CLINICAL DOCUMENT APPROVAL SHEET

Clinical Document Number:	CTS-5043
Document Name:	Retrospective Data Collection Protocol for "Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion"
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Retrospective Data Collection Protocol

Protocol 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
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Version/Date:	V 1.0/18 Feb 2014

Confidentiality Statement

SYNOPSIS

Protocol Title:	Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion (WBCD)
Protocol Number:	CTS-5043
Target Population:	Patients who have undergone WBCD via the Spectra Optia Apheresis System which is likely to include patients with severe leukocytosis in acute leukemia (acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], or in chronic myeloid leukemia [CML]) or to prevent tumor lysis syndrome.
Device Description:	The Spectra Optia System for WBCD is comprised of (1) hardware (the actual apheresis machine) and a removable centrifuge filler (2) a sterile single-use disposable tubing set (the Spectra Optia IDL set) and (3) embedded software V7.2 or higher for WBCD.
Intended Use:	The Spectra Optia Apheresis System, a blood component separator, is intended for use in therapeutic apheresis and cell collections and may be used to perform WBCD.
Objective:	To gather a broader knowledge and information from routine clinical use on the performance and safety of WBCD via the Spectra Optia Apheresis System.
Outcome Measures:	1. Percent decrease in WBC count in patient blood following apheresis procedure. 2. Percent of processed WBC which are collected, i.e. Collection efficiency for WBC achieved by Spectra Optia. 3. Adverse events (AEs) during the WBCD apheresis procedure and for up 2 hours post-procedure.
Inclusion Criteria:	Patients having received a minimum of 1 WBCD procedure via the Spectra Optia Apheresis System.
Protocol Design:	This is a multicenter, retrospective data collection to evaluate the in routine use performance and safety of WBCD performed via the Spectra Optia Apheresis System.
Data Collection Duration:	Routine use data will be collected retrospectively from November 2011 to December 2013.
Statistical Methodology:	Patient demographics and performance parameters will be summarized with the mean, standard deviation, median, and range for continuous variables and with frequencies and percentages for discrete variables.
Protocol Date:	18 Feb 2014

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List of Abbreviations

AC	Anticoagulant
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AE	Adverse Event
ASFA	American Society of Apheresis
BP	Blood Pressure
CBC	Complete blood count
CE	Conformité Européenne
CE1	Collection efficiency 1
CLP	Clinical Project Leader
CML	Chronic myeloid leukemia
CRA	Clinical Research Associate
CRF	Case Report Form
DCF	Data Clarification Forms
EC	Ethical Committee
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
ID	Identification
IDL	Intermediate Density Layer
INR	International normalized ratio
ISO	International Organization for Standardization
L	liter
mL	milliliter
µL	microliter
MNC	Mononuclear Cells
NCCN	National Comprehensive Cancer Network
PLT	Platelet
PLTD	Platelet depletion
PMN	Polymorphonuclear leukocyte
PT	Prothrombin time
RBC	Red blood cell
RBCX	Red blood cell exchange
RR	Respiratory Rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SpO_2	Arterial oxygen saturation via pulse oximeter
WBC	White blood cell
WBCD	White blood cell depletion

1.0 INTRODUCTION

White blood cell depletion (WBCD) by apheresis procedures have been conducted in patients for the past 30 years to rapidly reduce the concentration of white blood cells (WBCs) that have proliferated to levels in the circulation that could cause serious injury. However, these depletion procedures are practiced infrequently and are performed emergently in patients at risk of life-threatening complications due to high WBC counts [1]. For these reasons, prospective, controlled trials have not been done as they are not feasible.

The purpose of this retrospective data collection is to gather routine use data to further support the use of the Spectra Optia Apheresis System for WBCD procedures, which has been in clinical use in Europe since November 2011.

1.1 Clinical Applications for Cellular Depletion by Apheresis

1.1.1 White Blood Cell Depletion in Hyperleukocytosis, Leukostasis or Tumor Lysis Syndrome

Leukemia is a type of cancer of the blood or bone marrow characterized by an abnormal increase of immature white blood cells (WBCs) called "blasts". Hyperleukocytosis is conventionally defined as a peripheral WBC count of > 100 x 10^9/L [2]. Hyperleukocytosis may cause impairment of organ function (e.g., respiratory failure, intracranial bleeding, or acute renal failure) and is often associated with profound metabolic abnormalities [1]. If the WBC count remains significantly elevated, the blood can become thick (hyperviscosity syndrome) resulting in impairment of blood flow in the microcirculation of the central and peripheral nervous system with symptoms such as headache, dizziness, vertigo, nystagmus, hearing loss, visual impairment, somnolence, coma, and seizures. Other possible findings include mucosal hemorrhage, such as epistaxis, gingival and gastric bleeding, and congestive heart failure [1]. Leukostasis, primarily in the lungs and central nervous system, is a frequent complication in acute leukemia and is associated with increased early mortality in the treatment of both adults and children with the disease [1].

WBCD is used to treat severe leukocytosis in acute leukemia (acute myeloid leukemia [AML] and acute lymphoblastic leukemia [ALL]) and in chronic myeloid leukemia [CML]). The age-adjusted incidence rates of acute leukemia per 100,000 men and women per year based on cases diagnosed in 2005-2009 were 3.6 for AML, 1.6 for ALL, and 1.6 for chronic myeloid leukemia [3]. While there are no published figures on the number of cases that require intervention with WBCD, it is a small percentage of these rare disorders. The goal of this procedure in these leukemic cases is to avoid or treat leukostasis and the potentially serious organ damage that can ensue, primarily lung and central nervous system complications.

Chemotherapy of acute leukemia with hyperleukocytosis can result in severe tumor lysis syndrome, which is the release of substances from lysed tumor cells resulting in electrolyte imbalances, coagulopathy, hyperuricemia, and renal damage. WBCD is occasionally used as a potential means to prevent tumor lysis syndrome [4].

1.2 Guidelines for Treatment with Cellular Depletion by Apheresis

Data on the use of apheresis in the treatment of individual diseases and disorders is often limited. For most diseases and disorders, randomized controlled trials of the use of apheresis have not been performed and for many, due to rarity of the condition, it is unlikely that they will ever be performed. The American Society for Apheresis (ASFA) has created and regularly updated guidelines on the use of apheresis in the treatment of disease [2]. These guidelines seek to summarize the literature on the use of apheresis in treating diseases, provide a critical review of this literature, and give practical guidance to apheresis practitioners.

According to the guidelines of the ASFA, leukodepletion as first line treatment (category I of evidence) is recognized only for symptomatic leukostasis in acute forms of leukemia [2]. The clinical role of therapeutic leukodepletion in AML with hyperleukocytosis with symptoms of leukostasis has been established [1, 5-7]. The role of therapeutic leukodepletion in ALL is less clear, but leukocyte counts above 400,000/μL have sometimes been associated with vascular complications, in which case apheresis can be beneficial [8, 9]. Hyperleukocytosis is more common in acute leukemia than in chronic leukemia. It's incidence ranges from 5% to 13% in adult acute myeloid leukemia and 10% to 30% in adult acute lymphoblastic leukemia [1].

In addition to the recommendations listed above by the ASFA, other medical societies have put forth clinical guidance for the use of cellular depletion protocols. The European Society for Medical Oncology has issued the following recommendation for treatment of adult patients with AML [10]: "Patients with excessive leukocytosis at presentation may require emergency leukapheresis before commencing chemotherapy." The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology have stated in their guideline for AML: "Patients with blast counts > 50,000/μL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis and hydroxyurea. Prompt institution of definitive therapy is essential"[11]. In the guideline for the treatment of ALL, the NCCN specify "Although leukapheresis is not typically recommended in the routine management of patients with high WBC counts, it can be considered with caution in cases of leukostasis unresponsive to other interventions"[12].

2.0 DEVICE DESCRIPITION

The Spectra Optia Apheresis System, a blood component separator, is intended for use in therapeutic apheresis and cell collections and may be used to perform WBCD.

The Spectra Optia System is comprised of (1) hardware (the actual apheresis machine) and a removable centrifuge filler (2) a sterile single-use disposable tubing set (the Spectra Optia Intermediate Density Layer [IDL] set) and (3) embedded software for WBCD.

The Spectra Optia System received Conformité Européenne (CE) Mark as a Class IIb Medical Device for Therapeutic Plasma Exchange (TPE) in 2007, for mononuclear cell (MNC) collection in 2008 and for red blood cell exchange (RBCX) in 2009. The WBCD protocol was CE – marked, along with polymorphonuclear leukocytes (PMN) collection and PLTD protocols in October 2011.

The Spectra Optia is replacing the predicate COBE Spectra® Apheresis System, which is reaching the end of its 20+ year commercial life, for these cellular depletion procedures.

3.0 INTENDED USE

The Spectra Optia Apheresis System, a blood component separator, is intended for use in therapeutic apheresis and cell collections and may be used to perform WBCD.

4.0 PUBLISHED CLINICAL EXPERIENCE

Routine use data have been summarized in a published manuscript in Vox Sanguinis December 2012 [13]. Given the paucity of patients in need of leucodepletions and marked differences in clinical presentation as well as blast properties (e.g., size, density), formal clinical trials comparing leucodepletion technologies have never been executed.

This study compared the results of the WBC depletion protocols from the Spectra Optia System with that of the COBE Spectra System. An evaluation was conducted of 8 leukodepletions performed with the Spectra Optia System in AML patients with clinical signs of leukostasis between November 2011 and July 2012, and from15 leukodepletions performed with the COBE Spectra System between June 2010 and October 2011.

Patients did not differ with respect to epidemiological data. However, the pre-apheresis leukocyte count (WBC) was significantly higher in Spectra Optia IDL patients. The indication for leukodepletion was patients with AML with clinical evidence of leukostasis. Tolerability was excellent with both devices. Basic apheresis denominators such as duration, processed volume, inlet pump rate, ACD-A consumption and product volume were similar. A negative correlation between pre-apheresis WBC and collection efficiency was noted. Mean collection efficiency for leukocytes with Spectra Optia IDL (47.3%) was similar to that with COBE Spectra MNC (50.5%). Platelet attrition was similar with both devices, approximately 30%.

5.0 RATIONALE FOR THE CURRENT STUDY

The rationale for this retrospective data collection is to gather multi-center routine use data to further support the use of the Spectra Optia® Apheresis System for WBCD.

6.0 OBJECTIVE

To gather a broader knowledge and information from routine clinical use on the performance and safety of WBCD via the Spectra Optia Apheresis System.

7.0 OUTCOME MEASURES

1. Percent decrease in WBC count in patient blood following apheresis procedure.
2. Percent of processed WBC which are collected i.e. Collection efficiency for WBC achieved by Spectra Optia.

3. Adverse events (AEs) during the WBCD apheresis procedure and for 2 hours post-procedure.

8.0 DATA COLLECTION PLAN

8.1 Protocol Design

This is a multicenter, single-arm, retrospective data collection to evaluate in routine use the performance and safety of WBCD performed via the Spectra Optia Apheresis System.

Routine use data will be collected retrospectively at 2-5 sites with a target of at least 20 WBCD procedures performed via the Spectra Optia Apheresis System between November 2011 and December 2013.

9.0 PATIENT POPULATION

Study staff will review patients' medical records to identify eligible patients for this data collection. Some patients may undergo more than 1 depletions procedure in which case data will be collected for each depletions procedure via the Spectra Optia System.

9.1 Inclusion Criteria

1. Patients having received a minimum of 1 WBCD procedure via the Spectra Optia Apheresis System.

9.2 Numbering

A unique identification (ID) number will be assigned to each patient in order to protect patient confidentiality, which is a combination of the site number (1) and a sequential number per patient. The ID will be consecutively assigned. For example:

- 1st patient at site #1: 101
- 2nd patient at site #1: 102

10.0 DATA COLLECTION

Clinical routine use data will be collected retrospectively, between November 2011 and December 2013, from center experiences with the Spectra Optia System's WBCD protocol and will include the following as available:

10.1 Baseline

1. Inclusion criteria.
2. Medical history.
3. Demographics (age, gender).
4. Height and weight.

10.2 Prior to Each Spectra Optia Apheresis Procedure

1. Diagnosis and current treatment(s).
2. Indication for leukodepletion.
3. Current symptoms.
4. Vital Signs (heart rate (HR), respiratory rate (RR), blood pressure (BP), temperature, and SpO_2.
5. Laboratory results
   a. Complete blood count (CBC) (WBC, PLT count, hematocrit, and RBC count)
   b. Coagulation: prothrombin time (PT), international normalized ratio (INR), if available
   c. Calcium (ionized and total), if available
6. Record blood products transfused within 24 hours prior to the apheresis procedure (s).
7. Equipment / disposables
   a. Record serial number of the Spectra Optia
   b. Record lot number and catalogue number of the Disposables

10.3 During/Post each Spectra Optia Apheresis Procedure

1. Procedure Data from Site Source Documents
   a. Date, time of apheresis
   b. Anticoagulant(s) and volume(s)
   c. Replacement fluid volumes and solution(s) (not administered via Optia)
   d. Apheresis product volume (mL), if available
2. Procedure Data from Spectra Optia Data Logs
   a. Date, time of apheresis
   b. Duration of apheresis procedure
   c. Inlet to AC ratio
   d. AC infusion rate
   e. Average inlet flow (mL/min)
   f. Average collect flow (mL/min)
   g. Waste bag (depletion product) volume (mL)
   h. Whole blood processed (mL)
   i. Fluid balance (%)
   j. Replacement fluid volume(s) and solution(s) (administered via Optia)
3. The following laboratory results from the cellular depletion product (waste bag), if available
   a. CBC (WBC, PLT count, hematocrit, and RBC count)
   b. Collected cellular depletion product (waste bag) volume
4. The following laboratory results, including collection dates/times, from the patient during and for 2 hours following apheresis, if available.
   a. CBC (WBC, PLT count, hematocrit, and RBC count)
   b. Coagulation: PT, INR
   c. Calcium (ionized and total)
5. Record blood products, medications, and fluids (beyond those mentioned above) administered during and for 2 hours following apheresis.
6. Record all adverse events (AEs) and serious adverse events (SAEs) during the apheresis procedure and for 2 hours post procedure.

7. Record device deficiencies or malfunctions.

11.0 ADVERSE EVENTS / EFFECTS

11.1 Anticipated Risks

11.1.1 Risks of Cytoreduction Procedure(s)

General risks associated with apheresis cytoreduction include [1, 4, 13-15]:

- Potential complications of catheter placement including bleeding or thrombosis around the catheter insertion site and/or infection
- Arrhythmia
- Hypo- or hypervolemia
- Citrate induced hypocalcemia, which if untreated could lead to tetany and cardiac arrhythmias
- Air emboli
- Vasovagal reactions
- Allergic or anaphylactic reactions
- Fluid balance and/or shift-related AEs

Fluid balance is of greater concern in WBCD than in other apheresis procedures due to the volume of waste cells removed. The Spectra Optia System can automatically maintain the desired fluid balance by controlling the anticoagulant, collect, and replacement fluid flows.

11.2 Adverse Event Recording / Reporting

11.2.1 Adverse Event/Effect Definition

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

11.3 Reporting of Adverse Events

For this data collection, all AEs from the start of the depletion procedure through 2 hours post-depletion will be captured.

This study will utilize the Common Terminology Criteria for Adverse Events [CTCAE] Scale, Version 4.0 for AE grading http://ctep.cancer.gov/reporting/ctc.html). The CTC includes a grading (severity) scale for each adverse event term. Grades were developed using the following guidelines:

Grade 0 – No adverse event or within normal limits
Grade 1 – Mild

Grade 2 – Moderate
Grade 3 – Severe
Grade 4 – Life threatening or disabling
Grade 5 – Fatal

11.4 Serious Adverse Event

11.4.1 Definitions

SAEs are defined as those AEs which meet any of the following criteria:
1. Results in death
2. Led to serious deterioration in the health of the subject, that either resulted in
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function, or
   - in-patient or prolonged hospitalization, or
   - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

The following are not considered SAEs:

- Planned hospitalization.
- Anticipated day-to-day fluctuations of pre-existing condition(s) present and that do not worsen.

11.5 Reporting of Serious Adverse Events

For this data collection, all SAEs from the start of the depletion procedure through 2 hours post-depletion will be captured.

12.0 STATISTICAL PLAN

Data of WBCD with Spectra Optia System will be collected retrospectively. Data from all procedures will be described over a defined time period without any formal hypothesis testing.

13.0 OUTCOME MEASURES

1. Percent decrease in WBC count in patient blood following apheresis procedure. Calculation: $(WBC_{pre}-WBC_{post}) / WBC_{pre} \times 100\%$.
2. Percent of processed WBC which are removed, i.e. Collection efficiency for WBC achieved by Spectra Optia system. Calculation: (WBC/µL depletion product x depletion product volume) / $(WBC_{pre}+WBC_{post}) / 2$ x total processed blood volume). Note, the literature refers to this calculation as CE1 (%) [13].
3. Adverse events (AEs) during the WBCD apheresis procedure and for 2 hours post-procedure.

13.1 Statistical Analysis – General Considerations

Patient demographics, depletion parameter, and AEs will be summarized with the mean, standard deviation, median, and range for continuous variables and with frequencies and percentages for discrete variables.

Given the retrospective nature of this protocol, there may be missing or incomplete data, thus not all metrics may be available for all patients.

14.0 STUDY MANAGEMENT

14.1 Investigator Agreement

Each investigator will provide the Sponsor a copy of his/her current curriculum vitae and a signed protocol signature page (Appendix 2) and Clinical Study Agreement prior to initiation of the data collection for this protocol.

14.2 Ethics Committee

The Institution's Ethics Committee (EC), or other committee functioning in a similar capacity, will review and approve the retrospective data collection protocol and protocol amendments, if applicable. After approval by the EC, documentation of approval will be sent to Terumo BCT/designee before any data is collected for this study.

14.3 Informed Consent

Obtaining patient consent retrospectively and in this very sick patient population is likely not feasible. Therefore, to protect patient privacy, patient identifier information (e.g., name, initials, birth date, and race) will not be collected in this retrospective data collection study. EC waiver to collect this de-identified data will be obtained.

14.4 Data Handling and Record keeping

All required data for this Protocol will be gathered from subject medical records and recorded in Case Report Forms (CRFs) either via paper or via electronic data capture (EDC). All data must be recorded in English.

Source data is all information, original records of clinical findings observations, or other activities necessary for the reconstruction and evaluation of the data. Source data are contained in source documents. Examples of these original documents and data records include hospital and clinic records, evaluation checklists, scan or laboratory results, etc.

Completed CRFs will be reviewed and signed by the investigator. The Clinical Research Associate (CRA) will verify the CRF/EDC data with the patient's source data; evaluate the data for accuracy, consistency, and completeness.

The Investigator/institution will permit direct access to source data and documents in order for data-related monitoring and, if applicable, audits, and regulatory inspections to be performed.

All data and information collected will be considered confidential. All data used in the analysis and summary will be anonymous, and without reference to specific patients. Files will be kept in a locked area with restricted access to authorized personnel or designee, the Investigator, site research staff, and authorized regulatory authorities.

14.5 Data Clarification Forms

Data Clarification Forms (DCFs), such as Queries may be used by Terumo BCT staff or designee to attempt to correct or clarify missing, incomplete, or illogical data. Queries must be reviewed and signed by an investigator/designee.

14.6 Study Files and Retention of Records

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.

14.7 Quality Control

This retrospective data collection will be conducted in accordance with Good Clinical Practice (GCP), International Organization for Standardization (ISO) 14155:2011, and applicable laws and regulations.

Monitoring will be performed according to current Sponsor's Standard Operating Procedures (SOP) for the monitoring of clinical studies and for clinical quality assurance. During the data collection, the Investigator shall permit the monitor to verify the progress of the data collection as frequently as necessary. The monitor will visit the site at appropriate intervals to review data for accuracy and completeness.

Personal information will be treated as strictly confidential and will not be made publicly available.

This data collection may be reviewed by the Sponsor's Quality Assurance Department or an independent designee and/or by Regulatory Authorities. This implies that auditors/inspectors will have the right to inspect the site at any time during and/or after completion of the data collection and will have access to source documents, including the subject's file and local SOPs at the Research Facility. By participating in this data collection, Investigator agrees to this requirement.

For any data transfer, measures will be taken to protect subject data against disclosure to unauthorized third parties, and subject confidentiality will be maintained at all times.

15.0 TERMINATION OF THE STUDY

For reasonable cause, either the investigator or the sponsor, Terumo BCT, may terminate the investigator's participation in this protocol, provided a written notice is submitted within the time period provided for in the Clinical Study Agreement. In addition, Terumo BCT may terminate the Protocol at any time upon immediate notice for any reason.

16.0 PUBLICATION POLICY

Terumo BCT recognizes the importance of communication of medical Protocol 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 Protocol must be provided to Terumo BCT for timely review in accordance with the terms of the agreement between the investigator, the Institution, and Terumo BCT. Terumo BCT shall not, in its scientific publications or promotional material, quote from publications by investigator without full acknowledgment of the source.

17.0 CONFIDENTIALITY

All information provided to the investigator by Terumo BCT, including nonclinical data, retrospective data collection protocol, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the investigator. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research. This information may be related in confidence to the EC or other committee functioning in a similar capacity. In addition, no reports or information about the Protocol or its progress will be provided to anyone not involved in the Protocol other than to Terumo BCT, or in confidence to the EC or similar committee, except if required by law.

18.0 REFERENCE LIST

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(11) O'Donnell MR, Abboud CN, Altman JK, et al: NCCN Clinical Practice Guidelines: Acute Myeloid Leukemia, Version 2.2013. National Comprehensive Cancer Network; 2013 Jan.

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(14) Hern B: Therapeutic leukapheresis in the patient with leukemia. Journal of Infusion Nursing 1996; 19(5):269-272.

(15) Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH: 2010 Guidelines on the use of therapeutic apheresis in clinical practice--evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher 2010; 25(3):83-177.

19.0 APPENDIX 1 SPONSOR SIGNATURE

Protocol Title: Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion (WBCD)

Protocol Number: CTS-5043

Version/Date: 1.0 /18 Feb 2014

This retrospective data collection protocol was subject to critical review and has been approved by Terumo BCT. The following signature documents this approval.

RAYMOND GOODRICH
Sponsor Signatory Name (Printed)

Signature

FEB 21, 2014
Date

20.0 APPENDIX 2 INVESTIGATOR SIGNATURE

Protocol Title: Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion (WBCD)

Protocol Number: CTS-5043

Version/Date: 1.0 / 18 Feb 2014

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this Protocol as described. I will conduct this Protocol in compliance with the protocol, ICH/GCP, and all applicable regulations. I will make a reasonable effort to complete the Protocol within the time designated.

I will provide involved personnel under my supervision with copies of the protocol and access to all information provided by Terumo BCT or designees. I will discuss this material with them to ensure that they are fully informed about the process.

_____ _____

Principal Investigator Name (Printed) Signature

_____

Date

Retrospective Data Collection Protocol Amendment 1.0

Protocol 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

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Version/Date:	Original version 1.0/18 Feb 2014 Amendment 1.0/28 Sep 2016

Confidentiality Statement

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AMENDMENT 1.0 SUMMARY OF CHANGES

Protocol Title:	Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion
Protocol Number:	CTS-5043
Version/Date:	Original version 1.0/18 Feb 2014 Amendment 1.0/28 Sep 2016
Rationale:	This amendment adds to the protocol original version 1.0, dated 18 February 2014. This amendment was made to address regulatory agency feedback and to extend the duration of safety data collection following the apheresis procedure.
Changes from Original Version 1.0:	Previously during this retrospective study, safety data were collected during the White Blood Cell Depletion (WBCD) apheresis procedure and for up 2 hours post-procedure. With this amendment, safety data (eg, adverse events [AE], blood product transfusions, and clinical laboratory results, as available) will be collected for the 24-hour time period following the WBCD procedure. No other changes are made to study conduct, subject enrollment, or data analysis.

SYNOPSIS

Protocol Title:	Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion
Protocol Number:	CTS-5043
Target Population:	Patients who have undergone WBCD via the Spectra Optia Apheresis System which is likely to include patients with severe leukocytosis in acute leukemia (acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], or in chronic myeloid leukemia [CML]) or to prevent tumor lysis syndrome.
Device Description:	The Spectra Optia System for WBCD is comprised of (1) hardware (the actual apheresis machine) and a removable centrifuge filler (2) a sterile single-use disposable tubing set (the Spectra Optia IDL set) and (3) embedded software V7.2 or higher for WBCD.
Intended Use:	The Spectra Optia Apheresis System, a blood component separator, is intended for use in therapeutic apheresis and cell collections and may be used to perform WBCD.
Objective:	To gather a broader knowledge and information from routine clinical use on the performance and safety of WBCD via the Spectra Optia Apheresis System.
Outcome Measures:	1. Percent decrease in white blood cell (WBC) count in patient blood following apheresis procedure. 2. Percent of processed WBC which are collected, i.e. Collection efficiency for WBC achieved by Spectra Optia. 3. Adverse events during the WBCD apheresis procedure and for up 24 hours post-procedure.
Inclusion Criteria:	Patients having received a minimum of 1 WBCD procedure via the Spectra Optia Apheresis System.
Protocol Design:	This is a multicenter, retrospective data collection to evaluate the in routine use performance and safety of WBCD performed via the Spectra Optia Apheresis System.
Data Collection Duration:	Routine use data will be collected retrospectively from November 2011 to December 2013.
Statistical Methodology:	Patient demographics and performance parameters will be summarized with the mean, standard deviation, median, and range for continuous variables and with frequencies and percentages for discrete variables.

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AE	Adverse Event
CML	Chronic myeloid leukemia
CRF	Case Report Form
EC	Ethics Committee
INR	International Normalized Ratio
PT	Prothrombin time
SAE	Serious Adverse Event
WBC	White blood cell
WBCD	White blood cell depletion

1.0 INTRODUCTION

White blood cell depletion (WBCD) by apheresis procedures have been conducted in patients for the past 30 years to rapidly reduce the concentration of white blood cells (WBCs) that have proliferated to levels in the circulation that could cause serious injury. However, these depletion procedures are practiced infrequently and are performed emergently in patients at risk of life-threatening complications due to high WBC counts. For these reasons, prospective, controlled trials are not feasible and have not been done.

The purpose of this retrospective data collection is to gather routine use data to further support the use of the Spectra Optia Apheresis System for WBCD procedures, which has been in clinical use in Europe since November 2011. Additionally, the objective of this retrospective data collection is to gather a broader knowledge and information from routine clinical use on the performance and safety of WBCD via the Spectra Optia® Apheresis System.

1.1 Rationale for Amendment 1.0

The protocol original version 1.0 (dated 18 Feb 2014) was conducted and the device performance and safety data were summarized, including retrospective safety data for 2 hours following the apheresis procedure. Upon consideration of study results by the US Food and Drug Administration, regulators requested retrospective safety data not just for the 2 hours following the apheresis procedure, but also for the full 24 hours following the apheresis procedure.

This amendment was made to address regulatory agency feedback and to extend the duration of safety data collection following the apheresis procedure. With this amendment, safety data (eg, adverse events [AEs], blood product transfusions, and clinical laboratory results, as available) will be collected for the full 24-hour time period following the WBCD procedure, as requested by the US Food and Drug Administration. Under protocol version 1.0 (dated 18 Feb 2014), safety data were collected for the first 2 hours following apheresis; this amendment will collect safety data in the 22-hour time period from 2 hours postapheresis until 24 hours postapheresis.

This protocol amendment does not make changes to any of the following topics defined in the protocol original version (dated 18 Feb 2014): the study population, the definition of AEs and serious adverse events (SAEs), AE characterizations (eg, severity, action taken, relationship, outcome, SAE criteria), data analysis, or study management procedures.

This amendment does collect the following new information:

- Collection of AEs in the 22-hour time period from 2 hours postapheresis until 24 hours postapheresis
- Additional characterization of AE relationship to underlying disease or treatment for underlying disease (eg, chemotherapy)
- Reason for transfusion of blood products, if transfusions were administered in the 24-hour period postapheresis
- Postapheresis clinical laboratory results, as available

2.0 DATA COLLECTION

2.1 Ethics Committee

The Institution's Ethics Committee (EC), or other committee functioning in a similar capacity, will review and approve the retrospective data collection protocol amendment. After approval by the EC, documentation of approval will be sent to Terumo BCT before any data are collected for this study.

2.2 Informed Consent

Obtaining patient consent retrospectively and in this very sick patient population is not feasible. Therefore, to protect patient privacy, patient identifier information (e.g., name, initials, birth date, and race) will not be collected in this retrospective data collection study. An EC waiver to collect these de-identified data will be obtained.

2.3 Data Handling and Record keeping

All required data for this protocol will be gathered from subject medical records and recorded in unique Case Report Forms (CRFs) designed to specifically capture safety data for the 24-hour time period following the WBCD procedure. All data must be recorded in English.

2.4 Data for Collection

Clinical routine-use data have been collected retrospectively, between November 2011 and December 2013, from centers experienced with the Spectra Optia System's WBCD procedure.

With this amendment, additional safety data will be collected for the 22-hour time period from 2 hours postapheresis until 24 hours postapheresis.

Specifically, the following new data will be collected:

1. Adverse event data for AEs that occurred during the 24-hour time period following the WBCD procedure (eg, date/time of start and end, ongoing, severity, action taken relationship to device/apheresis procedure/underlying disease/treatment for underlying disease, outcome, SAE, unexpected adverse device effect).

   Note: The Investigator at each site will document his/her opinion of the relationship of the event to the procedures or underlying disease. The criteria below, in addition to good clinical judgment, should be used in determining relatedness.

   Not Related: The event is clearly related to factors other than the study device and/or procedure(s), such as the subject's clinical state.

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

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

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

2. Blood products transfused during the 24-hour time period following the WBCD procedure (eg, reason [AE or underlying disease], blood product, number of units, date/time of start and end).

3. Postapheresis clinical laboratory results, as available (eg, prothrombin time [PT], international normalized ratio [INR], WBC count, platelet count, hematocrit, red blood cell count).

APPENDIX 1 INVESTIGATOR SIGNATURE

Protocol Title:	Multicenter, Retrospective Data Collection of Routine Clinical Use with the Spectra Optia® Apheresis System for White Blood Cell Depletion (WBCD)
Protocol Number:	CTS-5043
Version/Date:	Original version 1.0/18 Feb 2014 Amendment 1.0/28 Sep 2016

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

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

Principal Investigator Name (Printed)	Signature

Date