STATISTICAL ANALYSIS PLAN
ADDENDUM

Study Title:	**Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion**
Device:	**Spectra Optia® Apheresis System for WBC Depletion**
Sponsor:	Terumo BCT Europe NV Ikaroslaan 41 1930 Zaventem Belgium
Protocol No.:	CTS-5043
Protocol Version/Date	Version 1.0/18 Feb 2014 Amendment Version 1.0/28 Sep 2016
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Analysis Plan Version/Date:	Addendum 1.0 / 28 Jun 2017

CONFIDENTIAL AND PROPRIETARY INFORMATION

SPONSOR APPROVAL

Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion

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Rationale for Addendum

The Clinical Investigation Plan (CIP) Version 1.0 states that data will only be captured for 2 hours post apheresis procedure. Additional data capture of safety information through 24 hours post transfusion has been requested. This addendum describes the analysis of the additional safety data.

Other notable modifications include:

- Analyses requested post database lock (from the original database) are now documented
- Analyses requested for additional safety discussion to be included in the Clinical Investigation Report

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1. INTRODUCTION

The original analysis was described in the final version of the Statistical Analysis Plan Version 1.0 (11-Nov-2014). Subsequent to the original database lock (17-Apr-2015), additional analyses were requested in an ad hoc manner to support the Clinical Investigation Report (CIR). More recently, additional data were requested to include safety information through 24 hours post procedure rather than 2 hours as originally captured.

This document describes the statistical analysis methods and data presentations to be used in the summary and analysis of the 24 hour safety data from Study CTS-5043. Related documents are the study protocol, case report forms, and original Statistical Analysis Plan (SAP).

All analyses will be conducted using SAS version 9.4 or higher.

1.1 Changes from original SAP Prior to Amendment

Subsequent to the initial database lock, the following tables and listings were requested in an ad hoc manner.

A WBCD procedure summary of specific parameters of interest were summarized. In particular:

- Platelets (pre and post procedure)
- Percent change in platelets
- WBCs (pre procedure)
- Whole blood processed
- Total blood volume processed
- Procedure duration
- Total waste bag volume
- Average whole blood flow

The following additional data listings were also provided:

- Blood products transfused
- Anticoagulants
- Replacement fluids
- Waste bag CBC
- Pre and Post procedure lab counts

Analyses by various subgroups were also requested. The first subgroup was defined as procedures that used an anti-coagulate containing hydroxyethyl starch (HES). It was noted that HES was used for most of the procedures at Site 3, and never at the other sites. Thus, the existing presentations provide information about procedures that used HES.

An additional subgroup analysis was requested to assess the potential impact of the use of blood warmers during the apheresis procedure. Blood warmers were exclusively used at Site 1. The existing presentations provide information about the use of blood warmers.

2. SOURCE DATA

The original data capture system was Open Clinica with data management provided by Terumo BCT. As noted earlier, safety data were only collected through 2 hours post procedure. This data management system was retired shortly after database lock so it was not available for collection of additional safety data.

The additional safety data collected primarily consist of laboratory data and adverse event data through 24 hours post procedure. To further support a safety discussion in the CIR, additional data for blood products transfused will also be collected.

A new EDC system (Merge) was established, which contains much of the original data as well as the additional data. The following CRF pages were implanted into Merge:

- Adverse event
- Apheresis procedure (date, time, duration)
- Blood products transfused
- Laboratory data
- Medical history
- Concomitant medications

All analyses related to these CRF pages will be based solely on the new EDC. Some CRF pages from the original database were not expected to contribute to the additional safety information. Thus, analyses with respect to those CRF pages will continue to use data from Open Clinica. These CRF pages are:

- Demographics
- Vital signs
- Procedure Information (other than date, time, duration)
- Replacement fluids
- Device deficiencies

The additional safety data will only be collected at Sites 1 and 3. While Site 2 is not participating in the additional safety data collection, the corresponding data will be included in the Merge system in order to have a single database with key CRF pages. This avoids the situation where data from the same CRF come from different sources.

3. EFFICACY ANALYSES

No new efficacy analyses will be performed. However, given additional laboratory data are collected, the efficacy analysis data will need to be re-created using the new EDC data. The newly created efficacy analysis data will be compared to the original to identify any potential changes.

During the collection of additional data, it is possible to have multiple records for a particular lab for the same timepoint (pre-procedure, within 2 hours post procedure, 2-24 hours post procedure). Due to database limitations, repeat tests are flagged using the character lab result field. Any value that is a repeat lab draw within the same timepoint will have a “Dx” in the field, where “x” is the repeat draw number. For the analysis of the primary and secondary

endpoint, the record with the largest WBC count will be used if there are multiple draws in the within 2 hours post procedure window. For supportive analysis of HCT and Platelets, the last draw will be used for analysis.

4. SAFETY ANALYSES

The initial set of safety summary tables will remain as the core safety analysis and describe the safety profile from the start of the procedure through 2 hours post procedure. Additional adverse event tables will be added to summarize (cumulative) adverse events from the start of the procedure through 24 hours post procedure. These new summary tables will only include information from Sites 1 and 3 since 24 hour data are not available from Site 2.

The individual tables repeated for the 24 hour safety analysis can be found in the Table of Contents in Appendix 1.

An update was made to the definition of treatment emergent. In this retrospective study, it was originally assumed that all adverse events entered were treatment emergent. Given the updates to the adverse event data collection, subjects with multiple procedures may have events repeated across subsequent procedures. In cases where the onset date is clearly prior to the procedure (ie, onset date < procedure date), these events will not be considered treatment emergent.

While additional safety data will be collected with respect to laboratory data through 24 hours, no summarization is planned. All 24 hour lab data will be listed.

A summary table of patients receiving blood products transfused will be provided by product and timepoint.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Efforts will be made to compare data extracted from the Merge database to the original database. However, some changes are expected. There are new variables such as the use of blood warmers, toxicity grade of some pre-existing conditions, and relationship to underlying disease or treatment for underlying disease (adverse events). Sites were also given the opportunity to correct any information previously recorded in the original database that they find incorrect.

There will be additional updates to the procedure duration. In the original CRF, the procedure duration was captured rather than the procedure end time. In the new EDC, procedure start times, durations, and stop times are available for sites to confirm. The stop times entered in EDC are based on existing data on duration. Due to the potential for sites to modify the stop time (suggesting the original duration was incorrect), this re-analysis will use a derived duration rather than the original. The procedure stop time is critical for data capture as it is used for defining the 24 hour post procedure period.

Given the number of safety tables (including subsets), some summary tables may not have sufficient data. Thus, some tables may be omitted from the final analysis due to insufficient data.

6. REFERENCES

None

7. APPENDICES

Appendix 1. Tables, Listings, and Figures

Appendix 1. Tables, Listings, and Figures

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