the in vitro study and precursor for this trial. This data was provided in the Response to FDA Request for Info: IDE29212/11 dated 30 May 2024.

The Sponsor conducted this in vitro study to determine if LR-RBCs collected on the Trima Accel system into investigational non-DEHP disposable sets meet established standards for a transfusable blood product. Analyses were conducted on 61 LR-RBC units from participants who underwent a Trima Accel AutoRBC collection procedure with AS-3 as the additive solution and stored in investigational non-DEHP disposable sets for up to 42 days. The mean total Day 0 residual white blood cell (rWBC) content was  $0.13 \times 10^6$  cells  $\pm 0.12 \times 10^6$  cells, Day 0 RBC Filtration Recovery was  $93.44\% \pm 4.28\%$ , Day 35 Hemolysis was  $0.19\% \pm 0.08\%$ , and Day 42 Hemolysis was  $0.21\% \pm 0.11\%$ . A 95/95 binomial approach was utilized to evaluate whether the LR-RBC units met the primary endpoint of Day 0 rWBC content ( $< 5.0 \times 10^6$  cells) and RBC filtration recovery ( $\geq 85\%$ ) along with both Day 35 and Day 42 hemolysis ( $\leq 1.0\%$ ). Based on  $n=61$ , 60 (98.4%) procedures met the 3-part FDA criteria with a one-sided 95% lower confidence limit of 92.46% which does not meet the 95/95 binomial approach. One unit did not meet the RBC filtration recovery criteria (value was 82.5%). An extensive evaluation of the cause of this failure has been conducted (Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091; submitted to FDA under IDE 29212/S011, Page 211 of 241). The most likely reason the unit did not meet the 85% filter recovery endpoint was an overestimated fingerstick hematocrit value during donor qualification, which was entered into the Trima Accel at the start of the procedure. The Sponsor asserted that this failure was not due to the Trima Accel system or the

investigational non-DEHP disposable set, as neither the system nor the filter underwent any changes, and the system was operating as expected. Despite the filter recovery being below 85%, the unit still met all requirements for a transfusable dose. Additionally, there were no serious PEAEs, severe PEAEs, serious device-related PEAEs, or UADEs reported.

**Table 6-1: Summary of Trima Accel Clinical Trials**

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
BCT07-14 Protocol 1- In Vitro Quality of RBC Units	A paired study comparing RBC products collected with an investigational RBC disposable tubing set for the Trima Accel system and the 510(k) cleared RBC disposable tubing set. The in vitro quality parameters of single and double RBC units collected with the investigational Trima Accel system RBC disposable tubing were evaluated against the FDA recommendations for LR, hemolysis, 85% recovery post LR, pH, ATP retention, and potassium concentration.	Collect in vitro RBC quality data to support two new features on the Trima Accel system: 1. Press-Through RBC LR 2. Automatic Addition of Metered RBC Preservative Solution.	157 participants were enrolled to achieve at least 60 evaluable paired single RBC collections and 60 evaluable double RBC collections.	The study found that 0/68 LR single RBC and 0/70 double RBC units had a residual white blood cell (rWBC) count $> 5 \times 10^6$ cells. The maximum rWBC count for both single and double RBC units was $0.81 \times 10^6$ cells. The study also found that 68/68 single RBC units and 70/70 double RBC units had collected doses $\geq 85\%$ of the targeted doses. Hemolysis after 42 days of storage was $< 1\%$ in 68/68 single RBC units (maximum value was 0.70%) and 70/70 double RBC units (maximum value was 0.95%). The collected RBC units also met the required FDA-CBER criteria for pH after 42 days of storage, ATP retention after 42 days of storage, and potassium concentration after 42 days of storage. The collection of concurrent platelet and plasma products did not negatively affect RBC collection. The Trima Accel system with Press-Through RBC LR and addition of metered preservative solution met the FDA-CBER criteria for in vitro RBC quality.
BCT07-13 Protocol 2 – In Vivo Autologous Recovery of Radiolabeled RBC Units	A single-arm study that collected double RBC units from donors using the investigational RBC disposable tubing set for the Trima Accel system. The in vivo recovery of radiolabeled RBCs at 24 hours post infusion after 42 days of storage was evaluated against the FDA recommendations for percent recovery.	Collect in vivo RBC recovery data to support two new features on the Trima Accel system: 5. Press-Through RBC LR 6. Automatic Addition of Metered RBC Preservative Solution.	30 participants were enrolled to achieve at least 24 evaluable radiolabel data points.	The study found that 26/27 LR RBC units had $> 75\%$ recovery of radiolabeled RBCs 24 hours post infusion after 42 days of refrigerated storage. There were no statistically significant differences in radiolabel recoveries between Unit 1 and Unit 2 of double RBC collections. The study concluded that single and double RBC units collected on the investigational Trima Accel system are acceptable for transfusion in terms of 24-hour radiolabeled recovery.

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
CTS-0049 Blood Collection Study in Healthy Donors: Evaluation of Products Acquired by Whole Blood and Apheresis Collections: In Vitro Testing of the Mirasol Pathogen Reduction Technology (PRT) System for Whole Blood (PAWS)	Feasibility (Exploratory)	Obtain fresh whole blood, apheresis platelets, plasma, and RBC units for in vitro development and testing of the Mirasol PRT System for Whole Blood. Safety was monitored for WB and apheresis collections using the FDA-cleared Trima Accel system.	Up to 500 healthy donors per year.	For WB donation, one of the WB donors had hematoma, but the information regarding AE was missing and was reported as “missing data.” The data from this subject was not included in the analysis. Nineteen (n=19) AEs were reported out of 1488 attempted WB donations (12 hematomas and 7 vasovagal reactions). Of the AEs reported, most of them were mild (n=12 hematoma, and n=6 vasovagal) and were resolved with routine intervention. One (1) vasovagal AE was reported to be moderate and an injury report was filed by the site and reported to the Sponsor. For apheresis blood components donations, one (1) hematoma AE was reported out of 21 attempted donations and was resolved with routine intervention. There were no incidence of vasovagal response, infiltration, and citrate reactions reported. All the AEs were previously reported as anticipated AEs from a venipuncture, WB donation, and/or apheresis blood components donations. There were no severe AEs, SAEs, UADEs reported for either WB or apheresis blood components. WB and apheresis collection procedures were safe and provided an adequate supply of WB or apheresis blood components to Sponsor laboratories for subsequent in vitro testing of the Mirasol PRT System for WB.
CTS-5011 Feasibility Study: Study of an Algorithm for Draw Flow Rate Adjustments on Trima Accel™ to Lower Operator Interventions	Feasibility (Exploratory)	Determine if manual and automatic adjustments to the draw flow rate during a Trima Accel collection procedure lowered the number of operator interventions and had an effect on the procedure time.	136 procedures and 70 completed donors.	Manual and automatic adjustments to the draw flow rate during a Trima Accel platelet or platelet + plasma apheresis procedure significantly reduced the number of operator interventions compared to a control apheresis procedure. A change to the draw flow rate did not significantly alter the collected product and did not result in a change in the occurrence or type of AEs experienced during an apheresis procedure.

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
CTS-5035 Use of Blood Products Acquired by Trima Accel System or Whole Blood Collections for Laboratory Evaluations (Generic)	Feasibility (Exploratory)	Provide an adequate supply of human blood and/or blood components for use in Terumo BCT laboratories in order to support the development of new devices and the ongoing product evaluation and improvement of marketed devices.	Up to 10,000 healthy donors per year.	Enrollment ongoing.
CTS-5051 (NCT02298842) In Vitro Study of Platelets Collected on Trima Accel System and Stored in Intersol Solution (In Vitro Intersol)	Pivotal	Verify that the in vitro quality of platelets collected on the Trima Accel system (software Version 6.4), diluted in Intersol solution, and stored for 1, 5, and 7 days met the FDA acceptance criteria for stored platelets.	60 paired donations (N=30/treatment arm).	The primary endpoint of a pH $\geq$ 6.2 at Day 5 and Day 7 was met, and all products met the FDA acceptance criteria. Morphology met the established acceptance criteria, but ESC, HSR, and P-selectin values did not; however, the ESC, HSR, and P-selectin values were comparable to what had been reported previously for platelets collected on another device and stored in Intersol Solution. There were no SAEs, UADEs, or device-related AEs and all reported TEAEs were mild and had been previously reported as anticipated AEs of an apheresis procedure. In summary, platelets collected on the Trima Accel system and stored in Intersol Solution met FDA criteria for pH and morphology after storage for 5 or 7 days.

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
CTS-5053 Feasibility Study to Evaluate Software Modifications to Enhance Trima Accel System for Platelet Product Collections	Feasibility (Validation)	<p><u>Phase 1</u> – Evaluate the software modification impact to platelet collection procedure time, yield, LR, and donor platelet post count.</p> <p><u>Phase 2</u> – Continued evaluation of platelet collection procedure time, yield and LR, with additional software modifications to evaluate venous access alarms and additional LR.</p> <p><u>Phase 3</u> – Continued evaluation of platelet collection procedure time, yield, and LR with additional software modifications to evaluate the procedure time savings and tubing set residuals with the new plasma rinseback protocol.</p>	<p>Phase 1: 200 donors; Phase 2: 550 donors; Phase 3: 450 donors.</p>	<p>A total of 1,083 healthy adult volunteers were enrolled who completed 1,027 evaluable procedures (136 participants for 135 procedures in Phase 1, 597 participants for 563 procedures in Phase 2, and 350 participants for 329 procedures in Phase 3).</p> <p>When compared to predicted outcomes based on previous software versions, the new software modifications improved platelet collection procedure time, yield, LR, and venous access alarms, while platelet product quality was maintained.</p> <p>Out of 1027 evaluable procedures, there were 114 AEs reported due to donations/procedures. The most common AEs reported were citrate reactions (n=51) and infiltrations (n=33) followed by hematomas (n=14), vasovagal reactions (n=7), and pain/discomfort at the venipuncture site (n=4). All these AEs had been previously reported as anticipated AEs during an apheresis procedure. All hematomas and 8 of the 9 vasovagal reactions were mild in nature. One vasovagal reaction was moderate. There were no deaths, SAEs, or UADEs reported. There were 8 DDs reported, but all were considered as appropriate functioning alarms.</p> <p>Blood component donation with the modified software was safe, and the study verified that software modifications to the Trima Accel system improved platelet collection procedure time, yield, LR, and venous access alarms, while maintaining platelet product quality.</p>

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
CTS-5054 (NCT02684630) A Multicenter Study to Evaluate Modified Postcount Algorithm Software on the Trima Accel® System in Volunteer Blood Donors	Pivotal	Determine if single and double platelet products collected on the Trima Accel system with modified platelet postcount algorithm software maintained donor postprocedure platelet count of $\geq 100,000$ platelets/ $\mu\text{L}$ .	120 donors (60 single unit and 60 double unit).	All donors who donated a single or double platelet product collected using the modified platelet postcount algorithm software had a postprocedure platelet count $\geq 100,000$ platelets/ $\mu\text{L}$ and all the platelets collected with the modified platelet postcount algorithm met the FDA's acceptance criteria for platelet quality. All reported TEAEs were mild, related to the apheresis procedure, and had been previously reported in the literature. There were no SAEs, UADEs, or device related AEs. Overall, this study found that collection of single and double platelet products on the Trima Accel system with the modified platelet postcount algorithm software was safe, effective, and maintained the donor's postprocedure platelet count $\geq 100,000$ platelets/ $\mu\text{L}$ .
CTS-5059 (NCT02754440) Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in Platelet Additive Solution	Pivotal	Verify that platelets collected on the Trima Accel system with Version 7.0 software enhancements and stored in PAS met the FDA requirements for LR ( $< 5.0 \times 10^6$ rWBC per transfusable unit).	The study included 279 evaluable platelet products (93 single, 93 double, and 93 triple) collected from 365 enrolled donors.	Single, double, and triple platelet products met the FDA acceptance criteria for rWBC level and platelet yield. Of the 279 evaluable platelet products, none had rWBCs above the applicable FDA acceptance criterion and 4 single platelet products had a platelet yield $< 3.0 \times 10^{11}$ (up to 16 failures were allowed to ensure with 95% confidence that 75% met criteria). There were no SAEs or UADEs reported, and most TEAEs were moderate and had been previously reported as anticipated AEs of an apheresis procedure. In summary, the collection of single, double, and triple platelet products on the Trima Accel system with the Version 7.0 software was safe and effective, and the final platelet products met the FDA acceptance criteria for LR and platelet yield.

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
CTS-5060 (NCT02754492) Evaluation of the Performance of Trima Accel® Version 7.0 Software Enhancements for the Collection of Platelets Stored in 100% Plasma	Pivotal	Verify that platelets collected on the Trima Accel system with Version 7.0 software enhancements and stored in 100% plasma met the US FDA requirements for LR ( $< 5.0 \times 10^6$ rWBC per transfusable unit).	The study included 279 evaluable platelet products (93 single, 93 double, and 93 triple) collected from 334 enrolled donors.	Single, double, and triple platelet products met the FDA acceptance criteria for rWBC level and platelet yield. Of the 279 evaluable platelet products, there was a single platelet product that had rWBCs $> 5.0 \times 10^6$ . Per FDA guidance, to ensure 95% confidence that 95% of products met rWBC requirements, up to 1 failure was allowed in 93 collections. Additionally, there was a single platelet product with a platelet yield $< 3.0 \times 10^{11}$ which ultimately met the FDA guidance of 95% confidence that 75% of products meet yield requirements. There were no SAEs or UADEs reported, and most TEAEs were moderate and had been previously reported as anticipated adverse effects of an apheresis procedure. In summary, the collection of single, double, and triple platelet products on the Trima Accel system with the Version 7.0 software was safe and effective, and the final platelet products met the FDA acceptance criteria for LR and platelet yield.
CTS-5066 (NCT03097289) An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution	Pivotal	Determine the in vivo recovery and survival of radiolabeled platelets collected on the Trima Accel system, resuspended in InterSol, and stored for 5 days. Platelet recovery was measured at 24 hours post transfusion.	The study enrolled 33 donors to collect 24 evaluable data points.	Apheresis platelets collected on the Trima Accel system and stored in 65% InterSol / 35% plasma for 5 days met the FDA acceptance criteria for both in vivo platelet recovery and in vivo platelet survival when compared to fresh controls. There were no SAEs, UADEs, or deaths reported; the AEs observed were mild to moderate in severity and had previously been reported as anticipated adverse effects of an apheresis procedure.

Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
PF24RT24 Trima Accel Automated Blood Component Collection System	This study was performed in conjunction with the FDA. Large volume plasma products were collected on the Trima Accel system from healthy donors. Half the volume from each collected plasma product was transferred to a second plasma storage bag. The paired plasma products were left to rest and were then placed in a freezer at $20 \pm 2^{\circ}\text{C}$ at either 7-8 hours post collection (Control) or 23-24 hours post collection (Test). All plasma products were held in frozen storage for at least 1 month. Subsequently, plasma products from each collection were thawed at the same time, and 11 plasma quality assays were conducted on samples from each product to provide within-subject paired data.	Provide information on differences in the plasma quality measures for plasma frozen within 8 hours of collection and within 24 hours of collection. The primary outcome measures were the post thaw assay results for ACD-A plasma products frozen 8 hours and 24 hours after collection on Trima Accel system. The following assays were performed: FVIII, PT, aPTT, Protein C, Protein S, FV, FXI, vWF/RCO, ATIII, aFVII, and FPA.	70 donors were enrolled for a total of 52 products analyzed.	For the series of plasma quality assays carried out, plasma collected on the Trima Accel system then frozen within 24 hours was shown to be non-inferior to that frozen within 8 hours.

CTS-5090 Collection of Blood Products Acquired by the Trima Accel System into Non-DEHP Disposable Tubing Sets for Laboratory Evaluations	Healthy volunteers who have consented to donate blood components for laboratory research will undergo a donation procedure on the Trima Accel system using non- DEHP disposables with storage bags.	Collect RBCs on the Trima Accel system into non-DEHP disposable sets using AS-3 as the RBC additive solution to determine if they meet established standards for a transfusable RBC product. This testing supports the development of the Trima Accel system's non-DEHP disposable tubing sets.	n=61 evaluable AutoRBC products	<p>The Sponsor conducted this in vitro study to determine if LR-RBCs collected on the Trima Accel system into investigational non-DEHP disposable sets meet established standards for a transfusable blood product. Analyses were conducted on 61 LR-RBC units from participants who underwent a Trima Accel AutoRBC collection procedure with AS-3 as the additive solution and stored in investigational non-DEHP disposable sets for up to 42 days. The mean total Day 0 residual white blood cell (rWBC) content was <math>0.13 \times 10^6</math> cells <math>\pm 0.12 \times 10^6</math> cells, Day 0 RBC Filtration Recovery was <math>93.44\% \pm 4.28\%</math>, Day 35 Hemolysis was <math>0.19\% \pm 0.08\%</math>, and Day 42 Hemolysis was <math>0.21\% \pm 0.11\%</math>. A 95/95 binomial approach was utilized to evaluate whether the LR-RBC units met the primary endpoint of Day 0 rWBC content (<math>&lt; 5.0 \times 10^6</math> cells) and RBC filtration recovery (<math>\geq 85\%</math>) along with both Day 35 and Day 42 hemolysis (<math>\leq 1.0\%</math>). Based on n=61, 60 (98.4%) procedures met the 3-part FDA criteria with a one-sided 95% lower confidence limit of 92.46% which does not meet the 95/95 binomial approach. One unit did not meet the RBC filtration recovery criteria (value was 82.5%). An extensive evaluation of the cause of this failure has been conducted (Appendix 1: CTS-5090 Filter Recovery Justification for CTS-5091; submitted to FDA under IDE 29212/S011, Page 211 of 241). The most likely reason the unit did not meet the 85% filter recovery endpoint was an overestimated fingerstick hematocrit value during donor qualification, which was entered into the Trima Accel at the start of the procedure. The Sponsor asserted that this failure was not due to the Trima Accel system or the investigational non-DEHP disposable set, as neither the system nor the filter underwent any changes, and the system was operating as expected. Despite the filter recovery</p>
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Study No. Study Title	Study Design	Study Objective(s)	Sample size	Findings/Conclusions
				being below 85%, the unit still met all requirements for a transfusable dose. Additionally, there were no serious PEAEs, severe PEAEs, serious device-related PEAEs, or UADEs reported.

Abbreviations: ACD-A = Anticoagulant Citrate Dextrose Solution, Solution A; AE = adverse event; aFVII = Activated Factor VII; aPTT = activated partial thromboplastin time; AS-3 = Additive Solution Formula 3; ATIII = Antithrombin III; ATP = adenosine triphosphate; DD = device deficiency; ESC = extent of shape change; FDA = Food and Drug Administration; FDA-CBER = Food and Drug Administration Center for Biologics Evaluation and Research; FPA = Fibrinopeptide A; FV = Factor V; FVIII = Factor VIII; FXI = Factor XI; HSR = hypotonic shock response; LR = leukoreduced/leukoreduction; PAS = platelet additive solution; PAWS = Blood Collection Study in Healthy Donors: Evaluation of Products Acquired by Whole Blood and Apheresis Collections: In Vitro Testing of the Mirasol Pathogen Reduction Technology System for Whole Blood; PRT = pathogen reduction technology; PT = prothrombin time; RBC = red blood cell; rWBC = residual white blood cell; SAE = serious adverse event; TEAE = treatment-emergent adverse event; UADE = unanticipated adverse device effect; US = United States; vWF/RCo = von Willebrand Factor/Risto cetin Cofactor.

## 7 RATIONALE FOR THE CURRENT STUDY

The Trima Accel system received US FDA clearance in 2002 (BK010046) and has been Conformité Européenne (CE) marked in Europe since 2001 for disposables manufactured with materials containing DEHP. Recently, Annex XIV of the REACH authorization list was amended to include DEHP on the list of substances that cannot be placed on the market or used after a given ‘sunset date.’ As the current Trima Accel disposables include DEHP, the Sponsor has developed investigational, non-DEHP plastics to replace all DEHP plasticized PVC in the existing Trima Accel disposables to comply with the REACH regulation.

This study is being conducted to evaluate whether the ACD-A/AS-3 RBCs, LR using an Auto RBC filter (hereafter referred to as LR-RBCs) collected on the Trima Accel system with investigational non-DEHP disposable tubing sets and storage bags and the RBC additive solution AS-3 meet the FDA criteria for 24-hour recovery after 42 days of refrigerated storage.<sup>8</sup>

## 8 OBJECTIVES

### 8.1 Primary Objective

The primary objective of this study is to demonstrate that LR-RBCs collected on the Trima Accel system using non-DEHP disposable tubing sets with AS-3 meet the FDA criteria for 24-hour recovery after 42 days of refrigerated storage in non-DEHP storage bags.<sup>8</sup> NOTE: blood products will not be transfused to recipient patients in this study but will be autologously reinfused to healthy adult volunteers.

The performance criteria are based on FDA criteria for in vivo RBC quality:

1. A one-sided lower confidence limit for the proportion of RBC components with 24-hour RBC in vivo recovery  $>75\%$  is  $70\%^*$ ,  
\*Allows for low recoveries ( $< 75\%$ ) in up to 3 out of 24 to 26 participants
2. A sample mean of in vivo 24-hour RBC percent recovery  $\geq 75\%$ , and
3. A sample standard deviation of in vivo 24-hour percent RBC recovery  $\leq 9\%$ .

If all 3 criteria are met, the Trima Accel system with the investigational non-DEHP disposable tubing sets will be deemed to have met the pre-established criteria for 24-hour in vivo RBC recovery. This performance criteria will be evaluated in healthy adult participants who receive radiolabeled, autologous reinfusions of LR-RBC components after 42 days of refrigerated storage.

## **9 ENDPOINTS**

### **9.1 Primary Endpoint**

The primary endpoint is the 24-hour in vivo RBC recovery after 42 days of refrigerated storage, determined using the single-label (using  $^{51}\text{Cr}$  only) and dual-label (using  $^{51}\text{Cr}$  and  $^{99\text{m}}\text{Tc}$ , if possible, dependent upon availability of  $^{99\text{m}}\text{Tc}$  labeling kits at both study sites) radiolabeling methods. The single label method for 24-hour RBC recovery uses Nadler's method<sup>9</sup> to estimate a participant's blood volume by accounting for their gender, height, and weight. The dual-label method uses a direct determination of the blood volume of the participant through the co-infusion of autologous, freshly collected  $^{99\text{m}}\text{Tc}$ -labeled RBCs.<sup>10-15</sup>

### **9.2 Safety Endpoints**

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

## **10 INVESTIGATIONAL PLAN**

### **10.1 Study Design**

This is a prospective, open-label, multicenter study designed to demonstrate that LR-RBCs collected on the Trima Accel system with the investigational non-DEHP disposable tubing sets with integrated AS-3 delivery meet the FDA criteria for 24-hour recovery after refrigerated storage for 42 days.<sup>8</sup> Healthy adult volunteers will undergo an AutoRBC collection procedure with AS-3 as the additive solution according to the Trima Accel Operator's Manual and site standard operating procedures (SOPs). After processing, complete blood count (CBC), product volume, spun hematocrit, and hemolysis will be measured per site procedures. The LR-RBC units will be stored at 2-6°C for 42 days away from the transfusion inventory, with bacterial testing occurring during the storage period per site SOPs.

After 42 days of refrigerated storage, the LR-RBCs will be tested for CBC, spun hematocrit, hemolysis, along with a visual quality check and confirmation of a negative bacterial screen per site SOPs. Both the single-label and dual-label radiolabeling methods can be used to determine the primary endpoint, 24-hour RBC recovery. For both single- and dual-label methods, an autologous aliquot of stored LR-RBCs will be radiolabeled with either Good Manufacturing Practice (GMP)  $^{51}\text{Cr}$  or qualified research-grade  $^{51}\text{Cr}$ , dependent upon the source of  $^{51}\text{Cr}$  available to study sites. If research-grade  $^{51}\text{Cr}$  is used, aseptic preparation steps will be conducted per site SOPs to qualify research-grade  $^{51}\text{Cr}$ , which may include but is not limited to syringe filtration and endotoxin testing. The dual-label method requires an additional autologous aliquot of fresh RBCs to be labeled with GMP  $^{99\text{m}}\text{Tc}$ , dependent upon the availability of  $^{99\text{m}}\text{Tc}$  labeling kits at the study sites. The labeled RBCs will be reinfused to the participant. The dual-label

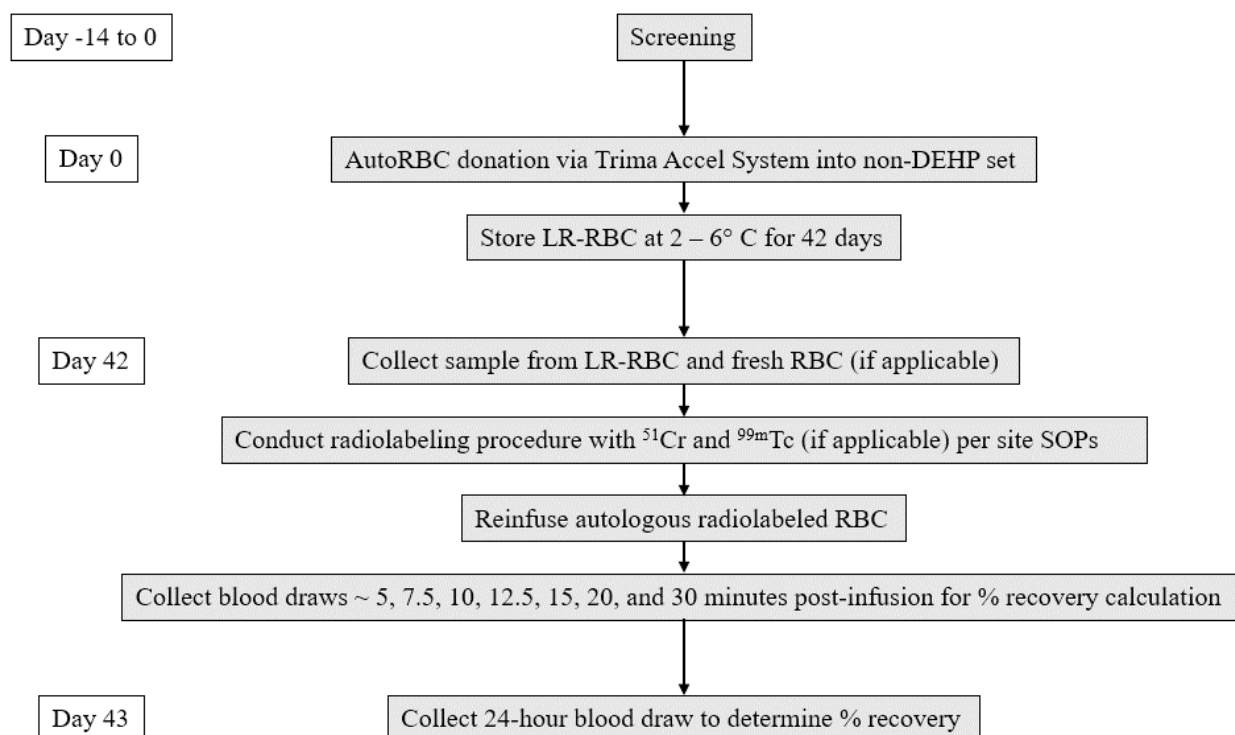
method will only be pursued if  $^{99m}\text{Tc}$  labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event  $^{99m}\text{Tc}$  labeling kits are expected to be unavailable, the dual-label method will not be pursued and only the single-label method will be conducted. For RBC recovery testing, blood samples will be collected at baseline and approximately 5, 7.5, 10, 12.5, 15, 20, 30 minutes, and 24 hours post reinfusion. Participants will be monitored for AEs throughout their participation in the study.

All radiolabeling procedures, including aseptic preparation steps (if applicable), labeling, reinfusion, and sampling, will follow the site's common standardized procedures and SOPs. The procedures for radiolabeling of RBCs to evaluate RBC recovery are based and adapted from methods recommended by International Committee of Standardization in Haematology (ICSH) Recommended Methods for Radioisotope Red-Cell Survival Studies and previously published literature by Moroff and colleagues.<sup>11,16</sup> The method of calculating the blood volume with  $^{99m}\text{Tc}$  is based on the ICSH Recommended Methods for Measurement of Red-Cell And Plasma Volume.<sup>17</sup>

## **10.2 Study Duration**

The total study duration is expected to last 8 months from the time of first participant enrollment. Each study participant will have a total of 4 study visits, including screening, within a time span of up to 58 days. Visit details are described in Section 12.1.

**Figure 10-1: Participant Study Flow**



A healthy adult volunteer is considered an enrolled participant upon giving informed consent for study participation; this timepoint represents the beginning of a participant's involvement in the study. A participant's involvement in the study will conclude upon participant screen failure, participant withdrawal, following completion of the Day 43 visit, or upon follow-up and stabilization/resolution of AEs, as applicable. A healthy adult volunteer can enroll more than once in the study but can only complete the study once with data included in the Evaluable Analysis Set (EAS).

## 11 STUDY POPULATION

### 11.1 Number of Participants and Selection

It is estimated that up to 50 healthy adult volunteers will be enrolled to generate the target of at least 24 and up to 26 evaluable participants. Healthy adult volunteers will be enrolled at two (2) centers. It is anticipated that each site will complete approximately 12 evaluable procedures. Study participants will come from the general population. Eligible healthy adult volunteers exhibiting normal health status and vital signs as determined by standard AABB blood donation criteria will be eligible to enroll. Healthy adult volunteers who cannot commit to completing all study requirements will not be considered for enrollment.

Participants will be recruited in a non-coercive manner. Participants will receive compensation for their involvement in the study according to IRB guidelines and approvals.

## 11.2 Inclusion Criteria

Inclusion criteria for participant selection:

1. Given written informed consent.
2. Age 18 years or older.
3. Normal health status as per AABB criteria for healthy donor.
4. Able to commit to the study schedule.
5. Meets the inclusion criteria defined by site SOPs for automated blood component collection systems or whole blood donation. These criteria are based on AABB standards and FDA regulations.
  - a. Note: Participants who are deferred from volunteer community donations due to certain restrictions may participate in the study, as products are not used for allogeneic transfusion; however, sites may or may not implement this depending on their standard procedures.
6. Participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study.
7. Female participants of childbearing potential must agree to take a pregnancy test prior to the apheresis procedure and prior to reinfusion of radiolabeled LR-RBCs.
8. Participants must agree to report AEs throughout their participation in the study

## 11.3 Exclusion Criteria

Exclusion criteria for participant selection:

1. Currently pregnant or nursing females.
2. Serum ferritin <12 ng/mL
3. Has previously completed this study with data included in the EAS.
4. Participation currently, or within the past 30 days, in another investigational trial that would potentially interfere with the analysis of this investigation (eg, pharmaceutical trial).
5. As determined by the Investigator:
  - a. Has been diagnosed with a blood disorder(s) affecting RBC characteristics (eg, Glucose 6 Phosphate Dehydrogenase Deficiency [G6PD]),
  - b. Reported history of RBC autoantibodies/autoimmune hemolytic anemia, RBC alloantibodies,

- c. Clinically significant acute or chronic disease, or
  - d. Reported history of hypersensitivity to technetium or chromium
  - e. Other unspecified reason that, in the opinion of the Investigator, makes the healthy adult volunteer unsuitable for enrollment.
- 6. Treatment with any medication as specified in site deferral list (based on AABB medication deferral list for apheresis donors).
  - 7. Previously transfused/reinfused with RBCs within the last 120 days.

## **11.4 Recruitment and Pre-Screening**

Recruitment and pre-screening activities to identify appropriate candidates for study inclusion will be conducted prior to obtaining informed consent. These pre-screening measures will be in accordance with IRB/EC guidelines and approvals.

Specific activities may include:

- 1. Conduct pre-screening measures to identify appropriate candidates from blood center donor lists including:
  - a. Review medical records for qualified donors. Review donor demographics and phlebotomy history.
- 2. Introduce the study to potential participants and suggest the possibility of their participation.
- 3. Provide information about the study including:
  - a. Informed consent process, required study schedule, specific study procedures, risks, benefits, and compensation for their time.
- 4. Provide a copy of the informed consent forms (ICFs) to potential participants for review.

## **12 STUDY PROCEDURES**

### **12.1 Informed Consent Process**

Prior to participant involvement in this study, the Investigator must obtain written IRB/EC approval for the CIP and ICF. A copy of the site-specific ICF must be provided to the Sponsor for review and approval prior to submission to the IRB/EC for their subsequent approval. The approved ICF will clearly reflect the IRB/EC approval date. Once approved, the ICF must be provided to the Sponsor prior to implementation in this study. All study participants must provide written informed consent using the Sponsor and IRB/EC approved ICF.

Once the healthy adult volunteer's initial suitability for study participation has been determined per pre-screening measures, 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 healthy adult volunteer, and ask the healthy adult volunteer to participate in the study. The study will be explained to the healthy adult volunteer in lay terms, in the English language, and in a quiet, non-disruptive setting. Potential participants will be given as much time and privacy as necessary to review the ICF before agreeing to participate in the study. Additionally, if the healthy adult volunteer requests, they can take a copy of the ICF with them so that they can discuss potential participation with others outside of the study team. If the healthy adult volunteer agrees to participate, has read the ICF, and has had all of their questions answered, then the ICF must be signed and dated by the healthy adult volunteer and the person completing the consent process. A copy of the signed and dated ICF will be provided to the study participant and the original will be placed in the study file.

Failure to obtain a signed ICF prior to participant involvement in the study constitutes noncompliance with the Declaration of Helsinki, ICH, GCP, 21 CFR 50 and 812, 45 CFR 46, and ISO 14155 and must be reported to the IRB/EC.

## **12.2 Participant Enrollment**

A healthy adult volunteer is considered an enrolled participant upon giving informed consent for study participation; this timepoint represents the beginning of a participant's involvement in the study. Participants will be identified by both a unique Donor ID and unique study identification (USID) number(s). The Donor ID (ie, a unique individual identifier) will remain constant for a healthy adult volunteer throughout the study. Since healthy adult volunteers are allowed to enroll in the study more than once, the Donor ID will be consistent across multiple instances of enrollment for a unique individual. Each instance of enrollment will be associated with both a new ICF and USID number. Each apheresis procedure initiated that is associated with an enrollment will be assigned a product number (eg, Donation Identification Number [DIN]) for that individual donation. Therefore, the Donor IDs, USIDs, and product numbers can be used to differentiate between unique individual healthy adult volunteers, enrolled participants (including re-enrollments), and initiated apheresis procedures, respectively. The Donor ID, USID, and product number will be the participant identifiers and will be captured on the electronic Case Report Form (eCRF) and corresponding source documents.

After informed consent has been obtained, participants will receive a 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.

## **12.3 Schedule of Procedures**

A study schedule of procedural events is provided in Table 12-1.

**Table 12-1: Schedule of Procedures**

Procedure	Days -14 to 0	Day 0			Day 42			Day 43
		Pre-Collection	Collection	Post-Collection	Pre-Reinfusion	Reinfusion	Post-Reinfusion	
Obtain informed consent	X							
Record Donor ID and assign USID number	X							
Collect demographics	X							
Assess eligibility criteria	X				X			
Collect blood sample for serum ferritin testing	X							
Record participant's height and weight		X						
Conduct fingerstick for Hct/Hgb determination		X						
Confirm eligibility criteria		X						
Confirmed negative pregnancy test for women of childbearing potential <sup>a</sup>		X			X			
Label product with product number			X					
Record serial numbers, lot numbers, and expiry dates (as applicable) <sup>b</sup>			X					
Perform venipuncture			X			X <sup>c</sup>		
Collect blood sample for testing (CBC, ABO/Rh, viral screen <sup>d</sup> )			X					
AutoRBC collection with the Trima Accel system with result from fingerstick Hct/Hgb as input			X					
Remove venous access			X					
Record procedure summary information				X				
Conduct in vitro product testing				X	X			

Procedure	Days -14 to 0	Day 0			Day 42			Day 43
		Pre-Collection	Collection	Post-Collection	Pre-Reinfusion	Reinfusion	Post-Reinfusion	
Store LR-RBCs at 2–6°C <sup>c</sup>				X				
Confirmation of aseptic preparation steps for research-grade <sup>51</sup> Cr ( <b>if applicable</b> ) <sup>f</sup>					X			
Confirmation of negative bacterial test on stored unit <sup>e</sup>					X			
Perform general visual assessment of unit for unacceptable characteristics					X			
Collect pre-infusion sample					X <sup>c</sup>			
Collect an aliquot of fresh WB from participant ( <b>if applicable</b> )					X <sup>c</sup>			
Radiolabeling of RBCs <sup>f</sup>					X			
Reinfusion of radiolabeled sample						X <sup>c</sup>		
Collect post reinfusion samples approximately at 5, 7.5, 10, 12.5, 15, 20, 30 minutes <sup>g</sup>							X <sup>c,g</sup>	
Collect 24-hour (±4 hours) sample <sup>g</sup>								X <sup>g</sup>
Complete post-reinfusion worksheet							X	X
Record vital signs (PR, BP, temp)		X			X		X	X
Record relevant medical history and current medications	X	X <sup>h</sup>			X <sup>h</sup>			X <sup>h</sup>
Record AEs, SAEs, and UADEs	X	X <sup>i</sup>	X	X	X <sup>i</sup>	X	X	X <sup>i</sup>
Record DDs <sup>j</sup>	X	X	X	X	X	X	X	X
Record PDs	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; DD = device deficiency; Hct = hematocrit; Hgb = hemoglobin; LR = leukoreduced; PD = protocol deviation; PR = pulse rate; RBC = red blood cell; SAE = serious adverse event; temp = temperature; UADE = unanticipated adverse device effect; USID = Unique Subject Identification; WB = whole blood.

<sup>a</sup> Pregnancy test is done by serum or urine test per site SOP.

<sup>b</sup> Record Trima Accel machine serial number and lot number and expiration date of the non-DEHP disposable set and ACD-A used.

<sup>c</sup> Record arm used. Opposite arms will be used for collections versus infusions.

<sup>d</sup> Part of AABB criteria. If not determined within 14 days prior to planned blood collection date, then as part of standard blood bank donor screening process (all viral screen results have to be negative for infections).

<sup>e</sup> Bacterial testing of the LR-RBC units will be done according to site SOPs during storage.

<sup>f</sup> Prescribed tasks will be done per site SOPs.

<sup>g</sup> Determine hematocrit or hemoglobin of each post-reinfusion sample.

<sup>h</sup> Or changes in health status and/or medications since last study visit (if applicable).

<sup>i</sup> To include changes in health status (including AEs) since last study visit (if applicable).

<sup>j</sup> Any DDs must be recorded as described in Section 17.1.

## **12.4 Enrollment and Initial Eligibility Assessment (Days -14 to 0 Visit)**

Enrollment and initial eligibility assessment can take place up to 14 days prior to the apheresis procedure for LR-RBC collection.

Enrollment and initial eligibility assessment will consist of:

1. Review and sign informed consent prior to initiating any protocol-required procedure that is not considered standard of care. This timepoint represents the beginning of a participant's involvement in the study.
2. Record Donor ID and assign USID number.
3. Collect demographics (date of birth, gender, race, ethnic origin).
4. Record relevant medical history and current medications (relevant to RBC viability and study procedures).
5. Assess participant eligibility.
6. Collect blood sample for serum ferritin testing.
7. Record AEs and protocol deviations (PDs) (if applicable).

## **12.5 Eligibility Confirmation and LR-RBC Collection via the Trima Accel System (Day 0 Visit)**

### **12.5.1 Prior to LR-RBC Collection**

Eligibility confirmation is required to be completed on Day 0, prior to the participant undergoing the LR-RBC collection procedure. Eligibility confirmation will consist of:

1. Record changes in health status (including AEs) and medications since last visit (if applicable)
2. Physical assessment
  - a. Record participant's height, weight, and vital signs (pulse rate, blood pressure, temperature).
3. Conduct the following laboratory tests per the site's SOPs:
  - a. Fingerstick for hematocrit/hemoglobin determination (to be used for eligibility and for input into the Trima Accel system)
4. Review and confirm eligibility.
5. After confirming eligibility, conduct the following additional laboratory tests per the site's SOPs:
  - a. Female participants will have a serum or urine pregnancy test. No test is needed if participant has history of bilateral oophorectomy, hysterectomy, postmenopausal for

1 year, or Principal Investigator (PI) confirmed justification. If a positive test results, the participant will be withdrawn from the study.

6. Record AEs and PDs (if applicable).

### **12.5.2 LR-RBC Collection**

The Trima Accel's AutoRBC collection protocol as well as sample testing will be performed in accordance with the device Operator's Manual in addition to the study site SOPs. The following activities will be performed and required procedure summary information recorded.

1. Assign product number (eg, DIN).
2. Record Trima Accel machine serial number and lot number and expiration date of the non-DEHP disposable set and ACD-A used.
3. Perform venipuncture and record date and time. This timepoint represents the point of participant exposure to the investigational non-DEHP disposable tubing set.
4. Draw blood for CBC, blood type (ABO/Rh), and standard viral screen.
5. Conduct a single AutoRBC collection procedure with AS-3 as the additive solution according to the Trima Accel Operator's Manual and site SOPs, but with the following specification:
  - a. Input into the Trima Accel the participant's hematocrit or hemoglobin from the fingerstick conducted prior to procedure.
6. Remove venous access and record time of removal. This timepoint represents the end of the collection procedure.
7. Record AEs, device deficiencies (DDs), and PDs (if applicable).

### **12.5.3 Following LR-RBC Collection**

7. Record the following procedure summary information:
  - a. Total AC used (mL)
  - b. AC to donor (mL)
  - c. End of run time (hh:mm)
  - d. Duration of run (min)
  - e. Post HCT (%)
  - f. Blood volume processed (mL)
  - g. Solution addition start time (hh:mm)
  - h. Packed RBC residual loss (mL)
  - i. Draw flow rate (mL/min)

- j. Plasma residual loss (mL)
  - k. RBC product: label as leukoreduced? (yes/no)
  - l. If no, reason(s)
  - m. RBC product values:
  - n. Total volume of product (mL)
  - o. Volume of AC in RBC (mL)
  - p. Volume of additive solution (mL)
  - q. Product flags (if applicable)
  - r. Alarms (if applicable)
8. To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs on the day of reinfusion (Day 42), the site must follow their standard labeling and handling process intended to eliminate errors in linking LR-RBC units with the correct study participant.
9. The following assessments will be conducted on the LR-RBC products from the collections.
- a. CBC
  - b. Product volume
  - c. Plasma free hemoglobin (used along with CBC hemoglobin and spun hematocrit to quantify hemolysis)
  - d. Spun hematocrit
10. The LR-RBC product will then be stored for 42 days at 2-6°C away from the transfusion inventory. Temperature monitoring and handling of excursions will be done per site SOPs.
11. Bacterial testing of the LR-RBC units will be done according to site SOPs during storage.
12. Record AEs, DDs, and PDs.

## **12.6 Reinfusion of Radiolabeled RBCs (Day 42 Visit)**

The radiolabeling procedures, including aseptic preparation steps for research-grade  $^{51}\text{Cr}$  (if applicable), during this visit will follow the site's procedures for labeling, reinfusion, sampling and RBC recovery/mass determination.

### **12.6.1 Prior to Reinfusion of Radiolabeled RBCs**

The following must be conducted prior to reinfusion of radiolabeled LR-RBCs:

1. Record changes in health status (including AEs) and medications since last visit (if applicable)
2. To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs for reinfusion, the site must follow their standard labeling and handling process intended to eliminate errors in linking LR-RBC units with the correct study participant.
3. A confirmed negative bacterial testing result (ie, “no growth”) determined during storage is required for a product to be eligible for autologous radiolabeled reinfusion. Products that test positive will not undergo autologous radiolabeled reinfusion and will be destroyed per site SOPs, and participants will be withdrawn from the study.
4. Conduct the following laboratory assessments/tests per the site’s SOPs:
  - a. Perform a general visual inspection of the LR-RBC unit for unacceptable characteristics (eg, discoloration indicative of bacterial growth, particulate, foreign objects, container integrity). Products that test positive will not undergo autologous radiolabeled reinfusion and will be destroyed per site SOPs, and participants will be withdrawn from the study.
  - b. Hemolysis testing of the LR-RBC unit. It will be ensured that the product meets the hemolysis requirement of < 0.8% prior to autologous radiolabeled reinfusion. Products that do not meet < 0.8% hemolysis will not undergo autologous radiolabeled reinfusion and will be destroyed per site SOPs, and participants will be withdrawn from the study.
5. Female participants will have a serum or urine pregnancy test. No test is needed if participant has history of bilateral oophorectomy, hysterectomy, postmenopausal for 1 year, or PI confirmed justification. If a positive test results, the LR-RBC product will not undergo autologous radiolabeled reinfusion and will be destroyed per site SOPs, and the participant will be withdrawn from the study.
6. Collect vital signs (blood pressure, pulse rate and temperature).
7. Record AEs, DDs, and PDs (if applicable)

#### ***12.6.1.1 Collection of Sample for Baseline Assessment and Fresh Sample for Radiolabeling (if Applicable)***

Fresh blood samples are required to be collected prior to reinfusion. A sample will be collected for baseline assessment to be used in the calculation of 24-hour RBC recovery (%). Additionally, if applicable (see Section 10.1), an aliquot of fresh blood may be taken from the participant and processed for RBC isolation. The freshly collected and prepared RBCs will be radiolabeled with <sup>99m</sup>Tc. The arm used for the blood draw(s) and time of blood draw(s) will be recorded.

### **12.6.1.2 Radiolabeling**

To ensure the study participant receives his or her own (autologous) radiolabeled LR-RBCs on the day of reinfusion (Day 42), the site must follow their standard labeling and handling process intended to eliminate errors in linking LR-RBC units with the correct study participant.

Qualified RBCs will be radiolabeled with  $^{51}\text{Cr}$  (LR-RBC) and  $^{99\text{m}}\text{Tc}$ , if applicable, (fresh blood) and then reinfused back into the original participant. Radiolabeling will be done per site procedures and SOPs, including aseptic preparation steps for research-grade  $^{51}\text{Cr}$  use (if applicable; see Section 10.1). If an issue is identified per the aseptic preparation steps, the  $^{51}\text{Cr}$  radiolabeled RBC will not undergo autologous radiolabeled reinfusion and will be destroyed per site SOPs, and the participant will be withdrawn from the study.

### **12.6.2 Reinfusion of Radioabeled RBCs**

Participant identifying information will be confirmed prior to reinfusion to ensure the radiolabeled RBCs are the autologous RBCs for the participant. After confirmation, the radiolabeled RBCs will be reinfused into the participant and the following information will be recorded:

1. Reinfusion start (ie, venipuncture) and end (ie, needle removal) times
2. Arm used for reinfusion (which will be the opposite arm than was used for the whole blood draw)
3. Record AEs and PDs (if applicable)

### **12.6.3 Following Reinfusion of Radiolabeled RBCs**

1. The following timepoints will be targeted for post reinfusion blood draws per the site's SOPs at approximately:
  - a. 5 min
  - b. 7.5 min
  - c. 10 min
  - d. 12.5 min
  - e. 15 min
  - f. 20 min
  - g. 30 min
2. The following information will be recorded on the site's post reinfusion worksheet including, but not limited to:
  - a. Exact time in minutes and seconds each post reinfusion blood sample was collected

- b. Arm used for all post reinfusion blood sample collections (which will be the opposite arm than was used for reinfusion)
  - c. Counts per minute (cpm) for  $^{51}\text{Cr}$  and  $^{99\text{m}}\text{Tc}$  (if applicable) for post reinfusion blood samples in duplicate or as many samples as required per site SOPs, background and empty counting tube cpm, weight of counting tubes and infusate, cpm at time 0
  - d. Hematocrit or hemoglobin of each post reinfusion sample
3. Collect vital signs (pulse rate, blood pressure, temperature).
4. Record AEs and PDs (if applicable)

## **12.7 24-Hour Post Reinfusion Blood Draw (Day 43 Visit)**

The final study visit, the Day 43 visit, will occur 43 days after the LR-RBC collection. The visit will follow site SOPs for determining 24-hour recovery. The following procedures will be conducted:

1. Record changes in health status (including AEs) and medications since last visit (if applicable)
2. A blood sample (6-10 mL) will be drawn  $24 \pm 4$  hours post reinfusion and the following information will be recorded on the site's post-reinfusion worksheet:
  - a. Date and time of the blood draw
  - b. Complete the worksheet(s) for cpm readings from blood sample taken in duplicate or as many samples as required per site SOPs, net cpm, and corrected cpm recorded on the worksheet for cpm readings from blood sample
  - c. Hemoglobin or hematocrit of the blood sample
  - d. 24-hour RBC recovery(ies) (%)
3. Collect vital signs (pulse rate, blood pressure, temperature).
4. Record AEs and PDs (if applicable)

The Day 43 Visit will conclude the participant's involvement in the study.

The primary endpoint, 24-hour RBC recovery, determined using the single-label and dual-label (if possible) methods will be calculated from the data of this visit and that of the Day 42 Visit according to the site's standardized in vivo RBC recovery procedure.

## **12.8 Long-Term Follow-Up**

All AEs will be reported. All AEs related to the study device or procedure(s) will be followed until resolution, except the expected AE of mild hematoma (bruise) and/or mild infiltration. As described in Section 15.5, mild hematomas and/or infiltrations will not be followed to resolution.

## **12.9 Participant Disposition**

### **12.9.1 Participant Screen Failure**

It is expected that some proportion of enrolled participants will not qualify for study inclusion per the screening and eligibility criteria. These participants will be considered screen failures.

### **12.9.2 Participant Withdrawal**

Participants will be considered withdrawals if following screening they are found unsuitable for continued participation or they do not otherwise complete the study procedures, as applicable. All participants are free to withdraw from participation at any time, for any reason, specified and unspecified, and without prejudice. The reason for participant withdrawal will be recorded as described in Section 19.5.

Reasons for the participant's withdrawal may include but are not limited to:

1. Development of an AE that interferes with the participant's continued participation
2. Participant refuses further participation and/or follow-up and withdraws consent
3. Investigator decision
4. Sponsor decision
5. Participant is lost to follow-up
6. Participant death
7. Circumstances beyond one's control (eg, natural disasters, power outages)
8. Issues that do not result in an AE but interfere with the participant's continued participation
9. Other (eg, positive pregnancy test, positive viral screen, positive bacterial test, positive endotoxin sample test, failed visual assessment, failed hemolysis testing, radiolabeling procedure issues including aseptic preparation of research-grade  $^{51}\text{Cr}$  per site SOPs [if applicable], or other specified reason)

### **12.9.3 Participant Study Completion**

A participant's involvement in the study will conclude upon participant screen failure (Section 12.9.1), participant withdrawal (Section 12.9.2), following completion of the Day 43 Visit (Section 12.7), or upon follow-up and stabilization/resolution of AEs (Section 12.8), as applicable. A healthy adult volunteer can enroll more than once in the study but can only complete the study once with data included in the EAS.

## **13      LABORATORY TESTS**

Laboratory tests will be performed at each study site at the timepoints outlined in Table 13-1. Copies of the current laboratory certifications and/or calibrations 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. Some samples may be shipped to designated central laboratory facilities if deemed necessary.

**Table 13-1: In Vitro Tests**

Test Type	Days -14 to 0	Day 0			Days 1 to 41	Day 42			Day 43
		Pre-Collection	Collection	Post-Collection		Pre-Reinfusion		Post-Reinfusion	
	Participant	Participant	Participant	LR-RBC Unit	Participant	LR-RBC Unit	Participant	Participant	
Serum Ferritin	X								
Hct or Hgb <sup>a</sup>		X							
Pregnancy Testing		X				X			
CBC			X	X <sup>b</sup>			X <sup>b</sup>		
ABO/Rh			X						
Viral Screen			X						
Product Volume				X			X		
Plasma free Hgb				X <sup>b</sup>			X <sup>b</sup>		
Spun Hct				X <sup>b</sup>		X	X <sup>b</sup>	X <sup>c</sup>	
Bacterial Screen <sup>d</sup>					X				
Visual assessment							X		
Required test(s) per site's aseptic preparation steps (if applicable) <sup>e</sup>							X <sup>e</sup>		

Abbreviations: CBC = complete blood count; Hct = hematocrit; Hgb = hemoglobin; WBC = white blood cell

<sup>a</sup> Collected via fingerstick.

<sup>b</sup> CBC hemoglobin, spun hematocrit, and plasma free Hgb will be used to quantify hemolysis.

<sup>c</sup> Spun hematocrit will be determined for all post-reinfusion blood samples collected at approximately 5, 7.5, 10, 12.5, 15, 20, and 30 minutes and 24 ± 4 hours.

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<sup>d</sup> Bacterial testing of the LR-RBC units will be done according to site SOPs during storage.

<sup>e</sup> Applicable if research-grade <sup>51</sup>Cr is used. Aseptic preparation steps will be defined by site SOPs and will be completed by Day 42, prior to reinfusion.  
Required testing may include but is not limited to endotoxin testing of the final, radiolabeled product.

## 14 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Current medications and/or treatment administered to treat AEs will be recorded.

## 15 ADVERSE EVENTS/EFFECTS

Blood component availability is assured by blood donation from healthy adult volunteers. While apheresis is considered to be reasonably safe, es may occur. Participant complications can be generally classified as local injuries (mainly caused by needle manipulation) and as systemic reactions triggered by the apheresis procedure or autologous radiolabeled RBC reinfusion. During a clinical investigation, all AEs occurring from time of exposure to the investigational non-DEHP disposable (as further described in Sections 15.4.2 and 18.4.2) until end of study participation will be recorded so that any effect of the investigational component of the Trima Accel system can be analyzed.

### 15.1 Anticipated Risks

#### 15.1.1 Venipuncture Related Risks

The risks associated with venipuncture for blood donation, or intravenous (IV) access include apprehension, pain, discomfort, venospasm, fainting, bruising, infiltration at the venipuncture site, clotting at the IV tubing and/or administrative errors. Occurrence rates of venipuncture AEs are summarized in Table 15-1 below.

**Table 15-1: 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 <sup>18-21</sup>	Apprehension	Presyncope <sup>a</sup>	Faint <sup>b</sup>			
At puncture site <sup>18,20-22</sup>		Hematoma		Nerve irritation	Arterial puncture	
		Pain		Infection		
Distant of puncture site <sup>20,21,23,24</sup>		Discomfort			Skin allergy	Phlebitis
					Neuropathic pain	DVT

Abbreviations: DVT = deep venous thrombosis

<sup>a</sup> Presyncope includes symptoms such as pallor, lightheadedness, dizziness, nausea, diaphoresis.

<sup>b</sup> Faint defined as a brief loss of consciousness, usually less than 30 seconds.

#### 15.1.2 Apheresis Related Risks

Apheresis donation is reasonably safe, and the majority of complications are mild. 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, require medical care and/or recovery time goes beyond 30 minutes.<sup>20-26</sup> Mild citrate reactions are very common with apheresis procedures. While vasovagal reactions do occur, they are substantially lower compared to whole blood donation.<sup>20,22</sup> Some donor reactions that have been 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 15-2 are general apheresis risks and are not specific to the Trima Accel system.

**Table 15-2: 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 <sup>18,20,22,27</sup>	Paresthesia	Nausea	Vomiting	Tetany	Arrhythmia	Cardiac arrest
		Lightheadedness	Cramps	Seizure		
		Metallic taste	Spasms			
			Chills			
Vasovagal Reactions <sup>a;20,22</sup>		Presyncope <sup>b</sup>	Vomiting	Convulsion	LOC with trauma injury	
		Weakness	Hypotension	Seizure		
			Syncope	Bradycardia		
Other Notable Events <sup>18,20,22,28</sup>						Respiratory distress
						Circulatory collapse
						Anaphylactic reaction
						Hemolysis
						Air emboli
						Death

Abbreviations: LOC = loss of consciousness

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

<sup>b</sup>Presyncope includes symptoms such as pallor, lightheadedness, dizziness, nausea, diaphoresis.

### 15.1.3 Trima Accel System Related Risks

The Trima Accel system has been designed to protect donor and patient safety across a wide range of use conditions. The Trima Accel system has specific design features intended to reduce the risk to the operator including:

- A fluid leak containment system surrounding the centrifuge

- The system shall contain a credible projectile from the centrifuge

These inherently safe design elements support the safe use of Trima Accel for donors and operators, regardless of the collection protocol being performed. These elements also reflect the basic level of system safety in the design of protocol specific evaluations.

Despite these measures, AEs still occur. A summary of AEs reported in previous clinical trials conducted with the Trima Accel system is presented in Table 15-3.

**Table 15-3: Summary of Adverse Events in Manufacturer Sponsored Clinical Investigations**

	<b>RBC Collection</b>	<b>Plasma Collection</b>	<b>Platelet Collection</b>	<b>Total</b>
Donors, n	187	70	2,041	2,298
Procedures, n	340	68	2,125	2,533
SAEs, n	0	0	0	0
Device related AEs <sup>a</sup> , n	0	0	18	18
UADEs, n	0	0	0	0
<b>Adverse Event Reported, n (rate<sup>b</sup>)</b>				
Citrate toxicity <sup>c</sup>	22 (0.065)	1 (0.015)	100 (0.047)	123 (0.049)
Injection site extravasation <sup>d</sup>	20 (0.059)	3 (0.074)	66 (0.031)	89 (0.035)
Hematoma	1 (0.003)	5 (0.074)	38 (0.018)	44 (0.017)
Paraesthesia oral	--	--	16 (0.008)	16 (0.006)
Dizziness <sup>e</sup>	5 (0.015)	--	11 (0.005)	16 (0.006)
Paraesthesia	--	--	11 (0.005)	11 (0.004)
Vasovagal	--	--	9 (0.004)	9 (0.004)
Presyncope	1 (0.003)	--	6 (0.003)	7 (0.003)
Nausea	--	--	4 (0.002)	4 (0.002)
Limb discomfort <sup>f</sup>	--	--	4 (0.002)	4 (0.002)
Discomfort	3 (0.009)	--	1 (0.0005)	4 (0.002)
Hypocalcaemia	--	--	3 (0.001)	3 (0.001)
Muscle spasm	--	--	3 (0.001)	3 (0.001)
Viral upper respiratory tract infection	--	--	2 (0.0009)	2 (0.0008)
Musculoskeletal pain	--	--	2 (0.0009)	2 (0.0008)
Post procedure reaction	2 (0.006)	--	--	2 (0.0008)
Numbness (head, chest)	1 (0.003)	--	--	1 (0.0004)
Dysgeusia	--	--	1 (0.0005)	1 (0.0004)
Headache	--	--	1 (0.0005)	1 (0.0004)
Asthenia	--	--	1 (0.0005)	1 (0.0004)

	<b>RBC Collection</b>	<b>Plasma Collection</b>	<b>Platelet Collection</b>	<b>Total</b>
Rash	--	--	1 (0.0005)	1 (0.0004)
Skin irritation	--	--	1 (0.0005)	1 (0.0004)
Oropharyngeal pain	--	--	1 (0.0005)	1 (0.0004)
Contusion	--	--	1 (0.0005)	1 (0.0004)
Peripheral swelling	--	--	1 (0.0005)	1 (0.0004)
Vomiting	--	--	1 (0.0005)	1 (0.0004)
Possible nerve irritations	--	--	1 (0.0005)	1 (0.0004)
Other	--	1 (0.015)	--	1 (0.0004)
<b>Total</b>	<b>55 (0.162)</b>	<b>10 (0.147)</b>	<b>286 (0.135)</b>	<b>351 (0.139)</b>

Abbreviations: AE = adverse event; RBC = red blood cell; SAE = serious adverse event; UADE = unanticipated adverse device effect.

<sup>a</sup> All AEs related to the device were also noted to be related to the procedure.

<sup>b</sup> Rate was calculated as number of AEs reported per 10,000 procedures (ie, [(# of AE × 10,000) / # of procedures] / 10,000).

<sup>c</sup> AEs recorded with the verbatim term of citrate reaction and anticoagulant (AC) reaction were included in the preferred term citrate toxicity.

<sup>d</sup> AEs recorded with the verbatim term of infiltration were included in the preferred term of injection site extravasation.

<sup>e</sup> AEs recorded with the verbatim term of lightheadedness were included in the preferred term dizziness.

<sup>f</sup> AEs recorded with the verbatim term of pain/discomfort at venipuncture site were included in the preferred term limb discomfort.

Trima Accel disposable tubing sets are sterilized with ethylene oxide which may cause anaphylactoid or anaphylactic reactions. Other risks associated with the Trima Accel system may exist but have currently not been identified.

#### 15.1.4 Investigational Non-DEHP Material

There are no known risks identified during preliminary testing conducted by the Sponsor regarding the investigational non-DEHP plasticizer.

#### 15.1.5 Risk of Autologous Radiolabeled Red Blood Cell Reinfusion

Since participants will be reinfused with a small amount of their own radiolabeled RBCs, the risk of a transfusion reaction is minimal; however, in very rare cases, a reaction may occur, causing severe illness or death.

The radiation exposure from <sup>51</sup>Cr and <sup>99m</sup>Tc, if used, received by the participant during this study is limited to reduce participant exposure and is not considered to be harmful.<sup>15</sup> 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 of childbearing potential will have a pregnancy test performed prior to LR-RBC collection and prior to reinfusion as an added

precaution. Any participant with a positive pregnancy test will not be given radiolabeled RBCs and will be withdrawn from the study. Additionally, participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study. The participant can discuss options for birth control with research staff.

Research-grade  $^{51}\text{Cr}$  may be used in this study, dependent upon the availability of GMP  $^{51}\text{Cr}$  at study sites. Since GMP  $^{51}\text{Cr}$  includes a sterilization step which is not included for research-grade  $^{51}\text{Cr}$ , an added sterility risk has been identified for research-grade  $^{51}\text{Cr}$ . To mitigate this risk, study sites will aseptically prepare research-grade  $^{51}\text{Cr}$  (such as by performing syringe filtration and endotoxin testing) according to their SOPs prior to reinfusion of radiolabeled RBCs.

#### **15.1.6 Bacterial Growth**

There is a possibility of bacterial overgrowth if bacteria have inadvertently entered the RBC storage bag or materials used to prepare RBCs for reinfusion. Samples of the stored LR-RBCs will be cultured using standard laboratory methods. The results from this testing will be available prior to the reinfusion of RBCs. Any participant with positive results will not be reinfused with their RBCs.

### **15.2 Risk Mitigation**

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

- 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 protocol/CIP training to include device and procedure training.
- Ensuring that enrolled participants meet all eligibility criteria.
- Following the Operator's Manual for the Trima Accel system and the package insert for the Trima Accel disposable tubing set, site SOPs, and any training provided by the Sponsor for apheresis procedures.
- Following all package inserts associated with RBC collection, site SOPs, site procedures, and/or any training provided by the Sponsor for collection procedures.
- Ensuring universal precautions are used for handling all study blood products in accordance with site SOPs.
- Stopping the procedure if any of the more moderate or severe AEs occur, as defined by site SOPs. The participant can also request that the procedure be stopped at any time.
- Ensuring that all participants meet the AABB and FDA recommendations for blood donation pertaining to the limits on the frequency of donation and the total amount of blood product that can be donated annually.

- Ensuring that all participants meet the minimum hematocrit limits for donation, as defined by AABB. The apheresis devices are programmed such that they only allow collection of products from participants who will meet projected hematocrit standards at the completion of the collection. These limitations are for the safety of blood donors and apply to this protocol.
- Ensuring the privacy and confidentiality of all research participants. 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 eCRFs. To ensure confidentiality, the eCRFs will be de-identified and any products sent to the Sponsor will only have the Donor ID, USID, and product numbers listed as participant identifiers.
- Ensuring participant safety throughout the procedures. Participants will be questioned concerning adverse experiences throughout the procedures. Participants will also be visually monitored for signs of distress during blood donation and reinfusion. Suspected adverse reactions will be treated according to site's SOPs and documented in the eCRFs.
- Participants of childbearing potential (either male or female) must agree to use a medically acceptable method of contraception throughout the study
- Female participants of childbearing potential must agree to take pregnancy tests prior to the apheresis procedure and prior to reinfusion of radiolabeled RBCs
- If research-grade  $^{51}\text{Cr}$  is used in this study, study sites will perform aseptic preparation steps (eg, syringe filtration and endotoxin testing) according to their SOPs to mitigate sterility risks prior to reinfusion of radiolabeled RBCs

### 15.3 Potential Benefits

There is no direct benefit to the participant for engaging in this study except for altruistic reasons as it will assist in gathering important information for safety and performance of the investigational non-DEPH plasticizers in the use of medical device equipment for the collection, processing, and storage of blood components.

### 15.4 Adverse Event/Effect Definitions

#### 15.4.1 Adverse Event

An AE is defined (ISO 14155:2020 Section 3.2) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. This definition includes events related to the investigational medical device or the comparator and events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

The Sponsor may limit the capturing of AEs related to “untoward clinical signs (including abnormal laboratory findings)” to only those with clinical significance, based on the Investigator’s medical judgment.

#### **15.4.2 Procedure-Emergent Adverse Event**

Procedure-emergent AEs (PEAEs) are defined as any AE that occurs upon or after the exposure to the investigational non-DEHP disposable tubing sets, specifically at the point of venipuncture for the LR-RBC collection procedure. As described in Section 15.5, AEs occurring after signing of the ICF and until participant study completion will be recorded and require follow-up; however, only PEAEs will be included in the safety analysis. Study timepoints (eg, point of exposure, start of study procedure, participant study completion) are defined in Sections 12.5 and 12.9.3.

#### **15.4.3 Serious Adverse Event**

An SAE is defined (ISO 14155:2020 Section 3.45) as an AE that leads to any of the following:

1. Death,
2. Serious deterioration in the health of the subject (3.50), users, or other persons as defined by one or more of the following:
  - a. a life-threatening illness or injury, or
  - b. a permanent impairment of a body structure or a body function including chronic diseases, or
  - c. in-patient or prolonged hospitalization, or
  - d. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
3. Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

#### **15.4.4 Adverse Device Effect**

An adverse device effect (ADE) is defined (ISO 14155:2020 Section 3.1) as any AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.

An AE is considered related to the use of the study medical device if the attribution is possibly, probably, or definitely related by the definition listed in Section 15.6.2, whereas the definition of “not related” is considered to be unrelated to the use of the study medical device.

#### **15.4.5 Unanticipated Adverse Device Effect**

A UADE is defined (21 CFR 812.3[s]) as any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Whether an ADE is anticipated or not will be analyzed and determined by the Sponsor upon receiving the report.

### **15.5 Adverse Event Recording**

Safety oversight and reporting during the course of this study will follow ICH GCP guidelines and CFR part 812. The Investigator will monitor the occurrence of AEs for each participant during the course of the study. All AEs reported by the participant, observed by the Investigator, or documented in medical records will be listed on the AE eCRF and assessed by the Investigator for severity and relatedness (Sections 15.6.1 and 15.6.2, respectively) to the procedure, investigational device, and/or participant medical history. Only PEAEs will be included in the safety evaluation. Collection of PEAEs will begin at the time of the first exposure to the investigational non-DEHP disposable set per Section 12.1 and continue throughout the entire study until study completion or upon follow-up and stabilization/resolution of AEs. Starting with the first baseline procedure, any new event/experience that was not present at baseline, or worsening of an event present at baseline, will be considered an AE.

During autologous radiolabeled RBC reinfusion, the participant will be monitored for AEs, including but not limited to fever, chills, dyspnea, urticaria, or pain (infusion site, chest pain or other). AEs will be recorded on the source documentation and eCRFs, and reported to the study Investigator with the following conditions:

- At each visit, AEs since the last visit will be actively assessed via participant interview, and if necessary, via physical exam, and will be documented.
- Ongoing and/or recurrent conditions that were documented on Day 0 will be recorded as AEs only if their severity or frequency increases.

## 15.6 Adverse Event Classification

### 15.6.1 Severity

Severity of AEs will be graded using the following guidelines:

- 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 hospitalization or prolongation of hospitalization indicated.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

### 15.6.2 Relatedness

The Investigator at each site will document his/her opinion of the relatedness of the AE to the investigational non-DEHP disposable sets (ie, if the AE is specific to the non-DEHP disposable sets and would not have occurred if DEHP disposable sets were used on Trima Accel), to the Trima Accel device (Trima Accel equipment and embedded software), to the apheresis procedure (ie, if the AE is attributed to the apheresis LR-RBC procedure regardless of the device used), to the autologous radiolabeled RBC reinfusion procedure, and to the participant's medical history (ie, if the AE is attributed to an underlying condition or disease) 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 or the relationship in time suggests that a causal relationship is impossible.
- **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 reasonably 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 study procedure(s), 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.

## 15.7 Adverse Event Follow-up

All AEs that occur during the study period must be recorded as described in Section 15.5. The Investigator should make a preliminary judgement regarding the relationship of each AE with the investigational non-DEHP disposable sets, Trima Accel device, apheresis procedure, autologous radiolabeled RBC reinfusion procedure, and/or participant's medical history (see Section 15.6.2).

Targeted treatment to all AEs will be provided as needed. All AEs must be followed at a minimum through to study completion and until return to baseline, resolution or until the Investigator deems the event to be chronic, the participant stable, or the participant is lost to follow-up in accordance with the ICH GCP guidelines. The expected AE of mild hematoma (bruise) and/or mild infiltration will not be followed to resolution.

## 15.8 Serious Adverse Event Reporting Requirements

In the interest of participant care and to allow the Sponsor to fulfill all regulatory requirements, any SAE, regardless of causal relationship to study treatment/procedure(s), and all UADEs must be reported to the Sponsor within 24 hours of knowledge of the event at the following email address: [ClinicalAffairs@TerumoBCT.com](mailto:ClinicalAffairs@TerumoBCT.com).

### 15.8.1 Reporting Requirements for SAEs and UADEs

Any SAE or UADE that occurs after participant signing of the ICF and until participant study completion/termination must be reported. Follow-up (regardless of relationship to the study treatment/procedure[s]) must be reported and an SAE/UADE Form must be submitted to the Sponsor within 24 hours of knowledge of the event via email: [ClinicalAffairs@TerumoBCT.com](mailto:ClinicalAffairs@TerumoBCT.com)

The Clinical Research Associate who monitors the email inbox will follow the process defined in SOP 377501-349 (SOP for Medical Safety Review Process) and Work Instruction 377501-350 (WIN for Medical Safety Review Portal).

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 IRB/EC as required by local policy.

## **15.9 Medical Monitoring**

It is the responsibility of the Investigator to oversee the safety of the study at his/her site. The Sponsor/designee will review participant data, SAEs, UADEs, and DD reports to oversee the safety throughout the study.

The Sponsor will monitor the safety of the study on an ongoing basis.

## **16 DATA MONITORING COMMITTEE**

A Data Monitoring Committee (DMC) will not be utilized for this study.

## **17 STUDY DEVICE**

### **17.1 Device Deficiencies**

A DD is defined (ISO 14155:2020 Section 3.19) as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, and includes malfunctions, use errors and inadequate labeling. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. This definition includes DDs related to the study device or the comparator.

All DDs involving the investigational non-DEHP disposable product must be reported, and a Device Deficiency Form must be submitted to the Sponsor within 24 hours of knowledge of the event via email: [ClinicalAffairs@TerumoBCT.com](mailto:ClinicalAffairs@TerumoBCT.com). Capturing of DDs is required from the time of receipt by the site of the investigational non-DEHP disposable product to final disposition (eg, use, destruction, return to the Sponsor).

Every attempt should be made by the site to save or collect the defective investigational disposable, and if appropriate, the packaging, for return to the Sponsor. If a deficiency occurs with the device, a service technician from the Sponsor may evaluate and determine whether service or replacement is necessary. 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. If unable to retain the device, photographs should be taken to assist in the root cause investigation.

If a DD is associated with an AE, refer to Section 15 to assess severity criteria and for reporting requirements in the event of an SAE or UADE.

## **17.2 Device Accountability**

### **17.2.1 Receipt of Study Device**

When devices and disposables are delivered to the study site, 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.

### **17.2.2 Storage**

The Trima Accel device and the investigational disposables will be stored according to the Operator's Manual and IFU. Proper care should be taken to ensure that the study inventory will not be damaged.

### **17.2.3 Accountability**

The Investigator shall maintain adequate records of the receipt and disposition of the investigational devices. This includes all investigational devices received, used, or returned, and includes those that malfunctioned and/or were discarded for any reason. Investigational Product (IP) Accountability Logs supplied by the Sponsor must be completed for all investigational devices. The disposition of all devices must be documented, including those that have been discarded and those returned to the Sponsor. During the course of the study, the IP Accountability Logs will be monitored on a regular basis. When the enrollment phase of the study is complete, the Investigator will return to the Sponsor any unused devices and a copy of the completed IP Accountability Logs. Any use of a device outside of this CIP is strictly forbidden and will constitute immediate grounds for removal of the Investigator and/or institution from the study.

All investigational devices that are not used must be returned to the Sponsor.

These devices may include the following:

- All unused investigational devices when enrollment is complete.
- All expired study devices.
- All investigational devices associated with a device malfunction or failure.
- All opened but unused devices that may be contaminated, have a defect in the sterile barrier prior to use, or have some other potential defect identified.

Devices that were opened in error, prepared incorrectly, or contaminated in the lab (eg, dropped on the floor), do not need to be returned to the Sponsor but must be properly discarded.

## 18 STATISTICAL PLAN

The following section summarizes the statistical methods that will be used in the analysis of the clinical data from this study. Please see the Statistical Analysis Plan (SAP) for full details.

### 18.1 General Considerations for Data Analysis

Inferential statistical tests and confidence intervals will either be one- or two-sided. Exact one-sided confidence intervals will be computed for the probability of success and used to guide the decision regarding the outcome of the study as described in Section 18.3. Continuous demographic parameters, such as the participant's age at the time of enrollment, will be summarized using descriptive statistics (number, mean, median, standard deviation [SD], minimum and maximum value).

In addition to examining the demographic and baseline parameters, adherence to the sampling preparation and reinfusion procedure will also be examined and presented as evidence of compliance. The examination for compliance to the study protocol will be performed on the participant-level. Failing to follow the sample handling and preparation procedures could have a demonstrative effect on the results. Including information from reinfusions where the sample was not properly prepared could impact the results by increasing variability and challenging the normality of the distribution of values used for calculating the average recovery values.

The following general conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, SD, and range.
- All mean and median values will be formatted to one decimal place than the measured value. Standard deviation values will be formatted to two decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percentage of responses will be presented in the form XX (XX %) where the percentage is in parentheses.
- All summary tables will include the analysis population sample size (ie, number of participants enrolled in the study).

### 18.2 Sample Size Rationale

The sample size is based on Table 18-1 and the US FDA's 3-part RBC recovery criteria.<sup>8</sup> The derivation of the sample size was based on the level of precision attained with at least 24 and up to 26 participants relative to the first criterion below.

1. The one-sided 95% lower confidence limit for the probability of success is greater than 70% where success of a unit is defined as the in vivo 24-hour RBC in vivo 24-hour percent recovery > 75%,

2. The sample mean of percent in vivo 24-hour RBC recovery  $\geq 75\%$ , and
3. The sample standard deviation of in vivo 24-hour RBC recovery  $\leq 9\%$ .

Estimates were prepared based on the 1st criterion with at least 24 participants, examining the one-sided confidence interval for the proportion of successes using the Clopper-Pearson exact method for a 95% confidence interval. Results are presented in Table 18-1. If the observed proportion of treatment successes is 21/24 (87.50%) or higher, the one-sided lower 95% binomial confidence interval will exceed 70% (lower confidence limit = 70.77%) and the study will be deemed to have met its primary endpoint. If a participant does not return for reinfusion of radiolabeled RBCs and/or 24-hour recovery sampling, an additional participant must be enrolled to replace the missing sample. This additional participant will then require sample storage for 42 days. To avoid this type of potential delay, up to 2 additional participants will be enrolled so the final sample size will be at least 24 and up to 26 participants. As shown in Table 18-1, 3 or fewer failures will meet the 1<sup>st</sup> FDA criterion with 24 to 26 participants. Comparison of the statistical scenarios between sample sizes of n=24 and n=26 demonstrates that the planned statistical method will not be impacted across this sample size range (ie, 3 failures would result in the one-sided lower 95% binomial confidence interval exceeding 70% [lower confidence limit = 70.77% for n=24 and 72.81% for n=26]).

**Table 18-1: Statistical Scenarios Estimation of LR-RBC Evaluation Sample Size**

Failures	4	3	2	1
<b>Sample Size n=24</b>				
Number of Treatment Successes	20/24	21/24	22/24	23/24
Percentage of Treatment Success	83.33	87.50	91.67	95.83
One-Sided Lower 95% Confidence Limit	65.82	70.77	76.02	81.71
<b>Sample Size n=26</b>				
Number of Treatment Successes	22/26	23/26	24/26	25/26
Percentage of Treatment Success	84.61	88.46	92.31	96.15
One-Sided Lower 95% Confidence Limit	68.18	72.81	77.71	83.02

In order to reach the total target number of evaluable participants, additional participants will be enrolled to replace those for whom the primary endpoints are not evaluable (as determined using study protocol analysis exclusion criteria, Section 18.5). It is anticipated that up to 50 healthy adult volunteers may need to be enrolled to accrue at least 24 and up to 26 evaluable participants for the primary endpoint analysis. All participants, regardless of the availability of their endpoint data, will be included in evaluations of in vitro data (where samples are available) and in evaluations of AEs.

## 18.3 Endpoint Analyses

### 18.3.1 Primary Endpoint Analysis

The analysis of the primary endpoint will be conducted using the EAS, defined in Section 18.4.3.

In vivo RBC viability has been assessed for decades using radiolabeled autologous RBCs to assess the proportion of RBCs remaining in the circulation 24 hours after autologous reinfusion (24-hr RBC recovery). Radiolabeling methods and reporting of recovery have been standardized, allowing comparison of data between studies. Calculation of the proportion of RBCs surviving at 24-hr post reinfusion requires that RBC mass be accurately estimated. This can be performed by extrapolating the early disappearance of cells to the midpoint of the reinfusion.

Calculation of the primary endpoint may be done using both the single-label and dual-label (if possible) method, dependent upon the availability of  $^{99m}\text{Tc}$  labeling kits at both study sites. The dual-label method will only be conducted with data reported if  $^{99m}\text{Tc}$  labeling kits are expected to be available at both sites for all participants in time for reinfusion start (Day 42). In the event  $^{99m}\text{Tc}$  labeling kits are expected to be unavailable, the dual-label method will not be pursued and only the single-label method will be conducted with data reported. If complete data are collected for both the single-label and dual-label methods, analysis will be conducted to evaluate the 24-hour RBC recovery primary endpoint and reported for each method. If there is discordance in the results between the two methods, the dual-label method will take precedence.

RBC recovery 24 hours after reinfusion will be reported using the method recommended by Moroff et al.<sup>11</sup> The  $^{51}\text{Cr}$  value at time = 0 (T zero, T0) is obtained by doing a regression analysis of the values obtained for  $^{51}\text{Cr}$  labeled samples drawn at different timepoints post reinfusion. The T0 is used to calculate the percent recovery at 24 hours. The calculated T0 may be falsely low if the labeled RBCs are removed by the reticulo-endothelial (RE) system in large numbers prior to the first blood being drawn at 5 minutes post injection. This would result in a falsely higher 24-hour recovery. Recovery at 24 hours will be calculated using the following equation:<sup>11</sup>

$$\% \text{ recovery} = (\text{Adjusted RBC cpm at 24 hours} / \text{Adjusted RBC cpm at time 0}) \times 100$$

Radiolabeled samples will be drawn at different timepoints post reinfusion. The counts will be adjusted for background counts and corrected for loss of label (elution) over time.<sup>10</sup>

The primary endpoint of RBC percent recovery at 24 hours post reinfusion will be assessed against the three FDA-specified criteria.<sup>8</sup> To evaluate the criterion related to the percentage of samples with at least a 75% recovery, each observed value will be categorized as a success (recovery  $\geq 75\%$ ) or failure (recovery  $< 75\%$ ). A one-sided 95% confidence interval for the proportion of successes will be calculated using an exact method. The study will meet this

primary endpoint criterion if the lower confidence limit exceeds 70% (equivalent to no more than 3 failures).

Summary statistics and one-sided confidence intervals will be presented to assess the actual RBC recovery values and to evaluate the remaining criteria specified by FDA.

### **18.3.2 Safety Endpoints Analysis**

The tabulation of AEs will be based on the reported incidence by system organ class and preferred term and summarized using counts and percentages.

Adverse events (AEs) will be summarized by the MedDRA Version 27.0 or later. Tables will describe the frequency and percentage of all AEs, SAEs, ADEs, and UADEs reported for participants in the SS. 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.

## **18.4 Analysis Populations**

### **18.4.1 Enrolled Set**

The Enrolled Set (ES) will include all participants enrolled in the study (ie, who have signed informed consent). Efforts will be made to obtain complete in vivo recovery data from all participants.

### **18.4.2 Safety Set**

The Safety Set (SS) will include all participants enrolled (ie, not unique individuals) in the study who meet all eligibility criteria and who are exposed to the investigational non-DEHP disposable (as defined in Section 12.5). The SS will be utilized to assess the safety of the device and the procedure. Participant disposition, safety measures (ie, PEAes, SAEs, ADEs, and UADEs), DDs, and PDs will be summarized for the SS. It is possible for a participant to be included in the SS more than once if they did not have an evaluable recovery endpoint.

### **18.4.3 Evaluable Analysis Set**

The Evaluable Analysis Set (EAS) will consist of the first 24 to 26 evaluable participants in the SS. An evaluable participant is defined as a participant who completes all study visits per the CIP with valid 24-hour recovery endpoint(s) for the single-label and dual-label (if used) methods without having met any of the protocol analysis exclusion criteria described in Section 18.5. Participants will only be included in the EAS once. The EAS is used in the analysis of the primary endpoint. The analysis of the primary endpoint in the EAS will be based on all recorded data. While the criteria outlined in the CIP allow for up to 26 participants, the final analysis will be based on all participants meeting the EAS.

Within the EAS, all attempts will be made to obtain complete recovery data from all participants for the analysis of the primary endpoint.

## **18.5 Protocol Analysis Exclusions**

There may be situations wherein the data will be considered non-evaluable and will not be included in the EAS.

Data will be excluded from the EAS in the following situations:

1. Inability to complete the procedure and/or study due to:
  - a. Participant issues (eg, inadequate access, reaction, needle abort)
  - b. Participant lost to follow-up or withdrawn from study
  - c. Equipment failure or malfunction (eg, filter plugs)
  - d. Compromised product sterility (eg, open weld, bag puncture)
  - e. Unanticipated processing failure
  - f. Decision to stop procedure by participant, Investigator, site staff or operator
2. Incomplete post-collection processing
  - a. Equipment failure or malfunction (eg, unrecoverable system failure)
  - b. Product damaged during storage
3. Protocol deviations (PDs) that affect the primary endpoint due to:
  - a. Failure to follow collection procedures outlined in the device Operator's Manual, IFU (Package Insert), CIP, MOP(s), and site SOPs
4. Product non-reinfusable due to:
  - a. Product not available
  - b. Product does not pass quality check for reinfusion (eg, positive viral screen, visual inspection, hemolysis, bacterial growth, radiolabeling procedure issues to include aseptic preparation of research-grade <sup>51</sup>Cr per site SOPs [if applicable] or failed endotoxin testing [if applicable])

## **18.6 Missing, Unused, and/or Spurious Data**

Details will be provided in the SAP for the handling of missing, unused and/or spurious data.

## **18.7 Interim Analysis**

There will be no interim analysis for the study.

## **19 STUDY MANAGEMENT**

### **19.1 Ethics**

This CIP will be submitted and reviewed by the IRB/EC. The study will not begin until approval for the study is received from the IRB/EC.

### **19.2 Investigator Responsibilities**

#### **19.2.1 Investigator Agreement**

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

#### **19.2.2 Institutional Review Board/Ethics Committee**

The Investigator/study staff is responsible for knowing and adhering to their IRB/EC requirements.

The institution's IRB/EC, or other committee functioning in a similar capacity, will review and approve the CIP, initial and revised ICFs, and CIP amendments. After approval by the IRB/EC, documentation of approval and the approved ICF will be sent to the Sponsor before any healthy adult volunteers are enrolled into this study.

#### **19.2.3 Informed Consent**

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

Prior to any participation in this study, the Investigator must obtain written IRB/EC approval for the CIP and the ICF. The approved ICF will clearly reflect the IRB/EC approval date.

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

#### **19.2.4 Study Files and Record Retention**

The Investigator must retain all study records until notified by the Sponsor that they are no longer needed. The Investigator will also notify the Sponsor in the event he/she relocates, or for any reason desires to dispose of the records.

## **19.3 Sponsor Responsibilities**

### **19.3.1 General Responsibilities**

As per 21 CFR 812, the Sponsor 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.

### **19.3.2 Amendments to the Clinical Investigation Plan**

Any amendment to the CIP, as deemed appropriate by the Sponsor, will be implemented as the study progresses. Amendments will be submitted to the IRB/EC and/or regulatory bodies as needed for written approval before implementation.

## **19.4 Joint Investigator-Sponsor Responsibilities**

### **19.4.1 Access to Information for Monitoring and Auditing**

The Investigator and investigative sites will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspections, providing direct access to source data/documents.

In accordance with ICH GCP guidelines, the Sponsor/auditor must have direct access to the participant's source documentation to verify the data recorded in the eCRF. The Sponsor is responsible for routine review of the eCRFs at regular intervals throughout the study and to verify adherence to the CIP, as well as the completeness, consistency, and accuracy of the data being recorded. The Sponsor/auditor must have access to any participant records needed to verify the entries in the eCRFs. The Investigator agrees to cooperate with the Sponsor/auditor to ensure that any problems detected in the course of these monitoring/auditing visits are resolved. This study will be source document verified by the Sponsor as per the criteria outlined in the Site Management and Monitoring Plan.

### **19.4.2 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.

## **19.5 Collecting and Recording Data**

The Investigator 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 will

also be secured to prevent loss of data. All required data for this study will be recorded from the source documentation onto standardized eCRFs.

### **19.5.1 Source Documents**

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

### **19.5.2 Electronic Case Report Forms**

Case report forms will be in electronic data capture (EDC) or paper format.

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 (CRA) will verify the eCRF 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.

### **19.5.3 Data Queries**

Data Queries may be used by Sponsor staff or designees to attempt to correct or clarify missing, incomplete, or illogical data. Queries must be reviewed by the Investigator or his/her designee.

## **19.6 Clinical Investigation Plan Compliance**

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

### **19.6.1 Protocol Deviations**

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

Protocol deviations (PDs) are prohibited during this study, except as described per ISO 14155:2020 Section 5.6.4(c): "Deviations from the CIP to protect the rights, safety and well-being of human subjects under emergency circumstances may proceed without prior approval of the Sponsor and the [IRB/]EC. Such deviations shall be documented and reported to the Sponsor and the [IRB/]EC as soon as possible."

All deviations must be addressed in study source documents and reported to the Sponsor. Requests for deviations and reports of deviations (if the deviation affects participant's rights, safety and wellbeing, or the scientific integrity of the clinical investigation), will be provided to the IRB/EC per their guidelines. Further details about the handling of PDs will be included in the MOP.

Additionally, for any PD that occurs, the PI will provide a preliminary determination of whether the PD should be classified as major or minor based on the following criteria.

A major PD is defined as one that may affect the scientific soundness of the study or affect the rights, safety, or welfare of study participants, which may include but is not limited to the following study procedures:

1. Informed consent process
2. Participant eligibility assessment
3. Reporting of SAEs
4. Reporting of DDs
5. Failure to follow collection procedures outlined in the device Operator's Manual, IFU, supplement(s), and site SOPs resulting in an incomplete or incorrect collection procedure that affects the primary endpoint.
6. Other (include rationale)

A minor PD is defined as one that does not meet any of the criteria of a major PD.

The preliminary determination provided by the PI will be reviewed and confirmed or refuted by the Sponsor with final determination made by the Sponsor.

## **19.7 Suspension or 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.

## **19.8 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 will

not, in its scientific publications or promotional material, quote from publications by Investigators without full acknowledgment of the source. For multi-site trials, all Investigators agree not to publish individual site data. All trial data will be published as one or more manuscripts based on the accumulated data from all trial sites.

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## 21 INVESTIGATOR SIGNATURE

**Study Title:** In Vivo 24-Hour Recovery Study of Leukoreduced RBCs  
Collected on the Trima Accel System Using Non-DEHP  
Disposable Sets and Stored for 42 Days

**Study Number:** CTS-5091

**Revision:** Revision B

I have read this Clinical Investigation Plan (CIP), including all appendices, and I agree that the CIP contains the necessary details for carrying out the clinical investigation as described. I will conduct this study in compliance with the CIP, Good Clinical Practices, and all applicable regulations. I will make every reasonable effort to complete the study within the time designated.

I will provide copies of the CIP and access to appropriate information furnished by the Sponsor to study personnel under my supervision who are involved in carrying out the study. I will discuss this material with them to ensure they are fully informed about the investigational device and the study.

I understand that under circumstances where an AE is likely to affect the safety of the participants, appropriate urgent safety measures will be taken to protect the participants against any immediate hazard. I understand that if it becomes necessary to protect the best interests of the participants, they may be withdrawn from the clinical investigation, enrollment of the clinical investigation may be suspended, or the clinical investigation may be terminated as described in the CIP. I will give prompt notice to the Sponsor of any such event. The Sponsor may terminate the clinical investigation at any time, with or without cause.

I have read the Confidentiality Statement of this CIP. The contents of this CIP may not be used in any other clinical investigation and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation (eg, submission to an Ethics Committee); however, I will give prompt notice to the Sponsor of any such disclosure.

**Name:**

**Title:** Principal Investigator

**Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_