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ClinStatDevice

IMPACT STUDY
IMproving **P**lasm**A** Collec**T**ion

Prospective, randomized, controlled, multicenter study to demonstrate safety and effectiveness of the proposed nomogram using the NexSys™ PCS.

STATISTICAL ANALYSIS PLAN

Version 1.0

26-Apr-2020

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VERSION HISTORY

Version #	Version Date (DD-Mmm-YYYY)	Reason and Summary Changes
0.5	22-Oct-2019	Initial Document
0.6	26-Mar-2020	Revision of definitions of analysis data set, sensitivity and secondary analysis, exploratory analysis. Updating interim analysis and adding stopping rules.
1.0	26-Apr-2020	Inclusion and Definition of Extended AE Information Data Set.

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulation
CI	Confidence Interval
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
IQPP	International Quality Plasma Program (Plasma Protein Therapeutics Association)
ITT	Intent to Treat
MITT	Modified ITT (Intent to Treat)
NI	Non-Inferiority
PPN	Percent Plasma Nomogram
QC	Quality Control
SAE	Serious Adverse Event

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1. INTRODUCTION

1.1. STUDY OBJECTIVES

1.1.1. PRIMARY OBJECTIVE

The primary objective of the IMPACT clinical trial is to evaluate the safety of plasmapheresis performed on the NexSys® PCS device with Percent Plasma Nomogram (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 (See Appendix 1 IQPP Standard for Recording Donor Adverse Events). 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 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.

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1.1.2. 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

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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.

1.2. SUMMARY OF THE STUDY DESIGN

1.2.1. BACKGROUND

Prior to 1992, there was no standard nomogram used by all plasmapheresis devices. Each manufacturer produced their own unique nomogram. These various nomograms were based on the variables of height, weight, and hematocrit. Traditionally, the 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

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plasma volume would donate 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 stepwise 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 target collection volume. To reduce this error by simplifying the process, the nomogram variables (height, weight, and hematocrit) were grouped by ranges. However, this simplification led to a significant decrease in specificity. For example, a small change in weight, height, or hematocrit could change the range group the donor belonged to, thus, having a large impact on the target collection volume.

Despite this effort to reduce errors by simplifying the manual calculation, additional risk of miscalculation/human error has remained. Given the possibility of the same site using devices from different manufacturers, multiple versions of lookup tables on the donor floor could occur simultaneously. The risk of a nomogram being used with the wrong device prompted the Center for Biologics Evaluation and Research (CBER) to publish the current Food and Drug Administration (FDA) nomogram in 1992.

1.2.2. GENERAL STUDY DESIGN AND PLAN

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. In an effort to prevent bias, the clinical trial will be blinded to select members of the sponsor study team in

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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 and there is no practical way to hide this from them with certainty (e.g., collection volume in bottle, time of procedure). 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. 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. Prior to enrollment, all subjects will be required to provide written consent.

1.2.3. RANDOMIZATION

Donors will be randomized 1:1 to the experimental or control groups. 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 study group per site. Adverse Event (AE) incidence rates and the expected proportions in the sample groups are expected to be drastically different between the following groups: Males vs females and first-time

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donors vs repeat donors. Thus, randomization will be further stratified by the donor's gender and first-time donor status. As the expected number of repeat donations is expected to be highly correlated with the AE incidence, stratification by expected number of repeat donations for the repeat donor groups might be done as well. This final step of the stratification will be possible under the condition of the availability of historic data through which calculation of expected number of donations for repeat donors could be completed.

Stratified permuted block randomization procedure with variable block sizes will be used. The sizes of the blocks will randomly vary with possible values of 6, 8 or 10.

Allocation of subjects to clinical trial groups will proceed based on the block randomization procedure as outlined above. Once subjects are enrolled, they will be 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. Sponsor will be monitoring the implementation of the randomization procedure for the QC purposes.

Allocation Miss-Assignment means administration of a study procedure other than that which was provided by the randomization assignment. Example: a subject was randomized to the Control group but received the Experimental procedure.

In the event of a protocol deviation caused by Allocation Miss-Assignment the following procedure will be used:

- If the Allocation Miss-Assignment happens at the first donation, the donor will be allowed to continue donating to the study group associated with the administered

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procedure. Their study group assignment will be changed to the administered procedure group and the donor will be expected to donate only in this study group.

- If the donor happens to donate in both study groups (Allocation Miss-Assignment happens after the first donation or it happens twice) the donor will be discontinued. The study group associated with the donor will follow the procedure that the donor administered at the first donation.

2. STATISTICAL CONSIDERATIONS

2.1. GENERAL CONSIDERATIONS

Continuous and discrete modeling techniques will be applied whenever applicable. Distribution summaries will be presented through summary tables data and visualization methods. Stratification analysis by each individual site will be presented. The relationship between covariates will be examined by appropriate statistical methods. The analysis will include distributional summaries, summaries of the means/measures of central tendency of the two (control and experimental) groups obtained by different methods.

Analysis will be performed using SAS 9.4 (or higher) statistical software.

2.2. DEFINITIONS OF ANALYSIS DATA SETS

2.2.1. DEFINITIONS

Study Donor is defined as a study participant who consented to the study and was randomized to a study procedure (control or experimental).

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Study Donation is defined as a donation that took place during the course of the study and is associated with the study donor.

Non-Study Donation is defined as a donation that took place either before the study start date or after the last date of the study.

Study Adverse Event is defined as an adverse event that was reported to be associated with the study donation.

2.2.2. STUDY POPULATIONS

The ITT data set will consist of all study donations were the apheresis procedure was started by "Begin Draw" on the NexSys® PCS device. The ITT population will include all Study Adverse Events.

The Modified Intent to Treat (MITT) data set is a subset of the ITT data set which consists of all complete study donations, as well as all donations associated with a moderate or severe adverse event [not just hypotensive (vasovagal/hypovolemia)] defined according to the IQPP and associated with the study donations. A donation is considered complete if the total plasma volume collected is at least 200 mL. A donation is considered incomplete if the total plasma volume collected is less than 200 mL.

The Per-Protocol (PP) data set will consist of all donations without major protocol deviations where the apheresis procedure is successfully completed collecting at least 90% of the target plasma volume, as well as all study donations associated with a moderate or severe adverse event [not just hypotensive (vasovagal/hypovolemia)] defined according to the IQPP.

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The Extended AE Population (EAEP) is defined as consisting of ITT population with the addition of all the AEs that were reported as associated with Non-Study donations in donors previously enrolled in the study and reported within two calendar weeks post study last day.

3. DATA ANALYSIS

3.1. PRIMARY ANALYSIS

Primary analysis will be conducted on ITT population. Sensitivity analysis will be conducted using MITT and PP populations. Additional sensitivity analysis may be conducted using EAEI population.

3.1.1. STATISTICAL ANALYSIS METHOD

Given the nature of the data where donors contribute multiple data samples (donations), Generalized Estimation Equations Logistic Regression (GEE Logistic) framework for the repeat measures will be used (Halekoh, 2006; Yan J, 2004). The regression equation is presented below with Patient ID representing the random effect, and plasmapheresis method (study group) being fixed effect. Additional covariates are age, gender, BMI, and first-time donor status.

$$Logit(P(AE_{i,t}=1)) = \beta_0 + \beta_{Treatment} \times Treatment_i + \beta_{Age} \times Age_{i,t} + \beta_{Gender} \times Gender_i + \beta_{First\ Comer} \times First\ comer_{i,t} + \beta_{BMI} \times BMI_{i,t} + \varepsilon_{i,t},$$

Corr($AE_{i,j}$, $AE_{i,k}$) is exchangeable across all donors.

$$Corr(AE) = \begin{bmatrix} 1 & \gamma & \gamma & \gamma \\ \gamma & 1 & \gamma & \gamma \\ \gamma & \gamma & 1 & \gamma \\ \gamma & \gamma & \gamma & 1 \end{bmatrix}$$

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AE represents the occurrence of a hypotensive AE (at least one), during the plasmapheresis procedure. *Treatment* is the variable representing plasmapheresis group (1=Experimental group, 0=Control group). For the *Gender* variable 1=Female, 0=Male. In *First comer* variable 1=First-time donor and 0=Repeat donor. First-time donors are those who have never undergone a plasmapheresis procedure. Age and BMI are continuous variables. i represents subject ID and t represents donation number for the given i subject.

Correlation structure within patients will be assumed to be exchangeable. Derivation of the final correlation model is currently in progress. The correlation structure can also be defined with the use of the historic data from the current study centers.

The above modeling will be used to obtain estimates of difference in proportions of significant hypotensive (vasovagal/hypovolemia) AE rates (P_{Exper} - P_{Ctrl}) in experimental and control groups along with its one-sided 97.5% upper limit of the CI calculated with Wald method.

3.1.2. HYPOTHESIS TESTING

Non-inferiority (NI) hypothesis testing framework will be used in the primary analysis.

$$H_0 : P_{Exper} - P_{Ctrl} \geq \delta$$
$$H_a : P_{Exper} - P_{Ctrl} < \delta$$

Where δ is the NI margin and is defined to be 0.0015.

The hypotheses will be tested using comparison of the upper limit of the one-sided 97.5% Confidence Interval (CI) for the rate difference (P_{Exper} - P_{Ctrl}) to the non-inferiority (NI) margin δ. H_0 will be rejected and NI will be demonstrated if the above mentioned upper limit is less than the NI margin δ. Some hypothetical examples are presented in the Figure 1 below.

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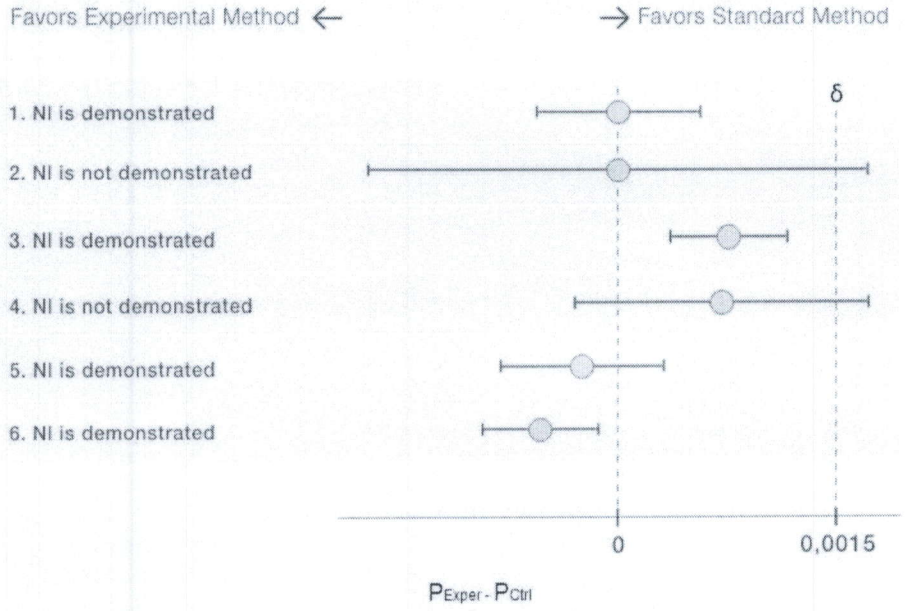
Figure 1: *Some hypothetical examples of Non-Inferiority hypothesis testing*



3.2. SECONDARY AND SENSITIVITY ANALYSIS

Secondary Analysis will be conducted using ITT population. Analysis involving plasma volumes will be conducted using MITT and PP populations.

Analysis of Severe Adverse Events. Given the historical 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 is 1/10000, with probability more than 88% there will be not more than 2 severe hypotensive (vasovagal/hypovolemia) adverse events in 12000 plasmapheresis procedures. Given this historic rate expected number of severe hypotensive (vasovagal/hypovolemia) adverse events will be 1.2

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in each study arm. Thus, formal hypothesis testing will be conducted if there are more than 2 severe hypotensive (vasovagal/hypovolemia) adverse events in any of the two study arms.

Estimates of significant hypotensive (vasovagal/hypovolemia) AE incidence rates will be provided separately for experimental and control groups along with their 95% CIs based on the modeling framework outlined in the primary analysis section.

Secondary analysis will also include the estimation of significant hypotensive (vasovagal/hypovolemia) AE by total collected plasma volume. Modeling framework outlined in the primary analysis section with an additional covariate representing total volume of the collected plasma will be used. Similar statistical modeling framework will be used to estimate the incidence rates of significant hypotensive (vasovagal/hypovolemia) AE by collection time, and the number of collection cycles.

Survival analysis will be used to analyze the time-to-AE (significant hypotensive (vasovagal/hypovolemia)) data. Time to event is defined as time between the procedure start and the occurrence of the AE. Kaplan-Meier curves will be presented. Non-parametric Log-Rank tests will be conducted to evaluate differences between the two study groups. Survival modeling and hazard estimation will be used to obtain parameter estimates for the variables of interest.

Other secondary objectives will be assessed with the use of continuous and discrete modeling techniques whenever applicable. Assessment and comparison of the relative rates will be conducted using repeat measure models and descriptive statistical techniques.

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

Descriptive statistical summaries and advanced data visualization techniques will be used for data presentation.

Detailed description of the analysis related to the other secondary endpoints will be included in later versions of the SAP.

3.3. EXPLORATORY ANALYSIS

Exploratory analysis will be conducted as deemed appropriate. Exploratory analysis will include the estimation of significant hypotensive (vasovagal/hypovolemia) AE occurring during the plasmapheresis procedure at first donation. For this endpoint, every subject will only contribute their first donation to the analysis. Modeling framework outlined in the primary analysis section will be used.

Logistic regression and/or advanced CI estimation methods for binary data will be used to estimate the proportion of donors who experience at least one significant hypotensive (vasovagal/hypovolemia) AE occurring during any of his or her plasmapheresis procedures.

Continuous and discrete modeling techniques will be used whenever applicable. Distribution summaries will be presented through summary tables and visualization methods. Further versions of the document will outline more details related to the exploratory analysis.

Sensitivity analysis may be conducted using a Modified ITT (MITT) and the per-protocol data sets in order to assess the robustness of the findings. Furthermore, to test the sensitivity of the

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results to alternative modelling approach for model selection assumptions, primary and secondary analyses may be conducted using different statistical modeling (including different covariate structure for mixed effect model), different statistical tests and different methods for estimating CIs.

Analysis of key risk indicators, including but 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 will also be included in exploratory analysis.

Estimates of the incidence rate of 1.1 (Prefaint, No LOC (Minor)) hypotensive (vasovagal/hypovolemia) adverse events according to the plasma center adverse event reporting system, based on the IQPP definitions, along with their 95% CIs will be reported separately per experimental and control arms. Estimation will be conducted using Agresti-Coull method (Agresti, 1998). Modeling framework outlined in the primary analysis section may be used to statistically compare incidence rates of 1.1 (Prefaint, No LOC (Minor)) hypotensive (vasovagal/hypovolemia) adverse events between the two study arms. Similar statistical analysis and visualizations will be performed for total AEs by a study arm. The adverse event rates will statistically be compared between the two study arms by testing the null hypothesis of equal AE rates.

3.4. SUBGROUP ANALYSIS

Subgroup analysis will compare AE rates by groups in the subpopulations defined by the following variables:

- First-time donor status (First-time vs Repeat donors);
- Weight (subjects having Weight > 130lbs vs Weight ≤ 130lbs);

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- BMI (subjects having BMI > 30 vs BMI ≤ 30);
- Gender (Males vs Females).

Subgroup analysis may not be powered enough to detect statistically significant differences in AE rates. This may occur when the proportion of the mentioned subgroup in the whole sample is small.

3.4.1. SUBGROUP ANALYSIS DEFINED BY THE FIRST-TIME DONOR STATUS

First-time donors are defined as those who have never undergone plasmapheresis prior to the study. This status will be collected as combination of the donation site historic records and self-reporting by study subjects. This information will be collected prior to randomization as follows: If the donor previously donated at the clinical site then he/she will be automatically in the repeat donor group. If no record of prior donation exists at the site, then donor will self-report the first-time donor status.

There will be two separate analyses for these subgroups performed as follows:

- *Analysis one*: Incidence rates of significant hypotensive (vasovagal/hypovolemia) AE will be compared between the experimental and control arms separately in the first-time and repeat donors, using the data from the first donations only.
- *Analysis two*: Incidence rates of significant hypotensive (vasovagal/hypovolemia) AE will be compared between the experimental and control arms separately in the first-time and repeat donors, using the data from entire ITT dataset (i.e. all donation).

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For analyses one and two estimates of significant hypotensive (vasovagal/hypovolemia) AE incidence rates along with their 95% CIs will be reported for all the subgroups. Estimation will be conducted using Agresti-Coull method (Agresti, 1998). Sensitivity analysis will be conducted using exact method based on a binomial distribution, and Wald method with or without continuity correction. If data allow, additional model based analysis will be performed with the approach outlined in the primary analysis section with introduction of additional categorical covariate representing the first-time donor status (first-time donor=0, repeat donor=1). The coefficient estimate associated with this covariate will be reported along with its 95% CI.

3.4.2. SUBGROUP ANALYSIS DEFINED BY WEIGHT AND BMI

Information on Donors' weight will be collected prior to each donation. Three weight and three BMI groups will be defined.

- High weight group: Donors with weight more than 130lbs throughout the study;
- Low weight group: Donors with weight less or equal to 130lbs throughout the study;
- Borderline weight group: Donors who will have their weight group changed during the study (i.e. their weight will pass 130lbs threshold);
- High BMI group: Donors with BMI more than 30 throughout the study;
- Low BMI group: Donors with BMI less or equal to 30 throughout the study;
- Borderline BMI group: Donors who will have their BMI group changed during the study (i.e. their BMI will pass 30 threshold).

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For low and high BMI and weight subgroups estimates of significant hypotensive (vasovagal/hypovolemia) AE incidence rates along with their 95% CIs will be reported separately per experimental and control arms. Estimation will be conducted using Agresti-Coull method (Agresti, 1998). Sensitivity analysis will be conducted using exact method based on a binomial distribution, and Wald method with or without continuity correction. If data allow, additional model based analysis will be performed with the approach outlined in the primary analysis section with introduction of additional categorical covariate representing weight (or BMI) subgroups.

Data of the borderline groups will be analyzed separately as deemed appropriate.

3.4.3. SUBGROUP ANALYSIS DEFINED BY GENDER

For gender subgroups (Male vs Female), estimates of significant hypotensive (vasovagal/hypovolemia) AE incidence rates along with their 95% CIs will be reported separately per experimental and control arms. Estimation will be conducted using Agresti-Coull method (Agresti, 1998). Sensitivity analysis will be conducted using exact method based on a binomial distribution, and Wald method with or without continuity correction. If data allow, additional model based analysis will be performed with the approach outlined in the primary analysis section with introduction of additional categorical covariate representing gender subgroups.

3.5. SAFETY ANALYSIS

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All AEs will be captured per established site procedures in compliance with IQPP standards and with Code of Federal Regulations (CFR). Safety analysis will be conducted on ITT population. Sensitivity analysis will be conducted on MITT population.

Investigators and sponsor physicians will be reviewing individual subject data throughout the conduct of the trial to ensure subjects' well-being.

Listings of all AEs will be presented. It will include information on occurrence and resolution of AEs: time/date, description and symptoms, study group, etc.

The frequency of AEs will be calculated and summarized. The results will be presented and visualized by IQPP categories and study groups using frequency plots and summary tables. If appropriate, individual AE profiles of subjects will be visualized as well. Comprehensive statistical summaries and comparisons will be presented by a 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. Further safety analysis will include an analysis of the collected plasma volumes at the donations associated with significant or severe AEs. The analysis will be based on estimating the distribution of collected plasma volumes by study arms. Statistical summaries (mean, median, range) will be presented for collected plasma volumes. In addition, the collected plasma volume will be compared with the target plasma volume calculated using control arm algorithm.

Safety events that trigger withdrawal of a subject will be presented by means of a listing, visual summaries, and appropriate statistical analysis.

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3.6. 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. IMPACT EDC engine automatically detects occurance of the stopping rules as defined in the study protocol. Once detected, the system will send automated notifications to prespecified team members. The stopping rules are defined as follows:

Stopping Rule 1: Subject Death

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:

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- 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.

4. INTERIM ANALYSIS

One interim analyses may be conducted, when data from 16,000 apheresis procedures will be available. The interim analysis may result in sample size re-estimation of the sample size in accordance with the promising zone approach. It can be increased to include up to approximately 30,000 donations. Maximum 7,500 donors might be included.

Early termination of the trial due to safety concerns may be possible, when collected data at the interim analysis will provide strong evidence against establishment of non-inferiority at the end of the trial.

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Should the formal interim analysis be conducted, the exact boundaries and decision rules will be finalized at least one week prior to interim analysis unblinding. The SAP will be amended to accommodate these additions.

5. SAMPLE SIZE CONSIDERATIONS

In order to evaluate the operating characteristics of the study design and the analysis methodology, extensive Monte-Carlo simulation study was conducted. The experiment was designed with an objective to mimic the real study as closely as possible (with assumptions presented in Appendix 3). The historic data on significant hypotensive AE rates, study population demographics, first-time donor status etc. was analyzed to inform the simulation study.

This experiment evaluated the relationship between number of subjects, number of donations and the probability of rejecting the null hypothesis for the various assumptions of the true AE rates. Type I error was evaluated for multiple scenarios when the true AE rate of the experimental arm was unacceptably large: $P_{Exper} - P_{Ctrl} > \delta$

NI margin δ is set at level of 0.0015 (0.15%). For the power analysis, 5,000 simulations were conducted and power was calculated as follows:

$$Power = \frac{N(reject\ H_0)}{N_{sim}} * 100\%$$

Power is calculated for rejecting H_0 at significance level of 2.5% (using 97.5% one-sided CI for the AE rate difference).

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Incidence rate of AE in the experimental group is assumed to be 0.0015 (0.15%). The total sample size of 6,000 subjects (3,000 per group) with an expectation of 24,000 total donations yields acceptable profile of power and type I error.

In the scenario when the experimental procedure is at least as safe as the standard one there is greater than 85% power to establish the NI.

Type I error is below 2% for the scenario when $P_{Exper} - P_{Ctrl} = 0.00175$ and is as low as ~ 1% for $P_{Exper} - P_{Ctrl} = 0.0020$.

Performance of the estimation method during the simulations in terms of statistical power for detecting difference in levels of significant AE incidence rate in experimental versus control groups, given the δ=0.0015, in various scenarios is presented below in Table 1.

Table 1: *Performance of estimation method using 24,000 plasmapheresis procedures.*

$P_{Exper} - P_{Ctrl}$	≤0	0.0005	0.00075	0.0010	0.0015	0.00175	0.0020
Power	>85%	68.4%	49.4%	28.5%	5.7%	1.9%	1.1%

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6. REFERENCES

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7. APPENDICES

Appendix 1: IQPP Standard for Recording Donor Adverse Events

IQPP Standard for Recording Donor Adverse Events	IQPP_DAERS_V2.pdf

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Appendix 2: Assumptions for Sample Size estimation

PATIENT ID

100,000 *Pat_ID* are generated starting from 1 to 100,000 (size of population).

GENDER

The variable *Gender* is generated using *Female ratio* = 0.357 as mean. *Gender* follows Binomial distribution:

$$Gender \sim B(0.357)$$

Where *Gender* = 1 for females, *Gender* = 0 for males.

WEIGHT

The variable *Weight* follows Truncated Normal distribution with the following parameters:

Maximum weight: W_{max} = 400 lbs

Minimum weight: W_{min} = 110 lbs

Average weight: μ_{Weight} = 211.2 lbs

Standard deviation of weight σ_{Weight} = 50.85

The assumptions were used based on the clinical site historic information provided byHaemonetics.

HEIGHT

Similar, the variable *Height* follows Truncated Normal distribution with the following parameters:

Maximum height: H_{max} = 84 inches

Minimum height: H_{min} = 56 inches

Average height: μ_{Height} = 68.76 inches

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Standard deviation of height $\sigma_{Height} = 3.86$

The assumptions were used based on the clinical site historic information provided by Haemonetics.

BODY MASS INDEX (BMI)

BMI is calculated for each patient using the following formula:

$$BMI = \frac{Weight(lbs)}{Height^2\ (in)} \times 703$$

AGE

The following proportions of donors are included in the age categories described in Table 1.

Table 1: *Age distribution of patients.*

Age	18-20	21-24	25-44	45-64	65+
Proportions	0.0669	0.1512	0.5235	0.2530	0.0054

When generating ages for the patients we assume that the ages of patients are distributed uniformly within the categories.

ARM

The variable *Method* is generated using *Experimental method ratio* = 0.5 as mean. *Method* follows Binomial distribution:

$Method \sim B(0.5)$

Where *Method* = 1 for experimental arm, *Method* = 0 for standard arm.

NUMBER OF DONATIONS PER PATIENT

Average number of donations per patient is assumed to be 4. Thus, the expected number of occurrences $\lambda = 4$. Number of donations follows Truncated Poisson distribution with the

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following parameters: $\lambda = 4$, minimum number of donations equals 1, maximum equals 24, since FDA recommends that donors must not undergo plasmapheresis more frequently than once in a 2-day (48 hours) period or twice in a 7-day period.

FIRST COMERS

The variable *First comer* is generated from Binomial distribution with the mean parameter $\mu_{first\ comer} = 0.146$:

$$First\ comer \sim B(\mu first\ comer)$$

Where *First comer* = 1 for first comers, *First comer* = 0 for repeat donors.

GENERATION OF ADVERSE EVENTS

AEs for the patients are generated using the method of Emrich and Piedmonte for correlated binary data.

The corresponding function for generating AEs uses the mean vector *Mean AE*, and the correlation matrix *Corr AE* to generate AEs for the patients. Correlation between first donation and other donations within a patient is assumed to be 0.1, while the correlation between repeat donations is assumed to be 0.5.

For example, correlation matrix *Corr AE* for a patient with 4 donations is:

$$Corr\ AE = \begin{bmatrix} 1 & 0.1 & 0.1 & 0.1 \\ 0.1 & 1 & 0.5 & 0.5 \\ 0.1 & 0.5 & 1 & 0.5 \\ 0.1 & 0.5 & 0.5 & 1 \end{bmatrix}$$

Average rates of AEs for the age groups are presented in the Table 3.

Table 3: *Adverse event distributions by age groups of patients.*

Age	18-20	21-24	25-44	45-64	65+
AE rates	0.004579	0.002165	0.0011	0.000827	0.000951

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The mean vector *Mean AE* for a patient with 4 donations includes 4 values, which can be found using the following equation:

$$Mean\ AE = \beta_{Age} * Age + \beta_{Gender} * Gender + \beta_{Method} * Method + \beta_{First\ Comer,Female} * (First\ Comer, Female) + \beta_{First\ Comer,Male} * (First\ Comer, Male)$$

Where coefficient β_{Age} takes the five values of AE rates described in Table 2.

Average AE rate is 0.003831 for females, and 0.001145 for males, so $\beta_{Gender} = 0.003831 - 0.001145 = 0.002686$. The study also demonstrates that average AE rate is 0.01302 for female first comers, compared to 0.002098 for female repeat donors, thus $\beta_{First\ comer,Female} = 0.01302 - 0.002098 = 0.010922$. Average AE rate is 0.003061 for male first comers, compared to 0.00048 for male repeat donors, thus, $\beta_{First\ comer,Male} = 0.003061 - 0.00048 = 0.002581$. Additionally, we assume that donors stop the plasmapheresis after having an AE.

Table 4: *Comparison of variable values in the population data and theoretical targets/historical estimates.*

Variable name	Population data **0** difference of AEs between arms	Population data **0.0015** difference of AEs between arms	Target / historical estimate
Difference of AEs between arms	0.000001228461	0.001518541	0/0.0015

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Proportion of females	0.3570712	0.3578287	0.357
Average weight in lbs	213.7896	214.1136	211.2
Average height in inches	68.76917	68.75169	68.76
Proportion of people with age 18-20	0.06798374	0.06786572	0.0669
Proportion of people with age 21-24	0.1494797	0.1505201	0.1512
Proportion of people with age 25-44	0.5237046	0.5253826	0.5235
Proportion of people with age 45-64	0.2533512	0.2502998	0.2530
Proportion of people with age 65 and above	0.00548081	0.005931791	0.0054
Proportion of donors in experimental arm	0.4989608	0.4954739	0.5
Number of donations per patient	4.055597	4.04431	4
Proportion of first comers	0.14677	0.14501	0.146
AE rates for age group 18-20	0.003010082	0.003825555	0.004579
AE rates for age group 21-24	0.001789587	0.002595483	0.002165
AE rates for age group 25-44	0.00134408	0.002127249	0.0011
AE rates for age group 45-64	0.001201847	0.001669482	0.000827
AE rates for age group 65 and above	0.0002249213	0.002084202	0.000951
β_{Gender}	0.001733372	0.001720488	0.002686
$\beta_{First\ comer,Female}$	0.01431423	0.01592894	0.010922
$\beta_{First\ comer,Male}$	0.003890562	0.003096266	0.002581