IMPACT CLINICAL TRIAL

IMproving **P**lasm**A** **C**ollec**T**ion

Prospective, randomized, controlled, multicenter clinical trial to demonstrate the safety and effectiveness of the NexSys® PCS Plasma Collection System with the Percent Plasma Nomogram (PPN) Feature

INVESTIGATIONAL PLAN

IDE #: 19185

Clinicaltrials.gov ID: NCT04320823

Protocol #: TP-CLN-100467

Revision: AB

Clinical Trial Sponsor:

Haemonetics Corporation

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CLINICAL INVESTIGATIONAL PLAN (CIP) APPROVAL

Clinical trial Title: IMPACT Clinical Trial

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulation
CIP	Clinical Investigational Plan
CRO	Clinical Research Organization
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DAE	Donor Adverse Event
DHQ	Donor Health Questionnaire
DMC	Data Monitoring Committee
DMS	Donor Management System
eCRF	electronic Case Report Form
ECV	Extracorporeal Volume
EDC	Electronic Data Capture
FDF	Financial Disclosure Form
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IQPP	International Quality Plasma Program (Plasma Protein Therapeutics Association)
IRB	Institutional Review Board
ITT	Intent to Treat
IVD	Intravascular Deficit
LOC	Loss of Consciousness
lbs	Pound
MDR	Medical Device Reporting
MIR	Medical Incidence Report
MITT	Modified ITT (Intent to Treat)
mL	Milliliter
OPI	Octapharma Plasma Inc.
PPN	Percent Plasma Nomogram
PPTA	Plasma Protein Therapeutics Association
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operation Procedure
TBV	Total Blood Volume
UCN	Unit Collection Number

PROTOCOL SYNOPSIS

Name of Sponsor Company: Haemonetics Corporation	**Name of Investigational Product:** NexSys® Plasma Collection System with the Percent Plasma Nomogram (PPN) Feature
Title of Protocol: Prospective, randomized, controlled, multicenter clinical trial to demonstrate the safety and effectiveness of the NexSys® PCS Plasma Collection System with the Percent Plasma Nomogram (PPN) Feature	
Protocol Number: TP-CLN-100467	**Short Title:** IMPACT Clinical Trial

Clinical Trial Design:

This is a multicenter, randomized, prospective IDE clinical trial to evaluate the safety and effectiveness of the NexSys® PCS with the Percent Plasma Nomogram (PPN) feature during plasmapheresis. The clinical trial is designed to collect approximately 24,000 plasmapheresis procedures from around 5,000 - 6,000 donors. Donors will be randomized 1:1 to the experimental group undergoing plasmapheresis using NexSys® PCS with the PPN feature or the control group undergoing plasmapheresis using NexSys® PCS with YES® technology. As repeat donations by the same donor are expected, the donor will remain in the same study group during the entire course of the clinical trial. In an effort to prevent bias, the clinical trial will be blinded to select members of the sponsor study team in accordance with the blinding plan, and subjects will not be made actively aware to which group they have been randomized – however, subjects may be able to determine to which group they have been assigned. The sample size of the clinical trial may be reevaluated based on the number of donations and observed significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions.

Clinical Trial Duration:

Enrollment will be approximately 4 to 6 months. Prior to enrollment, all subjects will be required to provide written consent. Once enrolled, all subjects will remain in the clinical trial for their first and any subsequent donations per institutional guidelines until enrollment is completed or until they withdraw consent. For each subsequent donation, subjects will be required to meet all eligibility criteria (see eligibility criteria below). Subjects will be followed up according to established site procedures. The plasmapheresis procedure will follow standard of care practices at the centers, with the exception that the target plasma collection volume is determined per the PPN feature in the experimental group.

Monitoring of adverse events (AEs) will be conducted throughout the clinical trial. All AEs will be captured and reported per established site procedures in compliance with IQPP standards and with CFR. Reporting of AEs in study subjects will occur after the subject's donation has ended per established site procedures. The safety of the clinical trial will be monitored by a Data Monitoring Committee (DMC) which will meet regularly and will be operating according to the DMC charter.

Monitoring reports will be reviewed approved by a designated individual working for the sponsor who is not part of the study team in order to ensure intact blinding of the sponsor's study team.

The original assignment of the subject to the experimental group or to the control group, respectively, will be carried over. There will be no re-randomization for repeat donors.

Device Description and Intended Use:
The NexSys® PCS is intended to be used for plasma collection using automated apheresis technology. A modified version of NexSys® PCS embedded software is to be installed on current FDA-cleared NexSys® PCS device hardware, enabling the use of the PPN feature. The device communicates with NexLynk® DMS (the existing site Donor Management System). Donor biometric information is directly sent from the DMS to the devices in order to calculate the collection volume target for that donor. The PPN feature uses donor weight, height (Body Mass Index, BMI) and hematocrit to calculate the collection target. This allows a plasma collection volume target tailored to the individual donor. A larger plasma pooling bottle will be used in order to accommodate greater total collection volumes anticipated from some donors.

Clinical Trial Objective:
The objective of the IMPACT clinical trial is to evaluate the safety of plasmapheresis performed on the NexSys® PCS device with PPN feature. The clinical trial is designed to assess if the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events per donation in donors undergoing plasmapheresis in the experimental group is NOT inferior to that seen in donors in the control group. This incidence rate is defined as at least one (1) significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, per plasmapheresis procedure. For the purpose of this clinical trial, a hypotensive (vasovagal/hypovolemia) adverse event will be determined to be *significant* if it fulfills one or more of the criteria defined in rows 1.2 (Hypotensive: Prefaint, No LOC (moderate)) or 1.3 (Hypotensive: LOC (brief)) or 1.4 (Hypotensive: LOC (prolonged)) or 1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury) of the IQPP definition, as applied in the plasma center adverse event reporting system. See Appendix 16.1 IQPP Standard for Recording Donor Adverse Events. The signs/symptoms/findings for categories 1.1. to 1.6 that are listed in the far right column of the table may be defined slightly differently per center policy.

Secondary Objectives:

- To assess if the incidence rate of severe hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, per donation in donors undergoing plasmapheresis in the experimental group is NOT inferior to that seen in donors in the control group
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, relative to the actual plasma volume of plasma collected, comparing procedures in the experimental group and control group
- To study the time from the start of plasmapheresis “Begin Draw” to the first significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, comparing procedures in the experimental group and the control group
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors with a bodyweight of less than or equal to 130 lbs and those greater than 130 lbs

- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors with a body mass index (BMI) of less than or equal to 30 and of those greater than 30
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors defined by their respective status as a first-time donor or repeat-donor
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors defined by their gender
- To evaluate the total plasma volume collected per procedure in the experimental group and in the control group

Eligibility Criteria

Inclusion Criteria:
Subjects must meet all eligibility criteria in order to be enrolled in the clinical trial. Donors must be qualified to donate plasma per individual site's screening procedures which are in compliance with IQPP standards (see Appendix 16.2 IQPP Qualified Donor Standard). If donors do not meet inclusion criteria at subsequent donations but have already been enrolled in the clinical trial, they are eligible to remain in the clinical trial and to donate plasma in the future once they again meet eligibility criteria, except if they fulfill any of the exclusion criteria below.
Other site-specific regulations and procedures may apply.

Exclusion Criteria:
All subjects meeting any of the exclusion criteria listed below will be permanently excluded from the clinical trial. If any of the exclusion criteria are met, this will be documented in the Subject Exclusion Log.

- Subject not able or willing to give consent to participate in the clinical trial.
- Subject donated plasma outside of the present clinical trial after enrolling in this clinical trial.
- Subjects are withdrawn from the clinical trial due to safety concerns by the qualified healthcare providers.
- In addition, all donors for whom a BMI for use in the PPN feature cannot be reliably calculated will be excluded.

Number of Clinical Trial Centers:

The IMPACT clinical trial will recruit subjects at 3 centers in the USA. The sponsor has chosen three geographically distributed plasma collection centers that have a typical donor distribution, as determined by analysis of PPTA data and a >100,000 donations database from the clinical partner, Octapharma Plasma Inc.

Up to three additional centers will be selected as alternates or to expand the number of trial sites, aiming to maintain the geographical and donor distribution.

Primary Endpoint:

The primary endpoint of the clinical trial is the incidence rate of at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions. For the purpose of this clinical trial, a hypotensive (vasovagal/hypovolemia) adverse event will be determined to be *significant* if it fulfills one or more of the criteria defined in rows 1.2 (Hypotensive: Prefaint, No LOC (moderate)) or 1.3 (Hypotensive: LOC (brief)) or 1.4 (Hypotensive: LOC (prolonged)) or 1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury) of the IQPP definition, as applied in the plasma center adverse event reporting system. See Appendix 16.1 IQPP Standard for Recording Donor Adverse Events. The signs/symptoms/findings for categories 1.1. to 1.6 that are listed in the far right column of the IQPP table may be defined slightly differently per center policy.

Secondary Endpoints:

- Incidence rate of severe hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, per donation in donors undergoing plasmapheresis
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, relative to the actual plasma volume collected
- Time from start of plasmapheresis “Begin Draw” to the first significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors with a body mass of less than or equal to 130 lbs and those greater than 130 lbs
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors with a body mass index (BMI) of less than or equal to 30 and of those greater than 30
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors defined by their respective status as a first-time donor or repeat donor
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors defined by their gender
- Total plasma volume collected per procedure

Exploratory Endpoints:

An example of an exploratory endpoint is the number of apheresis procedures per donor.

- The incidence rate of at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, occurring during the plasmapheresis procedure at first donation. For this endpoint, every subject will only contribute their first donation to the analysis
- The proportion of donors who experience at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, occurring during any of his or her plasmapheresis procedures

Statistical Analysis:

The details of the analysis will be outlined in the SAP. The primary analysis will assess and compare the significant hypotensive (vasovagal/hypovolemia) adverse event rates according to the plasma center adverse event reporting system, based on the IQPP definitions, across the two clinical trial groups. The analysis will be conducted using repeat measure mixed-effect logistic regression models. The primary endpoint, i.e., the incidence rate of at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, will be compared across the two groups in the framework of non-inferiority hypothesis testing. The secondary analysis – assessing time to adverse events – will be using the survival analysis modeling framework and hazard estimation. Other secondary analyses, assessing adverse event rates according to the plasma center adverse event reporting system, based on the IQPP definitions, per plasma volume or total number of collection cycles will be based on repeat-measure models and summary statistics. Subgroup analysis will be based on descriptive statistical summaries. Descriptive statistical summaries and advanced data visualization techniques will be used for data presentation. The analysis will be carried out using SAS version 9.4.

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1. Introduction and Background

1.1 Executive Summary

This is a multicenter, randomized, prospective IDE clinical trial to evaluate the safety and effectiveness of the NexSys® Plasma Collection System utilizing a Percent Plasma Nomogram (PPN) feature for plasmapheresis. The clinical trial is designed to collect approximately 24,000 plasmapheresis procedures from around 5,000 - 6,000 donors. Donors will be randomized 1:1 to the experimental group undergoing plasmapheresis using NexSys® PCS with the PPN feature vs. the control group undergoing plasmapheresis NexSys® PCS with YES® technology. As repeat donations by the same donor are expected, the donor will remain in the same study group during the entire course of the clinical trial. In an effort to prevent bias, the clinical trial will be blinded to select members of the sponsor study team in accordance with the blinding plan, and subjects will not be actively made aware to which group they have been randomized – however, subjects may be able to determine to which group they have been assigned. The sample size of the clinical trial can be reevaluated based on the number of donations and observed significant hypotensive (vasovagal/hypovolemia) events according to the plasma center adverse event reporting system, based on the IQPP definitions.

In the United States, the demand for plasma has increased four-fold over the past twelve years and is expected to continue rising[1]. The US Source Plasma Collectors will struggle to meet this demand[2]. The FDA plasma collection nomogram published by the Center for Biologics Evaluation and Research (CBER) in 1992 has been used by source plasma collectors for the past 25 years[3]. Field experience has demonstrated that the 1992 FDA nomogram is safe for donors, with a rate of significant hypotensive (vasovagal/hypovolemia) adverse events of approximately 0.15% according to the plasma center adverse event reporting system, based on the IQPP definitions[4].

The rates of the corresponding serious adverse events as defined by IQPP were even lower. The 1992 FDA nomogram utilizes donor weight as the only variable, leading to discrepancies in the percent of total donor plasma volume collected, ranging from approximately 15% to 42% with an average of approximately 777 mL of plasma drawn per procedure in a retrospective analysis performed by Haemonetics on a data set that was obtained in collaboration with Octapharma Plasma. It consisted of 111,916 donations from all 86 Octapharma Plasma collection centers, including the three selected for the clinical trial. The PPN feature will expand the use of the donor's physical characteristics to tailor the plasma collection target to each individual. The PPN feature will employ a combination of weight, height, and hematocrit to calculate the donor's total plasma volume. With the PPN feature, this variability will be reduced by utilizing Body Mass Index (BMI) and hematocrit to set the collection volume at 28.5% of the donor's total plasma volume with a cap of 1,000 mL to account for exceptionally high total plasma volume donors. The 28.5% threshold was chosen specifically to mitigate the risk of potential vasovagal reactions associated with extracorporeal volume), and is approximately at the mid-point of the range of percentages observed (15%-42%) with the existing nomogram. A benefit of the PPN feature is that, overall, the nomogram would allow for an increase in plasma collection across the donor pool compared with the current FDA nomogram with YES® technology.

1.2 The NexSys® PCS System

The NexSys® PCS (PCS 300 Plasma Collection System) is intended to be used for plasma collection using automated apheresis technology.

The plasma collected by the NexSys® PCS may be designated for use in therapeutic transfusion or be conserved, used as source plasma, and subsequently fractionated into plasma-derived products.

The NexSys® PCS system consists of distinctive parts which collectively function as a system:

- *NexSys® PCS device*: the electro-mechanical device and graphical user interface (GUI) screen
- *Protocol*: the embedded software that controls the process used to gather blood components from a donor
- *Disposable set*: the single-use collection material (supplied separately)
- *Solutions*: anticoagulant and saline solutions (supplied separately) for collecting and processing blood components

During the collection procedure, the device draws whole blood from the donor during the Draw cycle. The device mixes the appropriate amount of anticoagulant solution with the whole blood in the disposable tubing. The device then draws the anticoagulated blood into a disposable collection bowl where it is separated by centrifugal force into its various components. When the bowl reaches its collection capacity, the plasma component exits the bowl and is directed into a plasma collection bottle for conservation. When the collection of the plasma component in the bowl is complete, the non-selected blood components are returned to the donor during the Return cycle. The Draw and Return cycles repeat until the device collects the targeted amount of plasma programmed for the procedure.

Below is a diagram of the device with each of the external hardware components labeled.

1. Anticoagulant (AC) weigher
2. Anticoagulant (AC) pole
3. Anticoagulant (AC) pump
4. Anticoagulant air detector (ACAD)
5. Blood pump
6. Donor displays (x2)
7. Tubing guides (x2)
8. Blood line air detector (BLAD)
9. Donor valve
10. Donor pressure monitor (DPM)
11. Donor line air detector 1 (DLAD1)
12. Donor line air detector 2 (DLAD2)
13. Blood filter brackets
14. Barcode reader
15. Weigher arm
16. Plasma valve
17. Line sensor
18. Saline valve
19. Saline pole
20. Centrifuge
21. Touchscreen
22. Status beacon

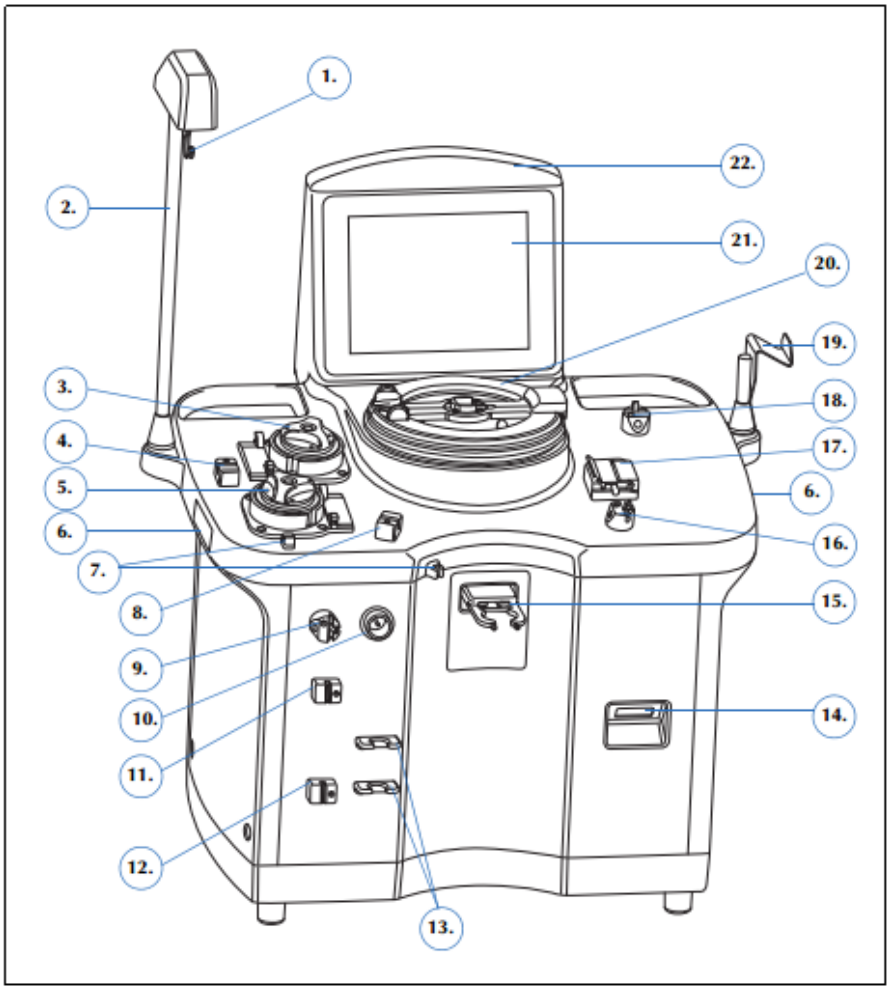

Figure 1 – Diagram of NexSys® PCS

The NexSys® PCS device was originally cleared under BK170045 in July 2017. A modification to the embedded software, introducing YES® technology as a means to collect additional plasma, was cleared under BK180185 in March 2018.

In this clinical trial a further modification to the embedded software of the NexSys® PCS, enabling plasma collection according to a modified nomogram (the Percent Plasma Nomogram, PPN), will be used. The volume of the plasma collection bottle (cleared under BK020001) will also be modified to allow for additional capacity. Today in the US, most source plasma collectors use 500 mL saline as a replacement fluid. In this clinical trial, a saline replacement will also be used as the primary form of re-hydration (if, under exceptional circumstances, saline cannot be administered, Octapharma Plasma (OPI) center policies have to be followed).

As the Percent Plasma Nomogram feature collects more plasma, it can take longer and require more anticoagulant. Today the procedure utilizes a 250 mL bag of 4% sodium citrate but for the trial, a 500 mL bag will be used – however, no more than 350 mL is expected to be used during the procedure.

1.3 Historical Background of the Percent Plasma Nomogram (PPN) Feature

Prior to 1992, there was no standard nomogram used by all plasmapheresis devices. Each manufacturer produced its own unique nomogram. These various nomograms were based on the variables of height, weight, and hematocrit. Traditionally, a plasma collection operator used a series of lookup tables to determine the appropriate plasma collection volume and would enter this volume manually into the corresponding plasmapheresis device. These earlier nomograms had a number of benefits. The use of both height and weight to determine the target collection volume was a step toward incorporating BMI, ensuring that those who appeared to have less total plasma volume would give less. These types of nomograms also utilized the donor's hematocrit to further tailor the collection volume to the donor's biometric data.

In addition to the lack of consistency between devices, the shortcoming of this approach was the step-wise calculation output. Prior to 1992, devices could not be programmed to automate all of the targeting steps. This left room for human error in the manual calculation of the target collection volume. In an effort to reduce this error by simplifying the process, the nomogram variables (height, weight, and hematocrit) were grouped by ranges. The consequence of this simplification, however, was a significant decrease in specificity. For example, a small change in weight, height, or hematocrit could affect which range group the donor fell in, thus having a large impact on the target collection volume.

Despite this effort to reduce errors by simplifying the manual calculation, additional risk remained. Since it was possible that the same site was using devices from different manufacturers, it was possible to have multiple versions of lookup tables located in the donor room simultaneously. The risk of a nomogram being used with the wrong device is said to have prompted CBER to publish the current FDA nomogram in 1992.

1.4 Performance and Limitations of the 1992 Nomogram

On November 4th, 1992, CBER published a simplified nomogram for source plasma manufacturers. The FDA nomogram designates three volumes of plasma collection based on three ranges of donor weight, as summarized in Table 1.

Donor Weight	Plasma Volume
110 – 149 lbs	625 mL
150 – 174 lbs	750 mL
175 lbs & up	800 mL

Table 1: Plasma Nomogram, CBER, 1992

By encouraging one nomogram across all manufacturers, FDA effectively eliminated the risk of an operator using an inappropriate nomogram. The risk of human error was also minimized by eliminating both height and hematocrit variables and by reducing the number of weight categories to three.

The consequence of this simplification and the main limitation of the current FDA nomogram is that the nomogram does not reflect the important donor biometrics that had been used to select a target collection volume more suited to individual donors. BMI and hematocrit have long been known to impact total plasma volume. Omitting these variables leads to a situation where donors with the smallest total plasma volume may donate the highest percentage of their plasma. As plasma donors tend to fall in the higher weight category, there is an increased chance that ignoring BMI could have unintended consequences.

Figure 2 is derived from a database of 111,916 donations from all 86 Octapharma Plasma collection centers, including the three selected for the clinical trial. The x-axis shows each donor's total plasma volume, adjusted for BMI and hematocrit. The y-axis shows the percentage of plasma collected from each donor using the 1992 FDA nomogram.

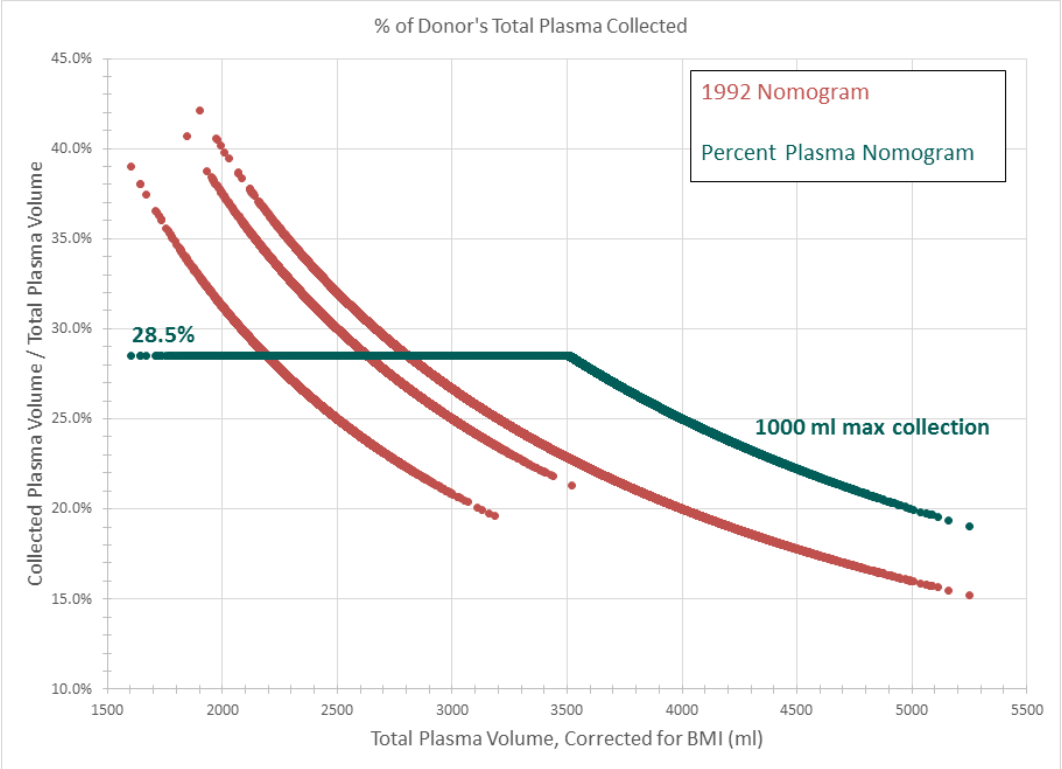

Figure 2 - Percentage of Plasma collected with 1992 Nomogram

The three distinct orange curves correspond to the three weight categories in the current FDA nomogram with YES® technology, with the lowest weight category on the left and the highest to the right. The green curve shows the hypothetical target percentage calculated with the Percent Plasma Nomogram (PPN).

Figure 2 highlights two major drawbacks to the current FDA nomogram. First, there is a large variation in the percentage of total plasma collected from donors. In the upper left quadrant of the graph, there are many donors who donate greater than 30% of their total plasma volume. On the right-hand side of the graph, however, there are donors who donate well below 20%, thus potentially under-utilizing the amount of plasma that could have been drawn. Second, there is an inverse trend in the graph, with the percentage of plasma collected inversely relating to the donor's total plasma volume. Thus, donors with

lower total plasma volume donate a higher percentage of their total plasma. These drawbacks suggest a need for a safer, more personalized approach to the nomogram.

1.5 Use of YES® Technology

YES® technology is an FDA-cleared yield-enhancing solution that optimizes the plasma collection to enable utilization of the upper limit of the volume of plasma allowed by the FDA nomogram rather than the upper limit of the total collection volume. Both YES® technology and the PPN feature target Actual Plasma volume as opposed to total collection volume.

2. Rationale and Endpoint Justification

This prospective, randomized, observational, multicenter clinical trial proposes to study a Percent Plasma Nomogram (PPN) feature for the Haemonetics NexSys® PCS device. The goal of the PPN feature is to personalize the plasma collection target by using both the donor's BMI and hematocrit and to maintain a safety profile that is at least not inferior to the current FDA nomogram with YES® technology. We hypothesize that the PPN feature will prove to be safe and that it will help to meet the growing demand (increased four-fold over the past 12 years) for critical plasma therapies without compromising donor safety.

2.1 Characteristics of the Percent Plasma Nomogram (PPN) Feature

The PPN feature will expand the use of the donor's physical characteristics to tailor the plasma collection target to each individual. It will employ a combination of weight, height, and hematocrit to calculate the donor's total plasma volume. The plasma collection target for each donor will be set at 28.5% of the donor's total plasma volume with a cap of 1,000 mL to account for exceptionally high plasma volume donors. The 28.5% threshold was chosen specifically to mitigate the risk of potential vasovagal reactions associated with extracorporeal volume, as detailed later in this document. The 28.5% threshold is well within the current practice that sees collections with a range of roughly 15% - 42% of the donor's total plasma volume.

For illustration, Figure 2 in section 1.4 shows the theoretical hypothetical impact on the donor database of 111,916 donations (green curve).

The plasma collection target would be 28.5% of the donor's total plasma volume for all donors (green line) with a cap of 1,000 mL.

Figure 3 shows the overall impact of the PPN feature.

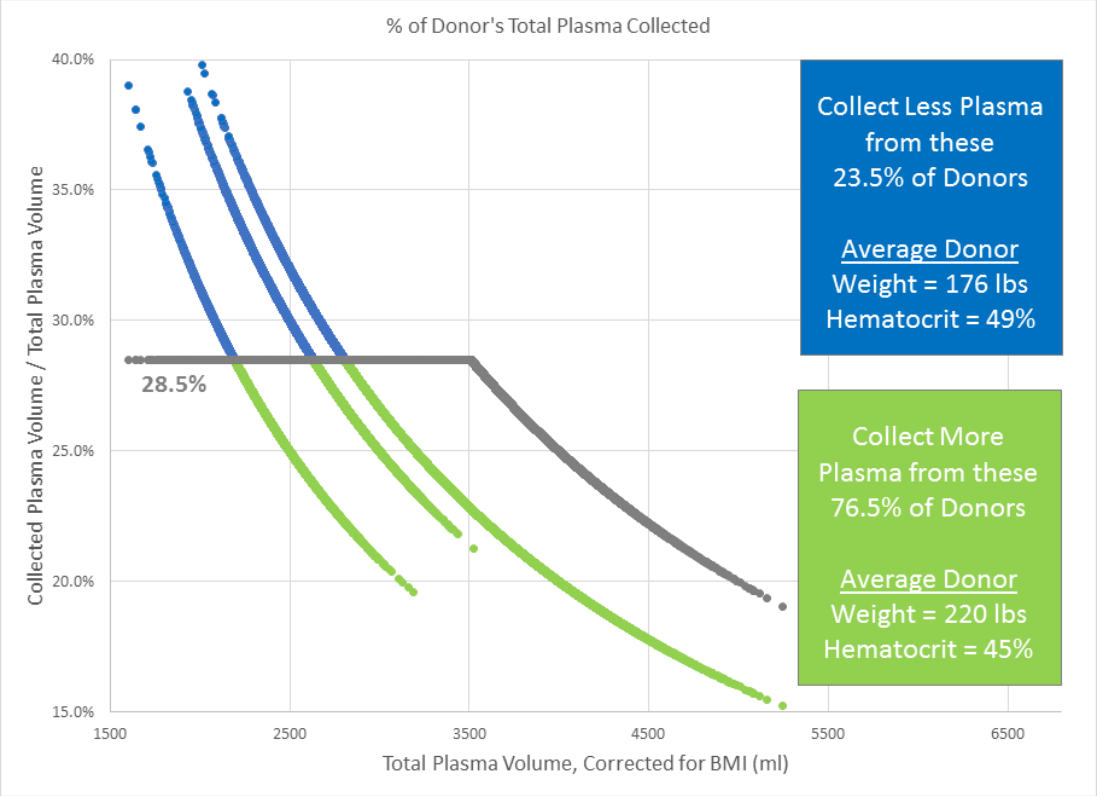

Figure 3 – Demographics of Impacted Donors

The target plasma collection volume would be decreased for approximately 23.5% of donors with the more personalized PPN feature. The donors who would donate less have, on average, a lower total plasma volume, a lower body weight and a higher hematocrit than the overall donor population, potentially placing them at a lower risk to develop significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, with the use of the PPN. Conversely, the donors who would donate more plasma have a higher total plasma volume and higher body weight than the average donor. Because of their higher calculated plasma volume, such donors may be at a lower risk to develop significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, occurring during plasmapheresis in comparison with individuals with a low calculated plasma volume. In summary, donors should not be anticipated to be at a higher risk for developing hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, with the PPN feature than with the 1992 FDA nomogram.

Another benefit of the PPN feature is that the average volume of pure plasma collected would be expected to increase from 777 mL to 848 mL. This would be a welcome benefit to a US health system struggling to meet the demand for critical plasma-based drugs and therapies.

Figure 4 shows a frequency distribution of the incremental plasma volumes. Note that the spike at 180-200 mL is due to those donors currently donating 800 mL who would be capped at 1,000 mL with the use of the PPN.

Figure 4 – Frequency Distribution of Incremental Plasma Volumes

2.2 Expected Impact on Safety

FDA has deemed plasmapheresis, as specified by the 1992 nomogram, as safe for donors. Currently, up to 800 mL of plasma are collected from donors, depending on which of the three weight categories they fall into. The FDA's rationale behind regulating plasma donations according to weight categories was presumably to adjust for body weight and, with that, for donors' total plasma volume. The 1992 nomogram did not include other relevant parameters such as body mass index (BMI) or hematocrit due to concerns at the time that such parameters could lead to more user errors when calculated and entered manually as the technology was not in place to process this information automatically. However, as a consequence of this triage, the current nomogram collects the highest percentage of total plasma volume from donors with the lowest weight and lowest total plasma volume (see Section 1.4, Figure 2, above). This leads to the undesirable result of potentially putting this group of donors at the highest risk of developing significant hypotensive (vasovagal/hypovolemia) adverse events. In spite of that, it is important to note that the safety profile of the current nomogram has extremely low rates of critical adverse events, even for donors who would be considered at increased risk[4].

This context is important for the proposed clinical study because it demonstrates that higher percentages of plasma have been collected from millions of donors in a real-world setting. Specifically, with the 1992 nomogram, plasma volumes ranging from approximately 15% to 42% of the total plasma volume have

been collected, which represents a variation of more than a factor of two between different donors. These data are from Haemonetics' internal analysis of a data set that was obtained in collaboration with Octapharma Plasma and consisted of 111,916 donations. Furthermore, with the current FDA nomogram, donors may end up in one weight category for any one donation, and then at the next donation end up being subjected to a more than 20% increased target collection volume, solely based on the increase of their weight by a single pound. This is within the margin of error of donor weight determination.

The Percent Plasma Nomogram is designed to address the above issues. It is a continuous nomogram and considers other important factors (i.e., BMI and hematocrit) to calculate the target plasma collection volume. The proposed harmonized target collection volume is standardized across donors in that it allows 28.5% of total plasma volume to be collected. This value is at the midpoint of a range that is considered safe as supported by a substantial body of real-world experience today. Moreover, Haemonetics has capped the absolute volume at 1,000 mL. This level has previously been shown to be safe and not to lead to a sustained plasma protein depletion[5,6]. As a further safety feature of the proposed protocol, in this clinical trial, a saline replacement will also be used as the primary form of re-hydration (if, under exceptional circumstances, saline cannot be administered, Octapharma Plasma (OPI) center policies have to be followed) (see Section 1.2).

With regard to the slight increase in the percentage of plasma collected from those donors who would currently donate less than 28.5% of their total plasma volume, there is no evidence in the literature of an association between such increase during plasmapheresis and circulatory effects[7]. Furthermore, the same authors provide evidence in their 2006 publication on the results from the SIPLA trial that an increase to 850 mL plasma in higher weight donors versus a donation of 750 mL plasma can be performed safely[8].

In other words, the risk of incurring significant hypotensive (vasovagal/hypovolemia) adverse events under the current nomogram is already very low. With the new nomogram, we would further reduce this risk for certain (presumably high-risk) donors, while presumably at worst only marginally increasing the relative risk for other donors. Therefore, Haemonetics proposes that the statistical risk of a significant hypotensive (vasovagal/hypovolemia) adverse event occurring is kept at least constant. Any possibly increased relative risk for those subjects who will donate slightly more plasma is expected to be outweighed by the benefits of the study.

2.3 Expected Impact on the Likelihood of Errors

Since 1992, plasmapheresis devices have advanced beyond the need for manual lookup tables, now allowing nomograms to be programmed directly into the device software. Further, many plasma centers now utilize a Donor Management System (DMS) that communicates directly with the devices. In the PPN configuration, donor biometric information will be sent directly from the DMS to the device, which will calculate the target collection volume for that donor. Thus, the chance of human error will be minimized.

In centers without this level of connectivity, the operator will manually enter the donor's height, weight, and hematocrit into the NexSys® PCS but the device will still perform the calculation of target collection volume for that donor.

2.4 Expected Impact on Hypotensive (Vasovagal / Hypovolemia) Reactions

Hypotensive (vasovagal/hypovolemia) donor adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, are influenced by the extracorporeal volume (ECV) during the procedure and the intravascular deficit (IVD) at the end of the procedure.

During the procedure, the peak ECV on the NexSys® PCS is reached when the full plasma product has been collected and the separation chamber contents are about to be returned to the donor for the last time. Since the PPN feature modifies the target plasma collection volume, it has an impact on peak ECV. Peak ECV will go down for donors whose target plasma collection volume is decreased and up for donors whose target is increased.

The range of peak ECV using the current FDA nomogram with YES® Technology is 12.2 % to 30.3%, with a median of 19.3% and a mean of 19.1%, in the database of donor biometric information from 111,916 plasmapheresis procedures (see above). This range is created by factors such as target plasma collection volume and donor plasma and blood volume. The use of the PPN feature would tighten the distribution since the target plasma collection volume would be personalized to the donors' total plasma volume, with a hypothetical range of 14.4% to 24.6%, a median of 20.3%, and a mean of 20.2%. The results of this analysis are shown in Figure 5 below.

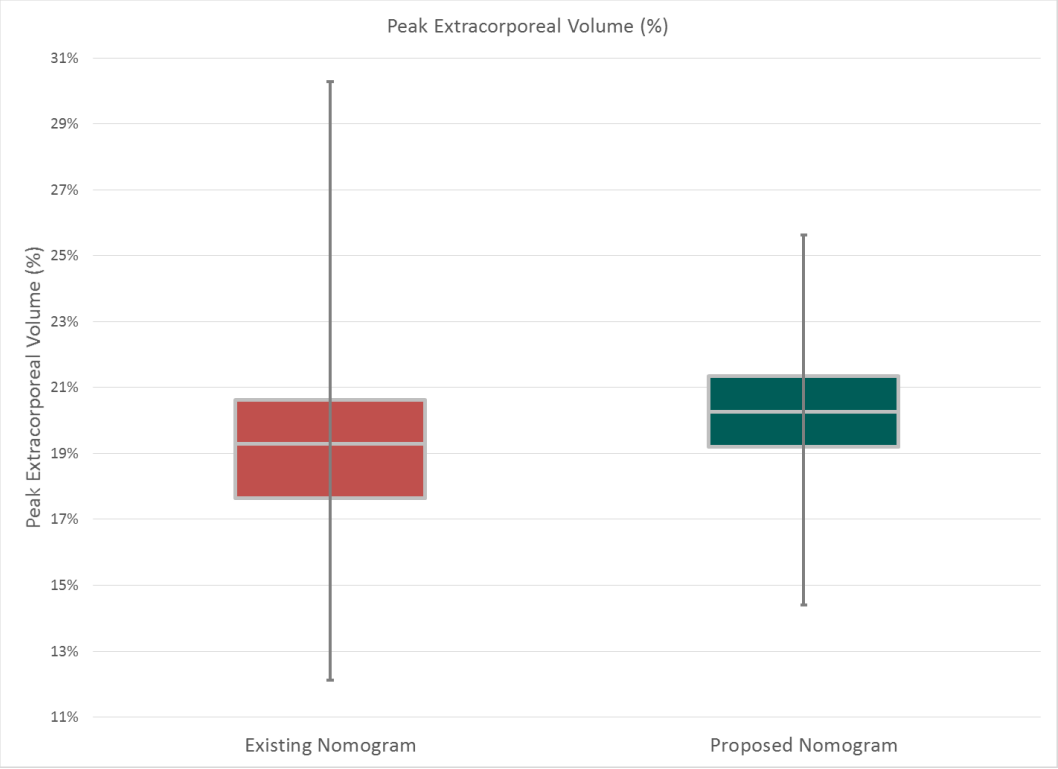

Figure 5 – Peak Extracorporeal Volume with existing nomogram and PPN

On the left, “Existing Nomogram” represents the ECV challenge that is experienced in the field today and that will be experienced in the clinical trial in all ‘Control’ procedures. On the right, “Proposed Nomogram” is the challenge predicted for the ‘Experimental’ procedures that will use the PPN feature in the trial.

The donors considered to be most at risk for significant hypotensive (vasovagal/hypovolemia) adverse events would be those in the upper quartile of the distribution. To assess the risk in the clinical trial, we analyzed this quartile of the donors in both the ‘Control’ and the ‘Experimental’ distributions.

We conclude that the donors in the ‘Experimental’ arm are not expected to have an increased risk of ECV-induced significant hypotensive (vasovagal/hypovolemia) adverse events compared to the ‘Control’ donors for the following reasons:

- The range of ECV for the upper quartile of ‘Experimental’ procedures (21.3%-25.6%) has a much lower upper limit than the ‘Control’ group (20.6%-30.3%). In addition, 16.8% of the donors in the upper quartile of the ‘Experimental’ procedures would experience a lower ECV with the ‘Experimental’ procedure than with the ‘Control’ procedure.
- The lower boundary of the upper quartile of ECV in the upper quartile is 20.6% in the ‘Control’ group versus 21.3% in the ‘Experimental’ group, while the maximum is 30.3% in the ‘Control’ group versus 25.6% in the ‘Experimental’ group.
- The average donor weight for donors in the upper quartile of the ECV range for the ‘Experimental’ group (178 lbs) is higher than that of the Control group (168 lbs). These donors should be more resistant to this type of challenge.

Intravascular deficit (IVD) is the amount of fluid the donor loses during the procedure. It can be calculated as the volume of plasma lost minus the volume of replacement fluids administered. The same dataset consisting of 111,916 plasmapheresis procedures was also used to simulate the effect on IVD:

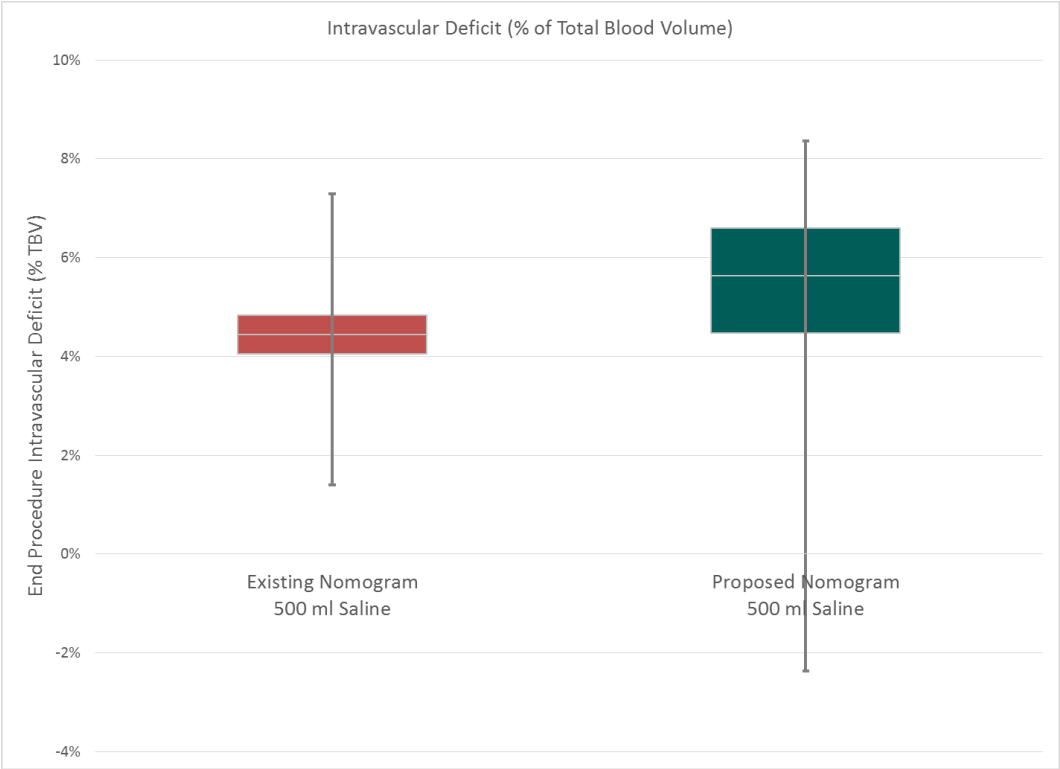

Figure 6 – Intravascular Deficit with existing nomogram and PPN

From Figure 6 it can be concluded that the subjects in the 'Experimental' arm have no significantly increased risk of IVD-induced adverse events compared to the 'Control' subjects for the following reasons:

- End-of procedure IVD is unlikely to be a source of increased risk in the clinical trial because all subjects, 'Experimental' and 'Control', will receive 500 mL of saline compensation as part of the plasmapheresis procedure as the primary form of re-hydration (if, under exceptional circumstances, saline cannot be administered, Octapharma Plasma (OPI) center policies have to be followed). As such, the levels for IVD expected in the trial are very low, as shown in the chart above.
- The clinically potentially relevant range of the top quartile for both 'Control' subjects (4.8%-7.3%) and 'Experimental' subjects (6.6%-8.4%) is similar.
- The subjects being challenged the most by IVD in the 'Experimental' procedures have a much higher average body weight (240 lbs) than the top IVD quartile of the 'Control' procedures (193 lbs). Higher weight donors should be more resistant to this type of challenge.

Today in the US, most source plasma collectors use 500 mL saline IV for fluid substitution. As a further safety feature, a saline replacement will be used in this clinical trial as the primary form of re-hydration (if, under exceptional circumstances, saline cannot be administered, Octapharma Plasma (OPI) center policies have to be followed) (see Section 1.2).

By keeping peak extracorporeal volume and intravascular deficit within the same or very similar range that has been proven safe over twenty-five years of industry experience, we have limited the risk of increased vasovagal reactions with the PPN feature.

2.5 Expected Impact on Anticoagulant Returned to Donor

During a plasmapheresis procedure, a citrate-based anticoagulant is mixed at a fixed ratio to the donor's whole blood to prevent clotting. While the anticoagulant serves a vital role during processing, it also has a deleterious effect as citrate reactions are a commonly reported donor adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions. Anticoagulant is returned to the donor during a plasmapheresis procedure on the NexSys® PCS when the concentrated cells in the separation chamber are returned to the donor at the end of each collection cycle. The total volume of anticoagulant returned is largely a function of the number of cycles performed to reach the target plasma collection volume. The concentration of the anticoagulant in the returned blood varies according to the donor's hematocrit and the ratio at which the anticoagulant is added to the whole blood drawn from the donor.

On the NexSys® PCS, using the current FDA nomogram with YES® technology, the volume of anticoagulant returned to the donor is approximately 36.1 mL per procedure. Roughly 8.5 mL of anticoagulant is returned with each collection cycle and the average number of cycles is 4.3.

With the PPN feature, the total amount of anticoagulant returned will be affected since the change in target plasma collection volume will lead to a change in the number of collection cycles for individual donors. Since the overall plasma collected across the entire donor population will increase with this proposal, the average absolute amount of anticoagulant returned will increase slightly from approximately 36.1 mL to approximately 40.1 mL. In terms of citrate toxicity, the additional absolute citrate amount is very low. The concentration of the citrate solution is unchanged (136 mmol/L), as is the amount of citrate administered per time (infusion rate). This is because it takes proportionately longer to collect the additional volume. Importantly, the subset of donors whose target plasma collection volume is decreased will receive lower relative amounts of anticoagulant returned. The ratio of anticoagulant to anticoagulated whole blood will remain unchanged at 1:16, with a range of volume of anticoagulant returned being 16.8mL to 68.0 mL versus 15.0 mL to 85.0 mL with the PPN nomogram.

It is important to point out that citrate reactions are not so much a function of the total amount of anticoagulant returned but more of the speed at which the anticoagulant is infused. With the PPN feature, neither the pump speed nor the citrate concentration in the solution, nor the ratio at which the anticoagulant is added to whole blood is changed. Therefore, the rate of anticoagulant returned to the donor is not impacted. In individuals with additional collection cycles and an increased absolute amount of anticoagulant returned there will also be a proportionally longer amount of time for the donor's calcium

homeostasis to be preserved and balanced. Importantly, the amount of anticoagulant infused into plasmapheresis donors is much lower than the amount of anticoagulant given during platelet apheresis, which is considered safe[9, 10].

In summary, the PPN feature is not expected to have an impact on the rate of citrate reactions because it creates only a small increase in the total volume of anticoagulant return while not changing pump speed or infusion rates (anticoagulant volume infused per time).

3. Device Description

3.1 Investigational Device

A modified version (version 1.3.90) of NexSys® PCS embedded software is to be installed on current FDA-cleared NexSys® PCS device hardware (PCS-300-US), enabling use of the Percent Plasma Nomogram feature. When the Percent Plasma Nomogram feature is enabled, YES® technology is used by default. The device communicates with NexLynk® DMS (the site's Donor Management System). Donor biometric information is directly sent from the DMS to the devices in order to calculate the plasma collection target for that donor. The PPN feature uses donor weight, height and hematocrit to calculate the collection target. This allows a plasma collection tailored to the individual donor. A larger plasma pooling bottle (0697S-00) will be used in order to accommodate greater total collection volumes anticipated from some donors.

3.2 Control Device

The same modified version (version 1.3.90) of NexSys® PCS embedded software is to be installed on current FDA-cleared NexSys® PCS devices (PCS-300-US) to be used as the control. The PPN feature will be disabled (by default) on the control devices. The device receives the donor weight and hematocrit from the NexLynk® DMS and calculates the plasma collection target for that donor using the current FDA-cleared YES® technology. The same larger plasma pooling bottle (0697S-00) will be used with the control devices in an effort to reduce bias.

3.3 Labeling

In an effort to reduce potential bias due to visible differences, the investigational and control devices will be labeled in the same way. The NexSys® PCS device (PCS-300-US) and the larger plasma pooling bottle (0697S-00) will bear a label stating, "CAUTION Investigational Device. Limited by Federal Law to Investigational Use Only." The User Interface (touchscreen) on the device will display a red banner stating, "CAUTION Investigational Device. Limited by Federal Law to Investigational Use Only." The existing user manual for the NexSys® PCS device will be provided, as well as an addendum describing the use of the PPN feature for the investigational devices.

4. Clinical Trial Objectives

4.1 Primary Objective

The objective of the IMPACT clinical trial is to evaluate the safety of plasmapheresis performed on the NexSys® PCS device with PPN feature. The clinical trial is designed to assess if the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events per donation in donors undergoing plasmapheresis in the experimental group is NOT inferior to that seen in donors in the control group. This incidence rate is defined as at least one (1) significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, per plasmapheresis procedure. For the purpose of this clinical trial, a hypotensive (vasovagal/hypovolemia) adverse event will be determined to be *significant* if it fulfills one or more of the criteria defined in rows 1.2 (Hypotensive: Prefaint, No LOC (moderate)) or 1.3 (Hypotensive: LOC (brief)) or 1.4 (Hypotensive: LOC (prolonged)) or 1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury) of the IQPP definition, as applied in the plasma center adverse event reporting system. See Appendix 16.1 IQPP Standard for Recording Donor Adverse Events**.** The signs/symptoms/findings for categories 1.1. to 1.6 that are listed in the far right column of the table may be defined slightly differently per center policy.

4.2 Secondary Objectives

- To assess if the incidence rate of severe hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, per donation in donors undergoing plasmapheresis in the experimental group is NOT inferior to that seen in donors in the control group
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, relative to the actual plasma volume of plasma collected, comparing procedures in the experimental group and control group
- To study the time from the start of plasmapheresis “Begin Draw” to the first significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the experimental group and the control group
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors with a bodyweight of less than or equal to 130 lbs and those greater than 130 lbs
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors with a body mass index (BMI) of less than or equal to 30 and of those greater than 30
- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP

definitions, of procedures in the experimental group and in the control group in the subgroups of donors defined by their respective status as a first-time donor or repeat donor

- To assess the incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, of procedures in the experimental group and in the control group in the subgroups of donors defined by their gender
- To evaluate the total plasma volume collected per procedure in the experimental group and in the control group

5. Endpoints

The endpoints are based on the definitions in the current IQPP Standard for Recoding Donor Adverse Events, as they are recorded per site policies at the respective donor centers. At the time of the writing of this protocol, version 2.0, implemented April 01, 2018, was the most up to date version[11].

5.1 Primary Endpoint

The primary endpoint of the clinical trial is the incidence rate of at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions below.

For the purpose of this clinical trial, a hypotensive (vasovagal/hypovolemia) adverse event will be determined to be *significant* if it fulfills one or more of the criteria defined in rows 1.2 (Hypotensive: Prefaint, No LOC (moderate)) or 1.3 (Hypotensive: LOC (brief)) or 1.4 (Hypotensive: LOC (prolonged)) or 1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury) of the IQPP definition, as applied in the plasma center adverse event reporting system. The table below is an excerpt from the current IQPP adverse event classification criteria. See Appendix 16.1 IQPP Standard for Recording Donor Adverse Events**.**

The signs/symptoms/findings for categories 1.1. to 1.6 that are listed in the far right column of the table may be defined slightly differently per center policy. For example, Octapharma Plasma uses a symptom-based approach for adverse event classification that entails at least two layers of internal review. Event categorization as a hypotensive (vasovagal/hypovolemia) adverse event is always confirmed by a physician per Octapharma Plasma policy. Per current policy, the following criteria are considered indicative of convulsions/seizures that are listed under criterion 1.5, last column on the right, in the table above: a. Bluish tinge to skin, lips (cyanosis) b. Breath-holding c. Curling of fingers/toes d. Drooling e. Muscle twitching f. Tongue biting. Any checkmark applied to one of these categories will be considered indicative of the convulsions/seizure criterion. The criterion “Nausea” under criterion 1.1 in the last column on the right of the IQPP criteria is not listed as a separate criterion in Octapharma Plasma’s Medical Incidence Report (MIR) system. As systolic blood pressure is determined and recorded under vital signs in each MIR and at least two reviews of the classification of an adverse event as hypotensive (vasovagal/hypovolemia) are required per Octapharma Plasma policy, a separate checkbox for the category "Hypotension", as under 1.1 under the IQPP criteria, is not required on the MIR.

DAE Classification	Description	Signs/Symptoms/Findings
1. Hypotensive (Vasovagal/Hypovolemia) Hypotensive reaction (vasovagal/hypovolemia) that falls into any of the following categories. *NOTE:* For the purposes of this IQPP Standard, "medical staff intervention" means the use of expertise from the physician or physician substitute to make decisions regarding the management of the DAE.		
1.1 Hypotensive: Prefaint, No LOC (Minor)	This reaction: a. must resolve without medical staff (e.g., physician substitute) intervention, AND b. Involves signs and symptoms that resolved quickly (e.g. within approximately 10 minutes).	May include one or more of the following: a. Abdominal cramps; b. Auditory disturbance (e.g. sounds coming from a distance or "buzzing" in the ears); c. Chills or Shivering; d. Clammy; e. Cold extremities; f. Dizziness; g. Epigastric discomfort; h. Facial pallor (e.g. pale skin or lips); i. Feeling of Warmth; j. Headache or neck ache; k. Hypotension; l. Lightheadedness; m. Nausea; n. Palpitations; o. Sweating; p. Visual Disturbance (e.g. blurred or faded vision); or q. Weakness.

DAE Classification	Description	Signs/Symptoms/Findings
1.2 Hypotensive: Prefaint, No LOC (Moderate):	This reaction: a. requires medical staff (physician substitute) intervention, OR b. involves signs/symptoms that did not resolve quickly (e.g. within approximately 10 minutes), OR c. additional signs/symptoms may be present.	May include any in 1.1 AND a. Vomiting.
1.3 Hypotensive: LOC (brief)	In this reaction, LOC lasts approximately less than sixty seconds.	May include any in 1.1 or 1.2.
1.4 Hypotensive: LOC (prolonged)	In this reaction, LOC lasts approximately sixty seconds or longer.	May include any in 1.1 or 1.2.
1.5 Hypotensive; Severe (With or Without LOC):	This reaction may or may not include LOC.	May include any in 1.1 through 1.4 AND any of the following: a. Chest Pain; b. Convulsions/Seizures c. Loss of Bladder/Bowel Control; or d. Prolonged signs or symptoms that do not resolve.
1.6 Hypotensive; Injury	A hypotensive event that results in ANY type of injury such as: a. Closed Head Injury; b. Dental Injury; c. Fracture; d. Laceration; e. Soft Tissue Injury (not phlebotomy- related); or f. Other.	May include any of 1.1 – 1.5 as well as any signs/symptoms related to the injury itself.
NOTE: If the donor exhibits symptoms of a hypotensive event (1.1 through 1.6), in addition to "anxiety," then the event should be classified according to "1.1 – 1.6 Hypotensive."		

5.2 Secondary Endpoints

- Incidence rate of severe hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, per donation in donors undergoing plasmapheresis
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, relative to the actual plasma volume collected
- Time from start of plasmapheresis "Begin Draw" to the first significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors with a body mass of less than or equal to 130 lbs and those greater than 130 lbs
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors with a body mass index (BMI) of less than or equal to 30 and of those greater than 30
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors defined by their respective status as a first-time donor or repeat donor
- Incidence rate of significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, in the subgroups of donors defined by their gender
- Total plasma volume collected per procedure

5.3 Exploratory Endpoints

Additional exploratory analyses will be conducted as deemed appropriate and may include any of the safety, efficacy and/or clinical data. An example of an exploratory endpoint is the number of apheresis procedures per donor. Other examples are:

- The incidence rate of at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, occurring during the plasmapheresis procedure at first donation. For this endpoint, every subject will only contribute their first donation to the analysis
- The proportion of donors who experience at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, occurring during any of his or her plasmapheresis procedures

6. Sites and Subjects

6.1 Subjects

The clinical trial will involve a total of approximately 24,000 donations from around 5,000-6,000 donors.

6.1.1 Enrollment and Informed Consent

Prior to participating in the clinical trial, the subject will give his/her written informed consent. The informed consent form (ICF) must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The ICF used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/Independent Ethics Committee (IEC) and Haemonetics before use. The informed consent will include an explanation of the clinical trial, duration, a description of the investigational product, risks and benefits of the clinical trial, compensation provisions, an explanation of manufacturing record access and subject anonymity, and how their coded data may be transferred or used for publications. The qualified healthcare provider, or a person designated by the qualified healthcare provider, will obtain written informed consent from each subject before any study-specific activity is performed. The qualified healthcare provider will retain the original of each subject's signed consent form.

6.1.2 Incomplete Donations

A donation is considered incomplete if the total plasma volume collected is below 200 mL, per donation center definitions or procedures.

6.1.3 Subject Withdrawal

Subjects will not be considered for further donations if any of the following occurs:

- Subject not able or willing to give consent to participate in the clinical trial.
- Subject donated plasma outside of the present clinical trial after enrolling in this clinical trial.
- Subjects are withdrawn from the clinical trial due to safety concerns by the qualified healthcare providers.
- In addition, all donors for whom a BMI for use in the PPN feature cannot be reliably calculated will be excluded.

Subject withdrawal for any reason will be documented on the Subject Withdrawal Log.

6.1.4 Subject Eligibility for Redonation

Subjects will not be considered for further donations if any of the following occurs:

- Enrollment is completed
- Subject donated plasma outside of the present clinical trial after enrolling in this clinical trial

6.2 Site Selection

The IMPACT clinical trial will recruit subjects at three centers in the United States. The sponsor will choose centers that are geographically distributed and that have a typical donor distribution, as determined by analysis of PPTA data and a >100,000 donations database from the clinical partner, Octapharma Plasma Inc. These centers follow PPTA guidelines and have adequate facilities, staff, and training.

Up to three additional centers will be selected as alternates or to expand the number of trial sites, aiming to maintain the geographical and donor distribution.

6.3 Site Training and Initiation

6.3.1 Training

Qualified healthcare providers and site personnel will be trained on the Clinical Investigational Plan (CIP) prior to site initiation and enrollment. Training will be documented in the Training Log and cover the following topics:

- Clinical trial objectives
- CIP review
- Delegation of Authority
- Process of Informed Consent as well as IRB requirements
- Electronic Case Report Form (eCRF) use
- Enrollment procedures
- Protocol Deviation documentation
- AE and SAE reporting
- Device Malfunction reporting
- Instructions for Use
- Device training
- Qualified healthcare provider responsibilities
- General Good Clinical Practice (GCP) guidelines
- The Declaration of Helsinki
- Regulatory requirements including essential documents

Changes to IMPACT clinical trial staff responsibilities, as documented on the Delegation of Authority log, or addition of new clinical trial personnel will require appropriate training and documentation.

6.3.2 Initiation

Haemonetics or a representative will conduct clinical trial training as described in Section 6.3.1.

Prior to actively recruiting/enrolling subjects, Haemonetics will provide the following documentation:

- IRB approval for the Investigational Plan
- IRB and sponsor approved ICF for the clinical trial
- Approval/notification from the FDA

Prior to actively recruiting/enrolling subjects, investigational centers must provide the following documentation:

- Qualified healthcare provider(s') curriculum vitae (CV)
- Financial Disclosure Form (FDF) for the trial principal investigator and sub investigators
- Signed Clinical Trial Agreement (CTA) including budget
- Training documentation to verify the appropriate clinical trial staff has been trained on the protocol, device, eCRFs and clinical trial conduct

Sites will be officially notified of site activation through receipt of an activation letter or email.

7. Clinical Trial Design

This is a multicenter, randomized, prospective IDE clinical trial to evaluate the safety and effectiveness of a PPN feature using the NexSys® PCS during plasmapheresis. The clinical trial is designed to collect approximately 24,000 plasmapheresis procedures from around 5,000 - 6,000 donors. Donors will be randomized 1:1 to the experimental group undergoing plasmapheresis using NexSys® PCS with the PPN feature or the control group undergoing plasmapheresis using NexSys® PCS with YES® technology. As repeat donations by the same donor are expected, the donor will remain in the same study group during the entire course of the clinical trial. In an effort to prevent bias, the clinical trial will be blinded to select members of the sponsor study team in accordance with the blinding plan, and subjects will not be made actively aware to which group they have been randomized – however, subjects may be able to determine to which group they have been assigned. The sample size of the clinical trial may be reevaluated based on the number of donations and observed significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions.

7.1 Clinical Trial Duration

Enrollment will be approximately 4 to 6 months. Prior to enrollment, all subjects will be required to provide written consent. Once enrolled, all subjects will remain in the clinical trial for their first and any subsequent donations per institutional guidelines until enrollment is completed or until they withdraw consent. For each subsequent donation, subjects will be required to meet all eligibility criteria (see eligibility criteria below). Subjects will be followed up according to established site procedures. The plasmapheresis procedure will follow standard of care practices at the centers, with the exception that the target plasma collection volume is determined per the PPN feature in the experimental group.

Monitoring of adverse events (AEs) will be conducted throughout the clinical trial. All AEs will be captured and reported per established site procedures in compliance with IQPP standards and with CFR. Reporting of AEs in study subjects will occur after the subject's donation has ended per established site procedures. The safety of the clinical trial will be monitored by a Data Monitoring Committee (DMC) which will meet regularly and will be operating according to the DMC charter.

The original assignment of the subject to the experimental group or to the control group, respectively, will be carried over. There will be no re-randomization for repeat donors.

7.2 Subject Eligibility Criteria

Subjects must meet all eligibility criteria in order to be enrolled in the clinical trial.

7.2.1 Inclusion Criteria

Donors must be qualified to donate plasma per individual site's screening procedures which are in compliance with IQPP standards (see Appendix 16.2 IQPP Qualified Donor Standard). If donors do not meet inclusion criteria at subsequent donations but have already been enrolled in the clinical trial, they are eligible to remain in the clinical trial and to donate plasma within the clinical trial once they meet eligibility criteria again, except if they fulfill any of the exclusion criteria listed below.

Other site-specific regulations and procedures may apply.

7.2.2 Exclusion Criteria

All subjects meeting any of the exclusion criteria listed below will be permanently excluded from the clinical trial.

- Subject not able or willing to give consent to participate in the clinical trial.
- Subject donated plasma outside of the present clinical trial after enrolling in this clinical trial.
- Subjects are withdrawn from the clinical trial due to safety concerns by the qualified healthcare providers.
- In addition, all donors for whom a BMI for use in the PPN feature cannot be reliably calculated will be excluded.

8. Clinical Trial Procedures

In general, procedures per clinical trial protocol will follow standard plasma collection procedures, as described in detail below.

All non-investigational procedures will be performed according to standard practice at each site. All routine examinations will be done according to each site's standard management protocol and will be properly documented in the subject's electronic records.

8.1 Screening

Screening against clinical trial inclusion/exclusion criteria will be completed to determine potential eligibility.

Medical and laboratory evaluation will be done per the site's Standard Procedures to determine the eligibility of the subject. There are no additional evaluations or interventions required for screening required for participation in the clinical trial.

8.2 Procedure and Proficiency Requirements

Plasmapheresis is done per site's Standard Procedures.

Sites not meeting proficiency requirements may be retrained or replaced by alternative study centers. After retraining, sites may be eligible to establish proficiency requirements in a subsequent number of apheresis procedures.

Proficiency Requirements

To ensure study centers' proficiency in conducting clinical study activities, proficiency will be assessed using the data up to approximately 50 apheresis procedures enrolled at each study center.

In order to meet the proficiency requirements, the study centers will be evaluated for the following criteria:

- Adverse events
- Proper administration of group assignment
- Donation center procedure deviations
- Clinical study protocol deviations
- Technical failures
- Operator error
- Data handling
- Subject consent

The proficiency testing period will allow the sponsor to see if the investigator team operates as expected and defined by the protocol. Proficiency data will be evaluated by the sponsor. In the event of failing proficiency requirements, the site cannot continue to enroll donors and may be retrained, or replaced by alternative study sites. Adverse events occurring during the proficiency period will be included in the study analysis.

Details of the proficiency requirements testing will be outlined in the Clinical Trial Proficiency Plan.

8.3 Schedule of Events

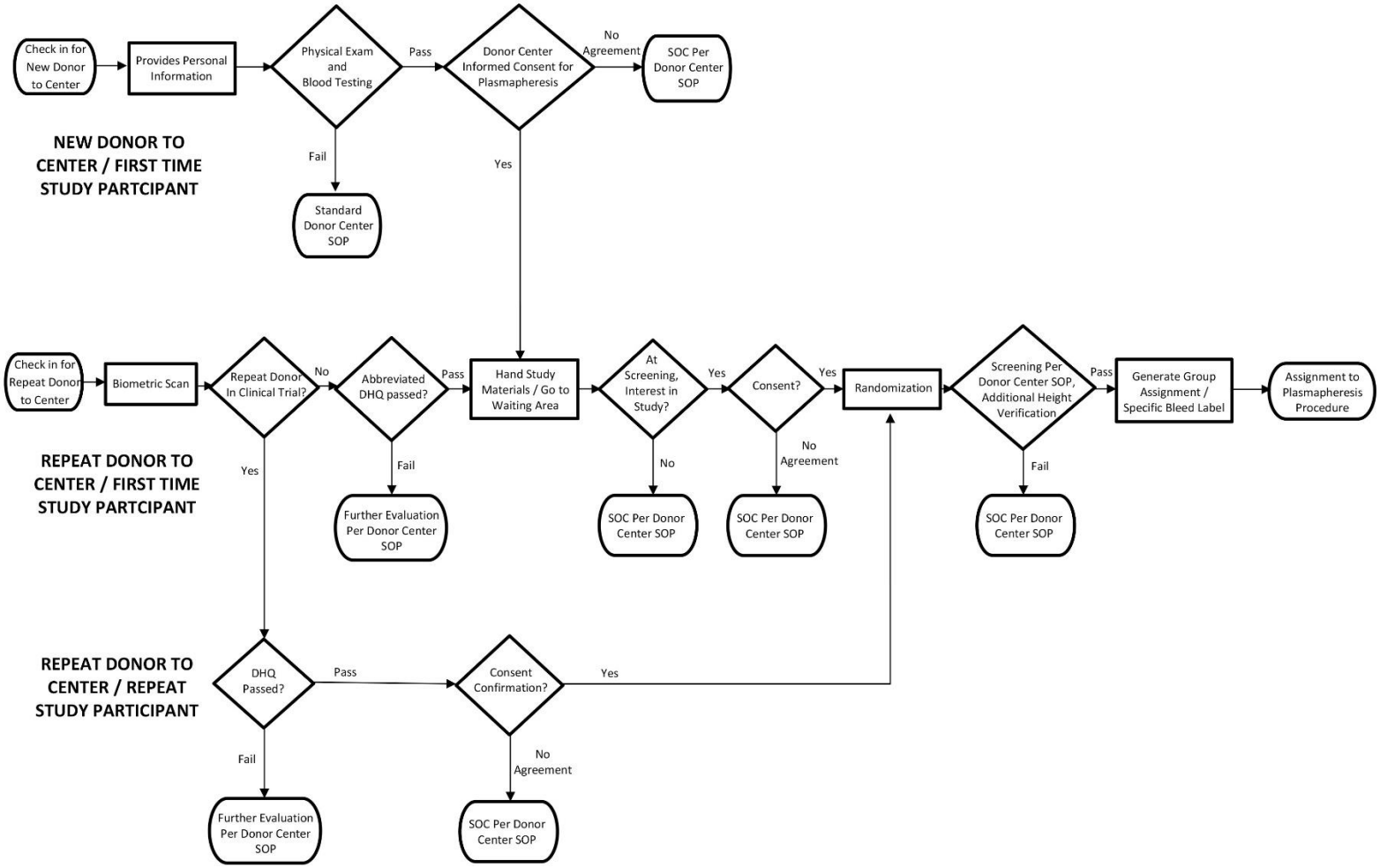

Figure 7 – Schedule of Events

Written consent to participate in the study will be obtained prior to donor screening per plasma donation center procedures. Donors are enrolled in the clinical trial from the time they sign informed consent for the first time. After providing consent, subjects will be electronically assigned to either the experimental group or to the control group. The original assignment of the subjects to the experimental group or to the control group, respectively, will be carried over to subsequent donations. There will be no re-randomization for repeat donors. Once enrolled, all subjects will remain in the clinical trial for their first and any subsequent donations per institutional guidelines until enrollment is completed or until they withdraw consent. For each subsequent donation, subjects will be required to meet all eligibility criteria (see eligibility criteria above). Subjects will be followed up according to established site procedures. Participation in the trial does not alter the standard sequence of steps that donors have to follow to become eligible to donate plasma, with the exception of establishing eligibility and confirming consent for any subsequent donations. The plasmapheresis procedure will follow standard of care practices at the centers, with the exception that the plasma collection volume is determined per the PPN feature in the experimental group.

All subjects who are enrolled in the clinical trial will be given a new product code that identifies whether they are assigned to the experimental or control group. Every subject will be verified by the phlebotomist at the time of identification verification. By contrast, all donors who do not consent to participate in the trial will continue to have their existing product code printed on the bleed label.

Devices that will be used for the purposes of the clinical trial will be located separately from devices used for donations outside of the clinical trial. Devices used in the clinical trial will be labeled “For Investigational Use Only.” In addition, devices used for donations in the experimental group will be located separately from those used for donations in the control group.

Monitoring of adverse events (AEs) will be conducted throughout the clinical trial. All AEs will be captured and reported per established site procedures in compliance with IQPP standards and with CFR. Reporting of AEs in study subjects will occur after the subject’s donation has ended per established site procedures

8.4 Plasmapheresis Aliquots for Exploratory Plasma Analysis

Aliquots from the plasmapheresis procedures may be obtained for exploratory plasma quality analysis at a later time. This exploratory analysis does not impact the plasmapheresis volume and aliquots will be obtained from the plasmapheresis product after the procedure has been completed. A potential collection of these aliquots will be discussed in the Informed Consent process.

9. Data Analysis/Statistical Methods

The detailed methodology for summary and statistical analyses of the data collected in this clinical trial will be documented in a statistical analysis plan (SAP) that will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions and/or their analyses will also be reflected in a protocol amendment.

9.1 Analysis Data Sets

The primary analysis will be conducted on the Intent to Treatment (ITT) data set. The ITT data set will consist of all donations where randomization was completed and the apheresis procedure was started by "Begin Draw" on the NexSys® PCS device.

Sensitivity analysis may be conducted using a Modified *ITT* (MITT) data set and the per-protocol data set. The MITT data set will consist of all complete donations (see Section 6.1.2), as well as all donations associated with a significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions.

The per protocol data set will consist of all donations where the apheresis procedure was successfully completed collecting at least 90% of target plasma volume as well as all donations associated with a significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions.

9.2 Sample Size Considerations

The clinical trial will use an adaptive design allowing for sample size re-estimation based on observed number of donations and observed significant hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions. The target sample size is approximately 24,000 donations which are expected to be contributed by around 5,000 - 6,000 donors (on average four to five donations per donor). The sample size of the clinical trial may be reevaluated based on the number of donations and observed significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions. The sample size adaptation rules and detailed sample size considerations will be specified in the SAP.

9.3 Randomization

Donors must meet all inclusion/exclusion criteria at the time of randomization. Donors will be randomized 1:1 to the experimental group or the control group. As repeat donations by the same donor are expected, the donor will remain in the same study group during the entire course of the clinical trial.

The randomization will target equal allocation of the number of donors in each group per site. Additionally, the randomization will be stratified by the donor's newcomer status (first-time donor vs. repeat donor) and the expected number of repeat donations. A block randomization procedure with variable block sizes will be used.

Allocation of subjects to clinical trial groups will proceed based on the block randomization procedure outlined above. Once subjects are enrolled, they will have been randomly assigned to the experimental or control group and the assignment information will be synchronized with the NexLynk® system. The randomization system will provide a confirmation report containing the subject number and the randomization code.

9.4 Analysis of Primary Endpoint

The primary analysis will be performed on the ITT population. The primary analysis will assess and compare the incidence rate of at least one significant hypotensive (vasovagal/hypovolemia) adverse event according to the plasma center adverse event reporting system, based on the IQPP definitions, across the two clinical trial groups. The analysis will be conducted using repeat measure logistic regression models. The primary endpoint, i.e., the significant hypotensive (vasovagal/hypovolemia) adverse event rates according to the plasma center adverse event reporting system, based on the IQPP definitions, will be compared across the two groups in the framework of non-inferiority hypothesis testing.

9.5 Secondary Analysis

Analysis of the secondary endpoints will be outlined in the SAP. Continuous and discrete modeling techniques will be used whenever applicable.

Effectiveness analysis will be conducted by comparing the distribution of collected plasma volumes across the two groups of the clinical trial.

The rates of AEs will be assessed relative to plasma volume, collection time, and the number of collection cycles. Assessment and comparison of the relative rates will be conducted using repeat measure models and descriptive statistical techniques. The secondary analysis – assessing time to adverse events – will be conducted using a survival analysis modeling framework and hazard estimation. Subgroup analysis will be based on descriptive statistical summaries. Descriptive statistical summaries and advanced data visualization techniques will be used for data presentation.

9.6 Exploratory Analysis

Exploratory analysis will be conducted as deemed appropriate. Continuous and discrete modeling techniques will be used whenever applicable. Distribution summaries will be presented by means of summary tables and visualization methods.

9.7 Interim Analysis

One or more interim analyses may be conducted. The interim analysis may result in the reassessment of the sample size or in early termination of the trial due to safety considerations. The sample size reassessment guidelines and statistical boundaries related to the primary endpoint will be outlined in the SAP.

9.8 Risk-Based Data Monitoring

Risk-based monitoring will be utilized for the trial based on a central statistical monitoring approach. Details will be outlined in the data monitoring plan. Key risk indicators may include, but are not limited to, device performance metrics, drop-out rates, assigned versus actual randomization, adverse event reporting, enrollment, subgroup imbalances, compliance to the protocol, and repeat donation frequencies. In the event where data monitoring indicates that a particular site, operator or machine is

not performing as expected, appropriate intervention may be made. Interventions may include but are not limited to, retraining, adjustment of the randomization scheme, site audits, enrollment suspension or site termination.

Safety monitoring on a real-time basis will be implemented, such that the sponsor, and independently the Principal Investigator, will be able to take appropriate steps to manage emergent safety signals, e.g., to put on hold or stop the clinical trial in case a safety signal is observed. In addition, an external Data Monitoring Committee will perform a review of the safety data for the interim analysis and will be making recommendations concerning the safe continuation of the clinical trial.

The sponsor will have real-time access to updates on adverse events occurring in the trial as reported by Octapharma Plasma (OPI). These will be reviewed by the medical/clinical experts in the sponsor organization on an on-going basis to monitor safety during the trial. The Principal Investigator will have access to the same information and will perform a review independently of the sponsor. Any significant hypotensive (vasovagal/hypovolemia) adverse events (primary endpoint) and Important Medical Safety Events (IMSEs), as well as confirmed or suspected MDR reportable events will trigger a notification to qualified sponsor personnel and to the Principal Investigator. Important Medical Safety Events have been defined by the sponsor's medical/clinical team, in alignment with the Principal Investigator, and are based on the OPI Medical Incidence Report (MIR) classification. These events are defined prior to the start of the trial (see Appendix 16.3) and will be used to identify acute important safety signals that may require urgent intervention by the sponsor.

The sponsor plans to hold regular weekly data review meetings, or more frequently if deemed necessary per event notifications described above. During these meetings the sponsor team will review new significant hypotensive (vasovagal/hypovolemia) adverse events (primary endpoint) and important medical safety events, as well as confirmed or suspected MDR reportable events to determine if any actions need to be taken. Further, an overview of adverse events grouped by the OPI Medical Incidence Report (MIR) classification will be reviewed to identify higher than expected frequencies of adverse events as compared with historic information (if available) or different distributions between the study arms.

OPI will continue MDR reporting and all MDR relevant events will be reported to the sponsor. Moreover, all MDR-relevant events will automatically be categorized as important medical safety events for the purpose of this study.

Safety signals will include: a) MDR reportable events in study subjects if they are unexpected, b) an accumulation of certain adverse events: (1) MDR reportable events, (2) important medical safety events, and (3) primary endpoint relevant events, if they occur beyond the expected rate (based on historical data, if available) or with a concerning statistically significant difference between the two study arms.

The sponsor will be informed of MDR reportable events within 24 hours.

Given the low anticipated frequency of adverse events, it will be nearly impossible to make statistically significant determinations about unusually frequent rates of events until late in the enrollment, unless the adverse event rate is dramatically increased. For this reason, unless there is a statistical determination by the study statistician, unusual safety signals will be independently reviewed by the Principal Investigator and sponsor (medical/clinical team) based on their medical/clinical expertise and experience. They will come to an independent assessment whether the event rate is unusual and whether the safety

signal requires further investigation. If necessary, the sponsor will request an ad hoc DMC meeting to solicit their feedback. The DMC will review adverse events during the 3-4 planned meetings during the course of the study, or during any of the before mentioned requested ad hoc meetings, and will provide independent advice.

Adverse events will be monitored in a real-time manner by the study statistician. Statistical summaries and model-based adverse event rate estimates will be used to present the current information on the adverse events by their categories (see three categories in section on safety signals above), and study arms (marked randomly as A and B). Study arm sample sizes, as well as 95% confidence intervals for adverse event rate estimates, will also be reported and visualized.

Whenever possible, the current AE rates will be compared with historic rates using metrics such as the likelihood of observing the current (or more extreme) AE rates under the relevant historic assumptions. If the observed rates are unexpectedly high (unlikely to observe under historic assumptions) notification indicating a safety signal will be generated and communicated to qualified sponsor personnel (medical/clinical team) and the Principal Investigator.

The adverse event rates will statistically be compared between the two study arms by testing the null hypothesis of equal AE rates (for the three above-defined AE categories). In the event that the between arm comparison suggests that the AE rates are significantly different, notifications indicating a safety signal will be generated and communicated to qualified sponsor personnel (medical/clinical team) and the Principal Investigator.

Upon identification of a safety signal the sponsor will fulfill its obligation to further investigate the safety signal and to appropriately respond to it. Remedial actions can include, but are not limited to, issuing queries, implementing operational changes to the conduct of the trial, retraining the sites, sending protocol deviation alert letters, amending the clinical trial protocol, requesting unblinding of the data for further analysis, etc.

Ultimately the sponsor may need to make a determination about the continuation of the study. Based on the available information, the sponsor (medical/clinical team) will decide to make modifications, to proceed without adjustments or to discontinue the study. The sponsor can reach out to the DMC to request an ad hoc meeting to review the safety signal and to provide an independent assessment to the sponsor. In line with the DMC charter the DMC may ask to review unblinded data as necessary to come to a reliable conclusion (this could allow the sponsor to stay blinded).

Safety signals will not automatically be raised to the DMC, with the exception of a death of a subject, which would be shared with the DMC within 24hrs of the sponsor's awareness of the event.

The Principal Investigator has access to the same information as the sponsor and will be informed of the sponsor's review and response to potential safety signals. The Principal Investigator will conduct an independent review of safety signals based on clinical experience and expertise and make an independent determination.

The sponsor will apply criteria by which to determine if it is safe to continue the study, such as the ones listed below.

1) Is the re-evaluated individual and collective risk profile outweighed by the benefits of the study?

2) Is it likely that a given adverse event may re-occur during the remainder of the study, and that its occurrence will likely carry unacceptable risks?

3) Does the statistical and medical/clinical analysis of the safety signal conclude that there is a correlation and likely causative relation with the study intervention?

4) Has the event happened in the intervention group (please note that the sponsor team should stay unblinded to the extent possible, while fulfilling its safety monitoring obligations and responsibilities)?

These criteria will be shared with the DMC, which will determine, based on these or alternative criteria that they may independently develop, the safety of continuing with the study.

9.9 Safety Analysis

All safety data will be reported by means of the listings as well as summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations. All adverse events will be collected and summarized according to the plasma center adverse event reporting system, based on IQPP definitions. Comprehensive statistical summaries and comparisons will be presented by study arm, adverse event types (e.g., hypotensive, citrate reactions, phlebotomy-related), and severity, as defined by plasma center adverse event reporting system, based on IQPP definitions. Safety events that trigger withdrawal of a subject will be presented by means of a listing, visual summaries, and appropriate statistical analysis. Further details will be contained in the final Statistical Analysis Plan.

9.10 Stopping Rules

Close safety monitoring is in place throughout the trial to ensure that safety issues of any form and severity will be identified early on and appropriately responded to as laid out elsewhere. In addition, stopping rules are defined as follows:

<u>Stopping Rule 1: Subject Death</u>

If at any time during the study, including roll-in/proficiency testing and enrollment, there are:

- one or more subject deaths reported to the sponsor,

the DMC will be informed within 24 hours and will perform an unblinded review. The DMC should make a determination by the end of the next business day after the event was reported to the sponsor.

If the DMC determines relatedness and decides that the safety profile of the study should be reconsidered, the study is put on hold immediately. Information of the event and DMC's decision is transmitted to FDA immediately. The study is not resumed unless and until FDA has decided that it is safe to do so.

If the DMC determines that the event is unrelated, or that the safety profile of the study remains unchanged, the study can be continued without interruption. In this case all information and the documentation of the DMC's decision is immediately brought to FDA's attention for further review at FDA's discretion.

Stopping Rule 2: Occurrence of Severe Hypotensive Events

If, during the roll-in/proficiency testing period of approximately 150 donations across three sites, there are:

- 1 or more severe hypotensive events [1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury)] of the IQPP definition, as applied in the plasma center adverse event reporting system, reported to the sponsor,

Or if there are:

- 2 or more severe hypotensive events [1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury)] of the IQPP definition, as applied in the plasma center adverse event reporting system, at any point in the first 10,000 donations, reported to the sponsor,

the DMC will be informed within 24 hours and will perform an unblinded review. The DMC should make a determination by the end of the next business day after the event was reported to the sponsor.

If the DMC determines relatedness and decides that the safety profile of the study should be reconsidered, the study is put on hold immediately. Information of the event and DMC's decision is transmitted to FDA immediately. The study is not resumed unless and until FDA has decided that it is safe to do so.

If the DMC determines that the event is unrelated, or that the safety profile of the study remains unchanged, the study can be continued without interruption. In this case all information and the documentation of the DMC's decision is immediately brought to FDA's attention for further review at FDA's discretion.

10. Risk/Benefit Analysis

10.1 Main Potential Benefits

The potential benefit of the PPN feature lies in its personalized approach to the calculation of the target plasma collection volume. Consequently, the target plasma collection volume would be decreased for approximately 23.5% of donors. The donors that would donate less have, on average, a lower total plasma volume, a lower body weight, and a higher hematocrit than the overall donor population. It is possible that this population of donors will be at lower risk under the target volume using the PPN feature. An additional potential benefit of the PPN feature would be that, on average, more plasma will be collected from subjects, which will help to meet the growing demand for critical plasma therapies without compromising donor safety. Since it is expected that a greater plasma volume will – on the average – be obtained per donor, even in a situation where the number of adverse reactions per procedure will not change, it is possible that relatively fewer apheresis procedures will be required in comparison to current

practices and therefore it is possible that the total number of AEs reported will decrease vs. current practices.

By implementing the nomogram into the device software, the risk of human errors (using the wrong nomogram, misreading tables) is expected to be reduced in comparison to the manual processes that were used prior to 1992 as explained above.

10.2 Main Potential Risks

Since, on average, higher plasma volumes will be collected for the majority of donors, it is possible that the rate of hypotensive (vasovagal/hypovolemia) events in the clinical trial population may increase, although a collection of 28.5% of plasma volume per donor has been shown to be safe. It is also theoretically possible, but unlikely (as described above) that – due to the slightly higher average volume of citrate solution – the number of citrate reactions may increase. All donors who participate in this clinical trial -- in the control group as well as in the experimental group -- will be undergoing plasma collection procedures with an experimental system. Although donation center staff will receive special training on the proper operation of this system, it is possible that there is an increase in the number of operator errors or technical malfunctions. For example, instead of a 250 mL bag of 4% sodium citrate, a 500 mL bag will be used; however, no more than 350 mL is expected to be used during the procedure. Errors in the use of the system could potentially lead to adverse events due to blood volume changes or the unintended infusion of larger amounts of anticoagulant as is possible with the 250 mL bag. The unintended infusion of large amounts of anticoagulant is also a known potential complication with the currently cleared system. Additional risks that are associated with participation in this clinical trial are detailed in the informed consent.

In order to minimize the risk of confusing the two bags containing the citrate solution and the saline solution, the 500 mL bag with the citrate solution has a smaller hole than the bag with the saline solution. It will only fit on the designated pole of the device for the citrate solution and will not fit on the flat pole designated for saline.

Every effort will be made to train site personnel on the specific requirements of this clinical trial and to minimize the number of protocol deviations. For example, donor height will be verified by measurement prior to enrollment into the clinical trial. Subjects will be asked if they donated plasma outside of the clinical trial at a different center prior to each repeat donation in order to avoid too frequent donations that may jeopardize the donors' safety.

11. Deviations from the Clinical Investigational Plan

11.1 Protocol Deviations

A protocol deviation is defined as any change or alteration from the procedure stated in the clinical investigational plan, consent form or clinical trial materials that were originally provided by the sponsor and approved by the IRB where the change or alteration itself is not IRB approved.

All protocol deviations must be reported to Haemonetics or their authorized representatives (clinical trial monitors) through the eCRF protocol deviation form. All deviations, regardless of whether medically

justifiable (e.g., the subject's safety), shall be reported. In addition, the qualified healthcare provider is required to adhere to the IRB's reporting requirements for protocol deviations.

Qualified healthcare providers are required to maintain accurate, complete and current records, including documentation showing the dates of, and reasons for, each deviation from the protocol. Failure to comply with the protocol may result in qualified healthcare provider termination of participation in the clinical trial

12. Reporting of Adverse Events, Medical Device Reports, and Incidents

The safety of clinical trial subjects is of critical importance for the IMPACT clinical trial. Site qualified healthcare providers are responsible for the safety of subjects under their care.

12.1 Definitions

12.1.1 Regulations

In the United States, currently, the NexSys® PCS (PCS 300 Plasma Collection System) is a Class II medical device; therefore, Medical Device Reporting (MDR) will apply.

Medical Device Report

An MDR reportable event is:

1) An event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury, or
2) An event that manufacturers become aware of that reasonably suggests that one of their marketed devices:

   (i) May have caused or contributed to a death or serious injury, or

   (ii) Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Caused or contributed means that death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in death or serious injury, including events occurring as a result of:

1) Failure,
2) Malfunction,
3) Improper or inadequate design,
4) Manufacture,
5) Labeling, or

6) User error.

Serious injury means an injury or illness that:

1) Is life-threatening,

2) Results in permanent impairment of a body function or permanent damage to a body structure, or

3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended.

12.1.2 Adverse Events

For the purposes of this clinical trial, all adverse events (AEs) will be defined and categorized according to established local guidelines and operating procedures, which are in accordance with IQPP standards (see Appendix 16.1 IQPP Standard for Recording Donor Adverse Events).

12.2 Reporting Adverse Events, Medical Device Reports, and Incidents

The monitoring of AEs will be conducted and reported throughout the clinical trial. All AEs will be captured per established site procedures in compliance with IQPP guidelines and with CFR.

All device-related deaths and device-related serious injuries and device-related malfunctions should be reported to the sponsor within 24 hours of initial awareness of the event. In addition, sites (user facilities) are responsible for the submission of medical device reports (MDR) of device-related deaths and device-related serious injuries and device-related malfunctions to the manufacturer within 10 workdays of initial awareness. Sites are responsible for reporting MDR of device-related deaths to FDA within 10 workdays of initial awareness.

The manufacturer (sponsor) will submit medical device reports (reportable death, serious injury, and malfunction) to the FDA within 30 calendar days from initial awareness. The manufacturer (sponsor) will submit medical device reports (of reportable events requiring remedial action to prevent an unreasonable risk of substantial harm to the public health or a reportable event requested by the FDA) within 5 workdays from initial awareness.

The MDR form must be completed by the site and faxed to +1-781 356 9951 or emailed to PIRDesk@haemonetics according to the timelines specified above.

12.3 Data Monitoring Committee

This clinical trial will use an independent external Data Monitoring Committee (DMC). All voting members of the DMC will be external to Haemonetics. The DMC will meet regularly and will monitor the safety of the trial, according to the DMC charter.

The sponsor's criteria will be shared with the DMC, which will determine, based on these or alternative criteria that they may independently develop, the safety of continuing with the study. This evaluation will be based on a comprehensive review of the available safety information as the clinical trial progresses. The DMC may have access to additional information in its review, e.g., from a requested unblinded data review, that may allow them to come to a more informed decision. Their independent assessment will be shared with the sponsor team.

The DMC will also review data related to the stopping rules, as defined in section 9.10. The DMC will determine if it is safe to continue the trial or will decide to terminate the study. This decision is binding for the sponsor.

13. Data Handling and Quality Assurance

13.1 Documentation of Clinical Trial Findings

13.1.1 Electronic Data Records

Electronic data from the sites' NexLynk® Data Management System will serve as the primary data source for the clinical trial record. This data source will provide information about donor safety as well as effectiveness and will be integrated into a 21 CFR Part 11-compliant database. It will be combined with data from the electronic data capture system. The electronic data capture system will be used to collect trial-specific information, e.g., clinical study-specific protocol deviations, Screen Failure Log and Subject Exclusion Log, withdrawal information, Training Log, Study Staff Log, Site Visit Log, Monitoring Log, possibly informed consent, and randomization assignment.

The clinical trial staff will enter data into the EDC system. Electronic information will be reviewed routinely by the data management team and clinical trial monitors.

All electronic records are to be completed accurately and promptly and should be updated as needed so they reflect the latest information. All records are to be kept in conformance with applicable guidelines and standard operating procedures.

The clinical trial qualified healthcare providers must review and electronically approve all information entered into the database. Corrections to data will be tracked via an audit trail, and each correction will be identified by the person making the change. The time, date, and reason for change will be recorded.

Risk-based monitoring will be employed for this clinical trial to ensure the early detection of any data quality-related issues, e.g., site operator or device performance, to ensure final data integrity.

Details will be outlined in the Data Monitoring Plan, which is part of the Data Management Plan.

13.2 Site Monitoring

In accordance with ICH GCP guidelines, the clinical trial monitor will carry out source data verification at regular intervals to ensure that the data collected are accurate and reliable. The site investigator agrees to cooperate with the monitor. The frequency of remote and on-site monitoring visits will be based on the site's donor enrollment numbers as well as overall clinical trial performance.

The site investigator must permit the monitor, the institutional review board (IRB)/ethics committee, the sponsor's internal auditors, and representatives from regulatory authorities, as required, direct access to all clinical trial-related documents and pertinent manufacturing records for confirmation of data.

Qualified healthcare providers will immediately notify Haemonetics upon learning of planned or unannounced audits or inspections by regulatory agencies. Haemonetics will be given access to all site audit materials for audits conducted by regulatory agencies. It is important that the site investigator(s) and their relevant personnel are available during any audits or inspections and that sufficient time is devoted to the process.

It is important that the site investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

14. Ethical Considerations

The qualified healthcare provider(s) and all parties involved in this clinical trial will conduct the clinical trial in adherence to ethical principles based on ICH GCP guidelines and the applicable national and local laws and regulatory requirements.

14.1 Independent Ethics Committee or Institutional Review Board

It shall be the trial principal investigator's responsibility to determine the institutional requirements for the notification of an IRB/ethics committee and for obtaining approval of this protocol, the related informed consent document, and participant recruitment materials. The trial principal investigator must secure such approval prior to initiating clinical trial procedures. Written approval will be provided by the trial principal investigator for the clinical trial master file and must also be stored in the Site File.

The following information may be required to submit to the committees:

- Type of donor data collected: categorized, de-identified
- External access to donor data (e.g., for source data verification or audit)
- Purpose of the research

14.2 Regulatory Authorities

Relevant clinical trial documentation may be submitted to regulatory authorities, as required, according to local/national requirements.

14.3 Informed Consent

14.3.1 Written Informed Consent

Informed consent will be obtained from all participants in accordance with the IRB policy. The process of obtaining informed consent must be in accordance with applicable regulatory requirements and must adhere to GCP.

The qualified healthcare provider or designated personnel will inform the donor or his/her legal representative of the objectives, methods, anticipated benefits and potential risks and inconveniences of the clinical trial. The donor or his/her legal representative should be given every opportunity to ask for clarification of any points he/she does not understand and, if necessary, ask for more information. The donor or his/her legal representative will be required to sign and date the ICF. The ICF will be kept and archived. A signed and dated copy of the donor ICF will be offered to the donor.

Participation is strictly voluntary and donors may choose not to participate. Participation or lack of participation in the clinical trial will not affect the donors' relationship with the donation site and will not affect their ability to donate under the standard procedure.

If the subject withdraws from the clinical trial and also withdraws consent for disclosure of future information, no further clinical evaluations or procedures will be performed on the donor per the clinical trial protocol and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

14.4 Donor Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB(s)/ethics committees approving this research, and the FDA, as well as that of any other applicable agency(ies), will be granted direct access to the clinical trial donor' original donation records for verification of clinical trial procedures and/or data, without violating the confidentiality of the donors to the extent permitted by the law and regulations. In any presentations of the results of this clinical trial or in publications, the donors' identity will remain confidential.

Donors will be identified by their donor identification number per site procedures.

All personal data collected and processed for the purposes of this clinical trial will be managed by the site investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA)[12] applicable to US and/or state and/or local laws and regulations on personal data protection.

14.5 Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the clinical trial and quality of the data produced. After completion of the clinical trial (end of clinical trial defined as the date of the last donation in the clinical trial), all documents and data relating to the clinical trial will be kept in an orderly manner by the site qualified healthcare providers in a secure clinical trial file. This file will be available for inspection by the sponsor or its representatives.

Essential documents shall be retained for at least 3 years following clinical trial completion or as otherwise instructed by the sponsor or per local regulations if longer. It is the responsibility of the sponsor to inform the clinical trial center when these documents no longer need to be retained. The qualified healthcare provider must contact the sponsor before destroying any clinical trial-related documentation. In addition, all donor medical records and other source data will be kept for the maximum time permitted by the hospital, institution, or medical practice.

Any qualified healthcare provider/institution must seek the review and approval of the Sponsor in writing prior to any dissemination of information including publications, posters and oral presentations/abstracts of data and/or results of the clinical trial. Published data must not compromise the objectives of the clinical trial.

The first publication in a journal, or presentation at a congress, must be based on consolidated data from all centers. Any publications derived from data of this clinical trial must comply with all applicable Haemonetics standard operating procedures (SOPs).

This multicenter trial is designed to take full account of data accumulated from all centers (sample-sized, powered with appropriate error rates), and Haemonetics discourages presenting or publishing data gathered from a single, or small group of centers unless agreed to by clinical trial qualified healthcare providers and Haemonetics in writing.

15. References

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16. Appendices

16.1 IQPP Standard for Recording Donor Adverse Events

IQPP Standard for Recording Donor Adverse Events	IQPP_DAERS_V2.pdf

16.2 IQPP Qualified Donor Standard

IQPP Qualified Donor Standard	QualifiedDonorStdFinal1.pdf

16.3 Important Medical Safety Events

Important Medical Safety Events	Important Medical Safety Events.pdf