Statistical Analysis Plan

Sponsor:	Terumo BCT, Inc.
Protocol No:	CTS-5085
Protocol Title:	An In Vivo 24-Hour Recovery Study of Leukoreduced RBCs After Automated Separation of Whole Blood by the Reveos System and Storage for 42 Days
Document Date:	28-Apr-2022
Document Revision	1.0

APPROVAL SIGNATURES

Prosoft Personnel

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DOCUMENT HISTORY

Rev No	Date	Description
1.0	28-APR-2022	Original document

TABLE OF CONTENTS

List of Abbreviations

AABB	American Association of Blood Banks
ADE	adverse device effect
AE	adverse event
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
FDA	United States Food and Drug Administration
IFU	Instructions for Use
LR-RBC	Leukoreduced red blood cell
MedDRA	Medical Dictionary for Regulatory Activities
PEAE	procedure-emergent adverse event
RBC	red blood cell
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	standard deviation
SOP	standard operating procedure
UADE	unanticipated adverse device effect
WB	whole blood
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1 Study Background

Blood transfusions have been widely used in medical practice since the early 20th century and are the most common procedure during hospital stays in the United States.[1,2] Patients may receive a unit of whole blood (WB) or individual blood components to treat any particular condition. Whole blood consists of blood components with cellular elements, colloids, and crystalloids.

Having different relative densities, sedimentation rate, and size, blood components can be separated when centrifugal force is applied. This separation is controlled in part by the specific gravities of these components including, in increasing order, plasma, platelets, leukocytes, and RBCs.[3]

The Reveos® Automated Blood Processing System (Reveos System) can process up to four (4) WB units in one run. It combines balancing, centrifugation, component separation, and sealing into one platform. As an automated blood processor, the Reveos System is beneficial in reducing manual blood processing drawbacks including processing time, and variability in the procedures and end product leading to standardized blood component yield and quality.

The aim of this study is to evaluate the in-vivo 24-hour recovery of autologous RBCs produced with the Reveos System and stored for 42 days, in order to meet the FDA's criteria for manufactured RBCs.

1.2 Study Design

This is a prospective, open label multicenter study to evaluate whether the LR-RBC derived from WB processing with the Reveos System meet FDA criteria for in vivo 24-hour recovery endpoints. Up to 50 healthy adult volunteers will be enrolled to target 24 evaluable recovery endpoints. Volunteers will be enrolled at 2 centers, with approximately 12 at each center.

An evaluable recovery endpoint is defined as having been collected from an enrolled participant that exhibits normal health status and vital signs as determined by standard American Association of Blood Banks (AABB) blood donation criteria and has also given appropriate informed consent, met all eligibility criteria, did not meet any exclusion criteria described in section 2.3 throughout the duration of the study, and did not have a change in health status which would cause them to fail the inclusion/exclusion criteria at the time of infusion.

1.3 Study Objective

The primary objective of this study is to evaluate whether the LR-RBC derived from WB processed with the Reveos System meet FDA criteria for in vivo 24-hour recovery.

1.4 Outcome Measures

1.4.1 Primary Endpoint

The primary endpoint is the 24-hour in vivo RBC recovery. The FDA criteria requires LR-RBC mean 24-hour recovery ≥75% with standard deviation (SD) ≤ 9% and a one-sided lower confidence limit for the population proportion of RBCs in vivo recovery of 70% with a "success" being LR-RBC recovery >75%. This allows for low recoveries (<75%) in 2/20 or 3/24 volunteers.

2. STATISTICAL METHODOLOGY

2.1 General Principles

All analyses will be performed using SAS® software version 9.4. Concomitant medications used to treat AEs will be coded using World Health Organization (WHO) Drug Dictionary Enhanced September 1, 2021 or later. Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later.

Inferential statistical tests will be identified in the post-text tables as being either one or two sided, and the construct of the confidence limits will be defined (e.g. 90% or 95%). A one-sided confidence interval for the proportion of subjects classified as a treatment success will be determined using an exact 95% confidence limit. Asymptotic confidence limits will be presented based on the normal approximation to the binomial distribution for all other presentations.

Continuous parameters will be summarized by n, mean, median, standard deviation (SD), minimum, and maximum. Except for efficacy parameters, 2-sided confidence limits will also be provided for continuous variables. Categorical variables will be summarized by count and percent. The following general conventions will be applied to all data presentations and analyses.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more 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.X %) where the percentage is in the parentheses

- All summary tables will include the analysis population sample size (i.e., number of subjects enrolled in the study)

2.2 Sample Size Determination

Up to 50 volunteers will be enrolled to allow targeted twenty-four (24) evaluable recovery endpoints.

In order to reach the total target number of evaluable subjects, additional subjects will be enrolled to replace subjects for whom the primary endpoints are not evaluable (i.e., those subjects who are lost-to-follow-up or withdrawn; those subjects whose health status has changed prior to their reinfusion, thereby potentially affecting their safety after receiving a reinfusion or potentially confounding study results; or those subjects for whom recovery calculations cannot be made due to missing value). All subjects, 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.

Estimates were prepared based on FDA criteria outlined in Section 1.4.1 with 24 subjects, examining the one-sided lower 95% confidence limit relative to the a priori value of 70%. Results are presented in the table presented below. 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%).

Table 1: Statistical Scenarios 1-5 Estimation of LR-RBC Evaluation Sample Size

Scenario Number	1	2	3	4	5	6
Number of Treatment Successes	17/24	18/24	19/24	20/24	21/24	22/24
Percentage of Treatment Success	70.83	75.00	79.17	83.33	87.50	91.67
One-Sided Lower 95% Confidence Limit	52.13	56.53	61.09	65.82	70.77	76.02

Based on the binomial distribution, 24 evaluable LR-RBC products allow for 0, 1, 2 or 3 failures to establish 95% confidence that at least 70% of the products were successes.

If there are more than 24 evaluable recovery endpoints, then the allowable failure rate will be re-evaluated to meet the FDA primary endpoint described in section 1.4.1. The following table shows the one-sided lower exact 95% confidence limits for the maximum allowable failure rate for different numbers of evaluable subjects.

Table 2: One-Sided Lower Exact 95% Confidence Limits for the Maximum Allowable Failure Rate

Number of Evaluable	Number of Treatment Successes	Number of Treatment Failures	Percentage of Success	Lower Confidence Limit
24	21	3	87.50	70.77
25	22	3	88.00	71.83
26	23	3	88.46	72.81
27	24	3	88.89	73.73
28	24	4	85.71	70.23
29	25	4	86.21	71.16
30	26	4	86.67	72.01

2.3 Study Populations

The Full Analysis Population will include all participants enrolled in the study and who met the eligibility criteria. Efforts will be made to obtain complete recovery data from all participants.

The Safety Analysis Population will include all participants enrolled in the study who met the eligibility criteria and were exposed to Reveos Blood Bag Set. The Safety Analysis Population will be utilized to assess safety of the device and procedure. It is possible for a volunteer to be included in the Safety Analysis Population more than once if they do not have an evaluable

recovery endpoint. If this occurs, it will be noted in the relevant tables in the Clinical Investigation Report (CIR) though they will continue to be analyzed as separate participants.

The Evaluable Analysis Population will include participants who completed all study visits per protocol with a valid 24-hour recovery endpoint. The Evaluable Analysis Population will be used in the analysis of the primary endpoint. While the criteria allow for 20 or 24 participants, analysis will be based on all participants meeting the criteria of the Evaluable Analysis Population.

Data will be excluded from the Evaluable Analysis Population in the following situations:

1. Incomplete or incorrect procedure that affects the primary endpoint due to:
    a. Equipment failure or malfunction (eg, filter plugs)
    b. Unanticipated processing failure
    c. Results of primary endpoint tests are not available
2. Protocol deviations that affect the primary endpoint due to:
    a. Failure to follow collection procedures outlined in the device Operator's Manual, Instructions for Use (IFU) (Package Insert), Manual of Procedure(s), and site SOPs
3. Product non-reinfusable due to:
    a. Product does not pass quality check for reinfusion (residual WBC, LR-RBC mass recovery, visual inspection, hemolysis, bacterial growth)
4. Participant issues
    a. Participant lost to follow-up or withdrawn from study
    b. Other participant issues (eg, inadequate access, reaction, needle abort)

2.4 Participant Accounting and Baseline Characteristics

2.4.1 Participant Disposition

Enrollment and level of participation in the study will be summarized using the Full Analysis Population. The number and percent of participants per population will be summarized for each analysis population. The number and percentage of participants will also be presented for those participants who were screen failures or otherwise discontinued the study early and the reason for discontinuation will be noted.

Participant disposition data will be provided in a listing, which will cover each participant's eligibility for study participation as well as inclusion in or exclusion from each of the analysis populations (including enrollment and completion of study procedures, and/or evaluability).

2.4.2 Participant Characteristics

Demographic and baseline characteristics will be provided in the listings for the Full Analysis Population and will be summarized for the Full Analysis Population, Safety Analysis Population, and Evaluable Analysis Population. Vital signs will be summarized for the Safety Analysis Population and laboratory results will be summarized for the Evaluable Analysis Population.

2.4.3 Clinical Investigation Plan Deviations

A listing of CIP deviations will be provided by the Sponsor.

2.4.4 Device Deficiencies

A listing of Device Deficiencies will be provided by the Sponsor.

2.5 Analyses

2.5.1 Primary Endpoint Analysis

The analysis of the primary endpoint will be conducted using the Evaluable Analysis Population.

The primary endpoint of RBC recovery at 24 hours post-infusion will be used to assess each of the three criteria specified by FDA. To assess the criteria associated with the percent 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 the Clopper-Pearson exact method for a 95% confidence interval. If the one-sided 95% lower confidence limit is greater than 70% the study will have met its primary endpoint. Summary statistics will be presented to assess the actual RBC recovery values to evaluate the remaining criteria specified by FDA.

Primary endpoint will be reported with single label 24-hour endpoint recovery method. Dual label 24-hour recovery endpoint will also be reported as an exploratory method.

2.5.2 Safety Analyses

All adverse events collected will be provided for the Full Analysis Population by MedDRA system organ class and preferred term. Adverse event summaries for the purposes of device safety assessments will be limited to procedure-emergent adverse events (PEAEs), defined as any AE that occurs upon or after the exposure to the Reveos Blood Bag Set. PEAE summaries will be provided for the Safety Analysis Population.

Tables will describe the frequency and percentage of all PEAEs, serious PEAEs, adverse device effects (ADEs), and unanticipated ADEs (UADEs). Additional presentations will summarize PEAEs by maximum reported severity; maximum relatedness to device, procedure, and medical history (related, not related); and those leading to discontinuation/termination. Concomitant medications used to treat PEAEs will also be summarized.

2.5.3 Interim Analyses

No interim analyses are planned.

3. DATA HANDLING

3.1 Baseline and Study Visits

Baseline is defined as the last non-missing scheduled assessment prior to first exposure and all other visits and time points are as recorded in the electronic case report forms except for early termination visits. Study participation will consist of 4 visits: Visit 1 for screening, Visit 2 for the WB collection, Visit 3 for reinfusion, and Visit 4 for assessing 24-hour RBC recovery percentage.

3.2 Missing, Unused, and/or Spurious Data

No imputation for missing, unused, and/or spurious data will be performed.

3.3 Incomplete Adverse Event Dates and/or Times

If an AE has an incomplete start date and/or time, the AE will be assumed to be a PEAE unless the provided dates/times or partial dates/times, if any, are enough to conclude that the AE could not have started on or after the start of the procedure.

3.4 Incomplete Medication Dates

In accordance with the CIP, reporting of concomitant medications is limited to those used to treat AEs. If a reported medication used to treat an AE has an incomplete start or stop date, the medication will be assumed to have been taken upon or after procedure initiation (ie, concomitant medication used to treat a PEAE) unless no PEAE was reported for the subject or the provided dates or partial dates, if any, are enough to conclude that the medication could not have been taken upon or after procedure initiation.

4. CHANGES FROM THE PROTOCOL

	Summary of Changes	
Rationale:	This revision history captures the updates from Version 3.0 / 01 March 2022 of the CIP to Version 1.0 / 28-APR-2022 of the SAP. Significant changes include the following: 1) Changes and clarification were made to the definitions of the analysis populations. 2) The sample size discussion was updated to accommodate over enrollment. 3) The methods discussed for generating confidence intervals is inconsistent in the CIP. A one-sided lower exact 95% confidence limit will be provided for the proportion of treatment successes. Confidence limits presented for continuous demographic and safety parameters will be based on the normal approximation. 4) Dual label method endpoint for 24-hour recovery will also be analyzed which include mean, standard deviation, median, minimum, maximum, proportion of successes, one-side 95% lower confidence limit. Administrative changes, section numbering, typographical error corrections, and minor wording changes for clarity, to make consistent throughout the text, or to make tables consistent with text as a result of these changes have been made and will not be reflected in the table below. These changes did not result in changes to the conduct of the study, so no CIP Amendment was conducted.	
Change	**Language from the CIP**	**Language from the SAP**
Modification	19.3.1 Full Analysis Population The Full Analysis Population will include all participants enrolled in the trial.	Section 2.3 Study Populations The Full Analysis Population will include all participants enrolled in the study and who met the eligibility criteria. Efforts will be made to obtain complete recovery data from all participants.
Modification	19.3.2 Safety Analysis PopulationThe Safety Analysis Population will include all participants enrolled in the trial who are exposed to Reveos Blood Bag Set and experience adverse event that is related to the device or study procedure as determined per ; accordingly, the safety analysis will be limited to PEAEs (defined in Section 16.5). The Safety Analysis Population will be	Section 2.3 Study Populations The Safety Analysis Population will include all participants enrolled in the study who met the eligibility criteria and were exposed to Reveos Blood Bag Set. The Safety Analysis Population will be utilized to assess safety of the device and procedure. It is possible for a volunteer to be included in the Safety Analysis Population more than once if they do not have an evaluable

	utilized to assess safety of the device and procedure.	recovery endpoint. If this occurs, it will be noted in the relevant tables in the Clinical Investigation Report (CIR) though they will continue to be analyzed as separate participants.
Modification	19.3.3 Evaluable Analysis Population The analysis of the primary endpoint in the evaluable population will be based on all recorded data. Subjects are considered evaluable for the primary endpoints if they have: • Met all of the inclusion and none of the exclusion criteria at enrollment, • Were not found, after being enrolled in good faith, to be in fact, non-compliant with one or more of the inclusion/exclusion criteria, • The subject has not had a change in health status which would cause them to fail the inclusion/exclusion criteria at the time of infusion of radiolabeled cells • Have not met any other protocol exclusion criteria as defined in Section 19.4. The Evaluable Analysis Population will be included in the analysis of the primary endpoint. Within the enrolled population, all attempts will be made to obtain complete recovery data from all subjects for the analysis of the primary endpoint.	Section 2.3 Study Populations The Evaluable Analysis Population will include all participants who completed all study visits per protocol with a valid 24-hour recovery endpoint. The Evaluable Analysis Population will be used in the analysis of the primary endpoint. While the criteria allow for 20 or 24 participants, analysis will be based on all participants meeting the criteria of the Evaluable Analysis Population.
Added		Section 2.2 Sample Size Determination Based on the binomial distribution, 24 evaluable LR-RBC products allow for 0, 1, 2 or 3 failures to establish 95% confidence that at least 70% of the products were successes. If there are more than 24 evaluable recovery endpoints, then the allowable failure rate will be

<table>
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Table 2: One-Sided Lower Exact 95% Confidence Limits for the Maximum Allowable Failure Rate
<table>
<tr><th>Number of Evaluable</th><th>Number of Treatment Successes</th><th>Number of Treatment Failures</th><th>Percentage of Success</th><th>Lower Confidence Limit</th></tr>
<tr><td>24</td><td>21</td><td>3</td><td>87.50</td><td>70.77</td></tr>
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<tr><td>30</td><td>26</td><td>4</td><td>86.67</td><td>72.01</td></tr>
</table></td></tr>
<tr><td>Revised</td><td>Section 19 Statistical Plan

Asymptotic confidence limits will be presented based on the normal approximation to the binomial distribution for the proportion of subjects classified as a treatment success. Exact confidence intervals will be used for all other presentations.</td><td>Section 2.1 General Principles

A one-sided confidence interval for the proportion of subjects classified as a treatment success will be determined using an exact 95% confidence limit. Asymptotic confidence limits will be presented based on the normal approximation to the binomial distribution for all other presentations.

Section 2.5.1 Primary Endpoint Analysis

A one-sided confidence interval for the proportion of successes will be determined using the Clopper-Pearson exact method for a 95% confidence interval.</td></tr>
<tr><td>Revised</td><td>Section 19.2.1 Primary Endpoint

Additional exploratory analyses may be performed on estimates of RBC recovery using RBC mass derived from 99mTc radiolabeling.</td><td>Section 2.5.1 Primary Endpoint Analysis

Primary endpoint will be reported with single label 24-hour endpoint recovery method. Dual label 24-hour recovery endpoint will also be reported as an exploratory method.</td></tr>
</table>

5. REFERENCES

[1] Yaddanapudi S, Yaddanapudi L. Indications for blood and blood product transfusion. Indian J Anaesth.

2014;58(5):538-542.
[2] Pfuntner A, Wier LM, Stocks C. Most frequent procedures performed in U.S. hospitals, 2010. HCUP statistical
[3] Basu D, Kulkarni R. Overview of blood components and their preparation. Indian J Anaesth. 2014;58(5):529-537.

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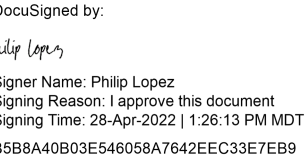
Philip Lopez phillip.lopez@terumobct.com Security Level: Email, Account Authentication (Required)	DocuSigned by:  Signer Name: Philip Lopez Signing Reason: I approve this document Signing Time: 28-Apr-2022 | 1:26:13 PM MDT B5B8A40B03E546058A7642EEC33E7EB9 Signature Adoption: Pre-selected Style Signed by link sent to phillip.lopez@terumobct.com Signature ID: B5B8A40B-03E5-4605-8A76-42EEC33E7EB9 Using IP Address: 208.51.143.189 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 4/28/2022 3:23:30 PM Viewed: 4/28/2022 3:25:43 PM Signed: 4/28/2022 3:26:17 PM
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Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

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