Official Title: Evaluation of Impacts of Continuous Non-Invasive Intra-Operative Hemoglobin and RPVi Monitoring on Intra-Operative and Post-Surgical Clinical Outcomes

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Evaluation of Impacts of Continuous Non-Invasive Intra-Operative Hemoglobin and RPVi Monitoring on Intra-Operative and Post-Surgical Clinical Outcomes

Sponsor: Masimo
52 Discovery
Irvine, California 92618

Lead Principal Investigator: [redacted]

Principal Investigators: [redacted]

Study Devices:

Masimo rainbow® SET Radical-7® pulse CO-oximeter with In Vivo SpHb and RPVi features

Masimo Root™ Patient Monitoring and Connectivity Platform

Masimo rainbow® SET pulse CO-oximetry sensors and accessories

Sponsor Protocol Number: BIGT0001

ClinicalTrials.gov NCT#: 02986789

Principal Investigator	Title	Signature	Date
Sponsor	**Title**	**Signature**	**Date**
Vikram Ramakanth	Director, Clinical Research		

1 INTRODUCTION

This document is a clinical investigation plan (CIP) for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with all stipulations of this plan, the conditions of IRB approval, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidelines ICH E6 GCP.

1.1 Background and Rationale

Acute and chronic anemia are associated with increased perioperative morbidity and mortality **[1-3]** Preoperative anemia is reported in many patients scheduled for surgery, with a greater prevalence in older and hospitalized patients.**[4]** However, transfusion of red blood cells is also associated with morbidity and mortality**.[2,5]** Evidence based transfusion guidelines are promoted to decrease unnecessary transfusion**.[6,7]**

Blood management programs are designed to improve patient outcome through preoperative anemia treatment, use of agents that improve hemostasis or clot stability, employing alternatives to transfusion of banked red blood cells, and making individual patient-specific transfusion decisions**.[8,9]** Despite these programs transfusions are sometimes administered to patients when hemoglobin (Hb) has not decreased to a specified minimum acceptable range (inappropriate transfusion) or is continued after this has increased above the specified target range (excessive transfusion**).[10-15]** Shander and colleagues estimated that up to two-thirds of transfusions given to surgical patients considered inappropriate in one study**.[16]**

Red blood cell transfusion is a specific treatment for perioperative anemia or surgical blood loss that is administered when clinicians judge the benefit to outweigh associated risks **[8, 11, 17].** Transfusion decision-making is guided by Hb measurements which are often invasive and intermittent, as well as observed bleeding in the setting of hemodynamic instability. Intermittent Hb measurement can be by blood sample analysis using clinical laboratory hematology analyzers (tHb). In patients undergoing procedures in which blood loss is likely, or ongoing blood loss is not obvious, intermittent Hb measurement can lag the clinical situation. This lag can be increased by long test turn-around time. A real-time and continuous monitor of Hb concentration could provide clinically useful information during surgery in which blood loss is likely or cannot be easily detected. Intravenous fluid is very important to improve hemodynamics of perioperative and critically ill patients. Before fluid infusion, evaluating volume status by monitoring some objective indicators to predict fluid responsiveness can ensure the fluid therapy reasonable and effective, avoiding excessive fluid infusion. Assessment of fluid responsiveness, described as the ability of the circulation to increase cardiac output in response to volume expansion, is essential to guide fluid therapy and optimize preload.

Multi-wavelength pulse co-oximetry is an advanced design pulse oximeter that reports oxygen saturation (SpO2) and uses multiple light wavelengths to additionally determine carboxyhemoglobin, methemoglobin, total hemoglobin (SpHb) in addition to Pleth Variability Index (PVi). Continuous trend monitoring of hemoglobin could be more useful than absolute values to clinicians caring for patients who are at risk for blood loss if changes in SpHb accurately reflect tHb changes. To date, this hypothesis has not been formally tested.

Dynamic indicators relying on cardiopulmonary interactions in mechanically ventilated patients, such as pulse pressure variation (PPV), systolic pressure variation, and stroke volume variation (SVV), consistently have been shown to be more accurate than static indicators in predicting fluid or preload responsiveness **[18–22].** More recently, interest has focused on the availability of pleth variability index (PVi), which is a dynamic variable that automatically and continuously measures the respiratory variations in the pulse oximeter waveform amplitude **[23].**

PVi has also been suggested to be an effective dynamic indicator of fluid responsiveness and is used in many institutions. Recently, Masimo has created a new parameter called RPVi, which is the next generation of the currently available PVi parameter. [redacted] Different from other invasive dynamic indices, PVi provides clinicians with a numerical value noninvasively, automatically, and continuously **[24, 25, 26].** Similar to PVi, RPVi is calculated on the basis of perfusion index (PI). The PI value is generated by pulse oximetry and the scale of absorption of red and infrared light. Division of pulsatile fraction (AC, caused by blood flow) and non-pulsatile fraction (DC, effected by skin and other tissues) of the red and infrared light is summarized by the following formula:

$$PI = (AC/DC) \times 100(\%).$$

RPVi reflects measurements of ventilation induced respiratory changes in PI over a constant period of time and is calculated as follows:

$$RPVi = [(PImax - PImin)/PImax] \times 100(\%)$$ **[27].**

Additionally, the combination of RPVi and SpHb as part of a widely used Pulse CO-Oximeter provides a great opportunity to continuously optimize for both fluids and blood products provided together instead of independently. This may provide the means for mitigating anemia due to fluid overload, thereby providing the benefits of reduced transfusion in addition to the benefits of optimal fluid managements like Length of Stay (LOS) in the hospital etc. **[28].** Hospitals may be able to benefit from quantifiable economic savings and enhanced safety standards. Clinicians may be able to benefit from a real-time feedback for total hemoglobin and fluid information. Patients may be able to benefit from the potential reduction of risk associated with excessive blood transfusions.

2 STUDY DEVICE

2.1 Study Devices

- Masimo rainbow® SET Radical-7® pulse CO-oximeter monitoring device (Radical-7®) with rainbow® parameters, including total hemoglobin concentration (SpHb) with In Vivo adjustment, and pleth variability index (RPVi).
- Masimo Root™ patient monitoring and connectivity platform.
- Masimo rainbow® pulse CO-oximetry sensors and accessories.

The Masimo devices are designed as an integrated system to provide real-time, continuous monitoring of subjects during the study. The Masimo rainbow® pulse CO-oximetry sensor is placed onto the subject during data collection. The sensor uses a multi-wavelength light-emitting diode (LED) to pass light through the subject's fingertip to the detector on the other side of the fingertip. Signal data are obtained by passing various visible and infrared lights through a capillary bed and measuring changes in light absorption during blood pulsatile cycles. The detector receives the light, converts it into an electronic signal and sends it to the Masimo Radical-7 pulse CO-oximeter monitoring device for calculation.

Once the Masimo Radical-7 device receives the signal from the sensor, it utilizes proprietary algorithms to calculate various parameters that reflect the subject's physical state. These parameters include functional oxygen saturation of arterial hemoglobin (SpO2), pulse rate, perfusion index (PI), carboxyhemoglobin saturation (SpCO), methemoglobin saturation (SpMet), total hemoglobin concentration (SpHb), respiratory rate (RRa), pleth

variability index (PVi), and/or RPVi. SpHb with In Vivo adjustment and RPVi are investigational features currently not cleared by the FDA.

The Masimo Radical-7 docks to the Masimo Root Patient Monitoring and Connectivity Platform. The Masimo Root acts as a display monitor and charging station for the Masimo Radical-7 Pulse CO-Oximeter.

The study devices are FDA-cleared Masimo devices that have been modified to include features not cleared by the FDA, rendering the devices as investigational devices. Refer to Table 1 for a summary of study devices.

2.1.1 Description of Investigational Features

2.1.1.1 SpHb with In Vivo Adjustment

In certain situations, there could be individual differences between the SpHb value and a laboratory hemoglobin measurement. These discrepancies may be due to sensor placement, anatomical variability, and/or measurement methodology of the lab device. The In Vivo Adjustment feature lets clinicians manually adjust the device's SpHb reading to match that of a corresponding laboratory reference. This feature is CE marked in the European Union.

2.1.1.2 RPVi

RPVi is a noninvasive and continuous measurement of the dynamic changes in perfusion index (PI) that occur during one or more respiratory cycles. [redacted]

Similar to PVi, RPVi is calculated on the basis of perfusion index (PI). The PI value is generated by pulse oximetry and the scale of absorption of red and infrared light. Division of pulsatile fraction (AC, caused by blood flow) and non-pulsatile fraction (DC, effected by skin and other tissues) of the red and infrared light is summarized by the following formula:

$$PI = (AC/DC) \times 100(\%).$$

RPVi reflects measurements of ventilation induced respiratory changes in PI over a constant period of time and is calculated as follows:

$$RPVi = [(PImax - PImin)/PImax] \times 100(\%)$$ **[27].**

2.1.2 Intended use of the Investigational Devices

The investigational devices are intended to be used for monitoring in accordance with K110028 (Radical-7), K142394 (Root), and K081659 (rainbow SET sensors). The cleared devices have been modified to include the following non-cleared software measurements/functions for the IDE study. These measurements/functions are:

- Noninvasive total hemoglobin (SpHb with In Vivo adjustment), and
- Pleth variability index (RPVi) FDA-cleared indications.

The Root with Radical 7 Pulse CO-Oximeter and accessories are indicated for the continuous non-invasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO2), pulse rate, carboxyhemoglobin saturation (SpCO), methemoglobin saturation (SpMet), total hemoglobin concentration (SpHb), and/or respiratory rate (RRa). The Root with Radical 7 Pulse CO-Oximeter and accessories are indicated for use with adult,

pediatric, and neonatal patients during both no motion and motion conditions, and for patients who are well or poorly perfused in hospitals, hospital-type facilities, mobile, and home environments.

Table 1.Summary of Study Devices

Device	**Is the Cleared Device Modified?**	[redacted]	**Does modification change the basic safety* of Device?**
Masimo Root Patient Monitoring and Connectivity Platform	Yes	[redacted]	[redacted]
Masimo Radical-7 Pulse CO-Oximeter Device	Yes	[redacted]	[redacted]
Masimo Rainbow Pulse CO-Oximetry Sensors (R1-25)	Yes	[redacted]	[redacted]

**** Basic safety definition: electrical, mechanical and fire in accordance with IEC 60601-1.***

2.2 Device Accountability

2.2.1 Device Records

The sponsor will keep records to document the physical location of all investigational devices from shipment of the investigational devices to the clinical sites until return or disposal.

The principal investigator or a designated site staff shall keep records documenting the receipt, use, return and disposal of the investigational devices using the Device Accountability Log provided by the sponsor.

2.2.2 Receipt of Study Device

Upon receipt of the study devices, an inventory must be performed and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

2.2.3 Use of Study Device

Use of devices and sensors will be documented on case report forms for each subject.

2.2.4 Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices and sensors shipped, devices/sensors used, and devices/sensors remaining. This reconciliation will be logged on the device accountability log. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed on site will only be upon written instruction from the sponsor and will be documented in the study files.

3 STUDY DESIGN AND OBJECTIVES

3.1 Overview of the Study Design

This is a sequential, stepped-wedge, controlled, multi-center study with a total enrollment of approximately 2304 subjects across all participating sites (See Figure 1). There will be six clinical sites participating in this study. One interim analysis and one final analysis will be performed.

All control group subjects at each participating clinical site will be enrolled prior to the enrollment of the intervention group subjects. [redacted]

The retrospective control group will involve the collection of historical medical records from patients who had undergone similar surgeries as the prospective control and intervention groups. Subjects for the retrospective control group will be selected at random from a list of eligible patients. Refer to Section 5.1.2 Subject Selection Methods for details on selection of the retrospective control subjects.

The prospective control group will be treated as per standard of care. The prospective control group subjects will be given the study device in order to collect In Vivo SpHb and RPVi data during the surgery for post-study analysis; the recorded In Vivo SpHb and RPVi measurements will not be viewable to the investigators, rendering them blinded to In Vivo SpHb and RPVi data during the surgery.

The prospective intervention group will be treated as per standard of care with the addition of non-invasive In Vivo SpHb and RPVi monitoring via the study device as per the procedure stated in the Study Procedure section in this CIP.

Subjects for both prospective control group and intervention group will be enrolled on a convenience sampling basis from hospital patients who are already scheduled for surgery. Refer to Section 5.1.2 Subject Selection Methods for details on selection of the prospective subjects.

Patients' characteristic data such as demographics, skin tone, ASA status, surgery type, etc. will be recorded as part of the study Case Report Form (CRF) and analyzed for comparability between control and intervention groups.

3.2 Rationale for the Study Design

The stepped-wedge design will minimize potential treatment contamination between control and intervention participants, by completing the enrollment of the control group before enrollment of the intervention group. The stepped-wedge design is being employed to mitigate for any potential temporal variability in patient population and variability in institutional standard of care procedures.

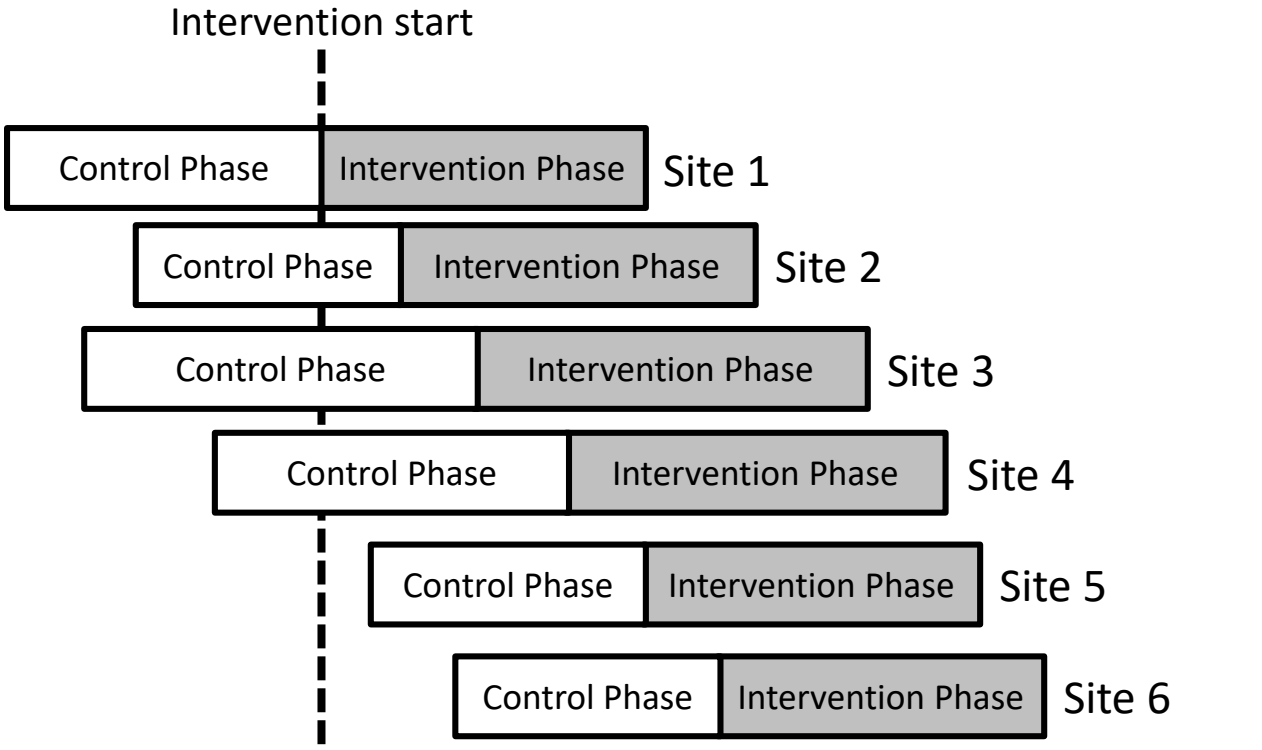


Figure 1. Overview of study design as a stepped wedge implementation. [redacted] Intervention phase each consist of 100% prospective cases. Note: the length of the Control and Intervention phases may be different from site to site depending on enrollment rate.

3.3 Minimization of Potential Bias

Investigator's behavior may be biased due to the Hawthorne/Observer effect. There is the possibility that by simply participating in the study, the investigator may change his/her behavior in terms of blood transfusions because he/she is aware of the study objectives.

By using retrospective controls which establish a historical baseline through chart review and by comparing the blood transfusion patterns/behaviors of the investigators in the prospective control group cases against the retrospective control group cases, possible alteration of behavior by the study investigators from past blood transfusion practice patterns, if any, can be identified and addressed during data analysis.

3.4 Hypothesis

The addition of real-time, continuous, noninvasive, intra-operative SpHb with In Vivo adjustment and RPVi monitoring via study devices to current hospital standard of care parameters will lead to reduction of total volume of blood transfusions during major surgical procedures. Reduction in total blood transfusion will in turn lead to reduction of complications related to blood transfusions thus shortening length of stay (LOS) for patients and improving clinical outcomes. The real-time, continuous In Vivo SpHb and RPVi data will help shorten the time between detection of patients' changing hemoglobin and fluid status and subsequent clinical decisions for transfusion and infusion.

3.5 Study Objectives

3.5.1 Primary

To determine whether the addition of SpHb with In Vivo adjustment and RPVi monitoring using the study device will reduce overall allogenic transfusion, where reduction is defined as the decrease in volume of transfusion of the intervention group relative to control group, intra-operatively.

[redacted]

3.6 Study Outcome Measures

3.6.1 Primary

Volume (mL) of allogenic red blood cells (RBC) transfused intra-operatively.

[redacted]

3.7 Study Safety Endpoint

All investigational devices in the study are non-invasive and present minimal risks to the subjects. Safety data, including the number of occurrences of Adverse Events, Serious Adverse Events, and Unanticipated Adverse Device Effects for each study group will be collected during the study. The safety data will be periodically evaluated by the Sponsor and the Data Safety Monitoring Board to ensure subject safety. At the end of the study, all safety data will be analyzed to determine whether or not there was a significant difference between the occurrences of Adverse Events seen between the intervention group and the control group.

4 CLINICAL TEST SITES AND KEY PERSONNEL

There are six clinical sites participating in this study: Sites may start enrollment in any order, except for Baylor University Medical Center, which shall be the first site to enroll.

Table 2. List of Participating Clinical Sites and Principal Investigators.

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

Approximately 2304 adult subjects undergoing major surgical procedures associated with possibility of significant blood loss will be enrolled into this study. [redacted]

5.1.1 Study Groups:

[redacted]

[redacted]

5.1.2 Subject Selection Methods:

- For the retrospective control group, the study biostatistician will receive a list of patients whose surgeries were overseen by study anesthesiologists. Only the patients' medical record number (MRN) will be provided. Patients from this list will be selected randomly for screening and enrollment. The selected patients will be screened based on study eligibility criteria, and those who meet eligibility criteria will be enrolled to the retrospective control group. Ineligible patients will be replaced by randomly selecting additional patients from the list.
- Prospective control and prospective intervention groups will be selected based on a convenience sampling from eligible patients that have scheduled surgery at the clinical site based on a screening review of their medical records. Patients will be enrolled into the control group until the required number of control subjects have been met, after which time the intervention group enrollment shall commence.

5.2 Inclusion Criteria

- Adult patients undergoing major surgeries associated with possibility of significant blood loss (e.g. such that blood is cross-matched and available before the start of the case as per hospital routine practice) under general anesthesia.
- At least one finger available and accessible for performing non-invasive hemoglobin monitoring.

5.3 Exclusion Criteria

- Patient has skin abnormalities affecting the digits such as psoriasis, eczema, angioma, scar tissue, burn, fungal infection, substantial skin breakdown, nail polish or acrylic nails that would prevent the proper fit and application of the sensors
- Procedures performed using robotics surgery
- Any patients with a known hemoglobinopathy
- Any patients undergoing Cardio-Pulmonary Bypass (CPB)
- Any patients who cannot be transfused or has refused consent for a blood transfusion
- Patients being treated by any artificial oxygen carriers within 30 days of hospital stay
- Patients being managed outside of an operating room in the participating centers, or in operating room with conditions not conducive to perform and complete the study procedures (including use of the hemoglobin monitoring device)
- Patients younger than 18 years old
- Patients who are pregnant
- Patients with cardiac arrhythmia
- Patients with tidal volume setting < 6ml/kg
- Patients with PEEP >= 10cm H_2O
- Patients undergoing cardiac and/or any open chest procedures

- Emergency patients due to the foreseeable difficulty in consenting
- Patients deemed not suitable for study at the discretion of the Principal Investigator

5.4 Study Timelines

Enrollment period for the study is set to be 6-12 months with possible extension depending on individual site's enrollment progress.

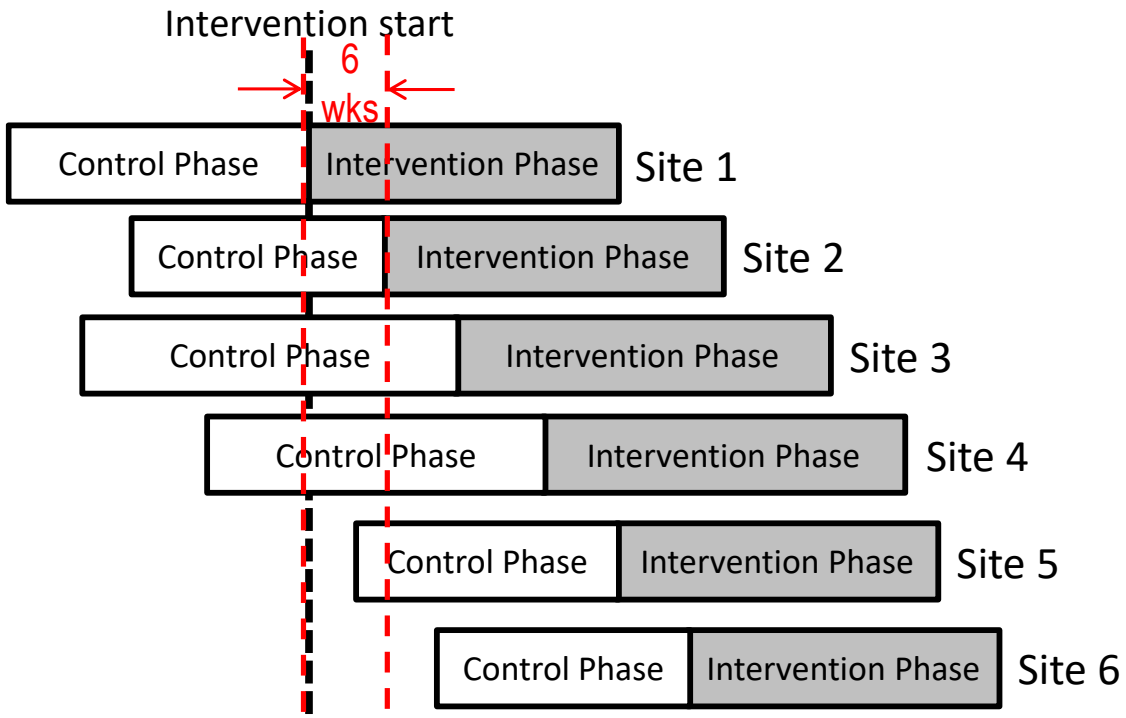


Figure 2. Study Timelines: at intervention start, the first site will begin prospective use of in vivo SpHb and PVI. Subsequent sites will start their respective Intervention Phase 6 weeks after the start of Intervention Phase of the previous site. Note: length of the Control and Intervention Phases may be different from site to site.

Following the stepped wedge design, Site 1 will start control phase enrollment. After all prospective control group subjects have been enrolled, Site 1 will commence enrollment in the intervention phase. All subsequent sites will start their respective intervention phase approximately 6 weeks after the intervention phase start time of the previous site. Therefore, after approximately 24 weeks or 6 months, all sites should be participating in the intervention group. The entire clinical investigation is anticipated to last approximately 12 to 24 months to complete depending on participating sites' enrollment progress.

5.5 Subject Recruitment and Screening

For the retrospective control group, the study biostatistician will receive a list of patients whose surgeries were overseen by study anesthesiologists. Only the patients' medical record number (MRN) will be provided. Patients from this list will be selected randomly for screening and enrollment. The selected patients will be screened based on study eligibility criteria, and those who meet eligibility criteria will be enrolled to the retrospective control group. Ineligible patients will be replaced by randomly selecting additional patients from the list.

Prospective control and prospective intervention groups will be selected based on a convenience sampling from eligible patients that have scheduled surgery at the clinical site based on a screening review of their medical records. Patients will be enrolled into the control group until the required number of control subjects have been met, after which time the intervention group enrollment shall commence. The site staff will clearly inform the patient regarding which group (control or intervention) the patient will be enrolled into.

All subjects will have their medical history reviewed at the time of screening, after informed consent has been obtained, by either the PI or study staff who are delegated for this task. Subjects will be evaluated based on the inclusion and exclusion criteria to determine eligibility to be enrolled into the study. If the subject meets all eligibility criteria, the subject will be enrolled in the study. Enrollment into the either the control group or the intervention group will depend on the phase of the study the site is conducting. Subjects will be informed prior to enrollment as to which group he/she will be enrolled into. The group that the subject is being enrolled into will be clearly indicated on the ICF.

Information regarding the subject's demographic (including, but not limited to age, weight, race, ethnicity, comorbidities, medications, etc.), preexisting allergies, skin abnormalities, and other preexisting diseases/conditions that may be relevant to the study will be recorded within the CRF.

5.5.1 HIPAA Waiver

The pre-screening of patients will require the investigators and designated study staff to access personal health information to identify prospective subjects without HIPAA authorization prior to obtaining written informed consent for the study. Informed consent and HIPAA authorization will be obtained during recruitment and screening procedures as described in previous sections of this clinical investigational plan; however, pre-screening process would require a waiver of HIPAA authorization, as the research study could not be practicably carried out without this implied waiver of consent. The participants' rights and welfare will not be adversely affected by this HIPAA waiver. Patients' protected health information (PHI) will not be inappropriately reused or disclosed to any other person or entity. To further safeguard all protected health information, the data collected during the study will not be labeled with any personal identifying information. The data will not be stored with any protected health information identifiers.

5.6 Informed Consent

The retrospective control group of this study meets the requirements for waiver of consent, as defined in FDA guidance document titled: "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects; Guidance for Sponsors, Investigators, and Institutional Review Boards", released July 2017. As approved by the IRB, documentation of informed consent will not be required for the retrospective control group involving only medical chart review and collection of de-identified historical information.

A written informed consent will be required for the prospective groups in the study. All items of the Informed Consent will be explained in a way that is easily understandable for the patient. The patient will be given adequate time to read through the Informed Consent, and they will be given adequate time and privacy to consider the decision of whether or not to sign the Informed Consent Form. Once all of the patient's questions have been answered and the Informed Consent Form signed, the patient will be

enrolled as a study subject, at which time the subject will be assigned a unique study identification number.

5.7 Withdrawal of Subjects

Informed consent discussions will explicitly include emphasis that neither patient enrollment nor patient withdrawal from the study will result in any alterations to the standard clinical care that he/she will receive. Subjects may elect to withdraw from the study at any time.

In order to obtain the required number of subjects at each clinical site, if a subject withdraws or is withdrawn from the study, the site staff should make arrangements to enroll an additional subject as a replacement. See Section 7.7 Handling Missing Data in Statistical Analysis for details regarding how data from withdrawn subjects will be handled when analyzing study outcome measures.

6 STUDY PROCEDURES

6.1 Control Group

6.1.1 Retrospective Control Group

Approximately [redacted] will be retrospective data collected from the site's medical records. The retrospective data will be collected by designated site personnel only and reported to the sponsor via CRFs.

6.1.2 Prospective Control Group

Approximately [redacted] will be prospective data collection from subjects undergoing surgery. Prospective subjects enrolled in the control arm will be treated per individual clinical site's standard of care (SOC) procedures during and after surgery. The amount of blood transfused, amount of fluid infused, along with other study outcome measures and physiological parameters will be reported on the CRF. In Vivo SpHb and RPVi data will be automatically recorded in the study devices or through a data collection laptop. The display on the study devices will be blacked out so that anesthesiologists will be blinded to the In Vivo SpHb and RPVi monitoring throughout the surgical procedure. All blood transfusion and fluid infusion decisions will be made by clinician's judgment and per SOC procedures. Subjects will receive a phone call from the clinical site staff for a 30-day post-op follow-up on the subject's conditions.

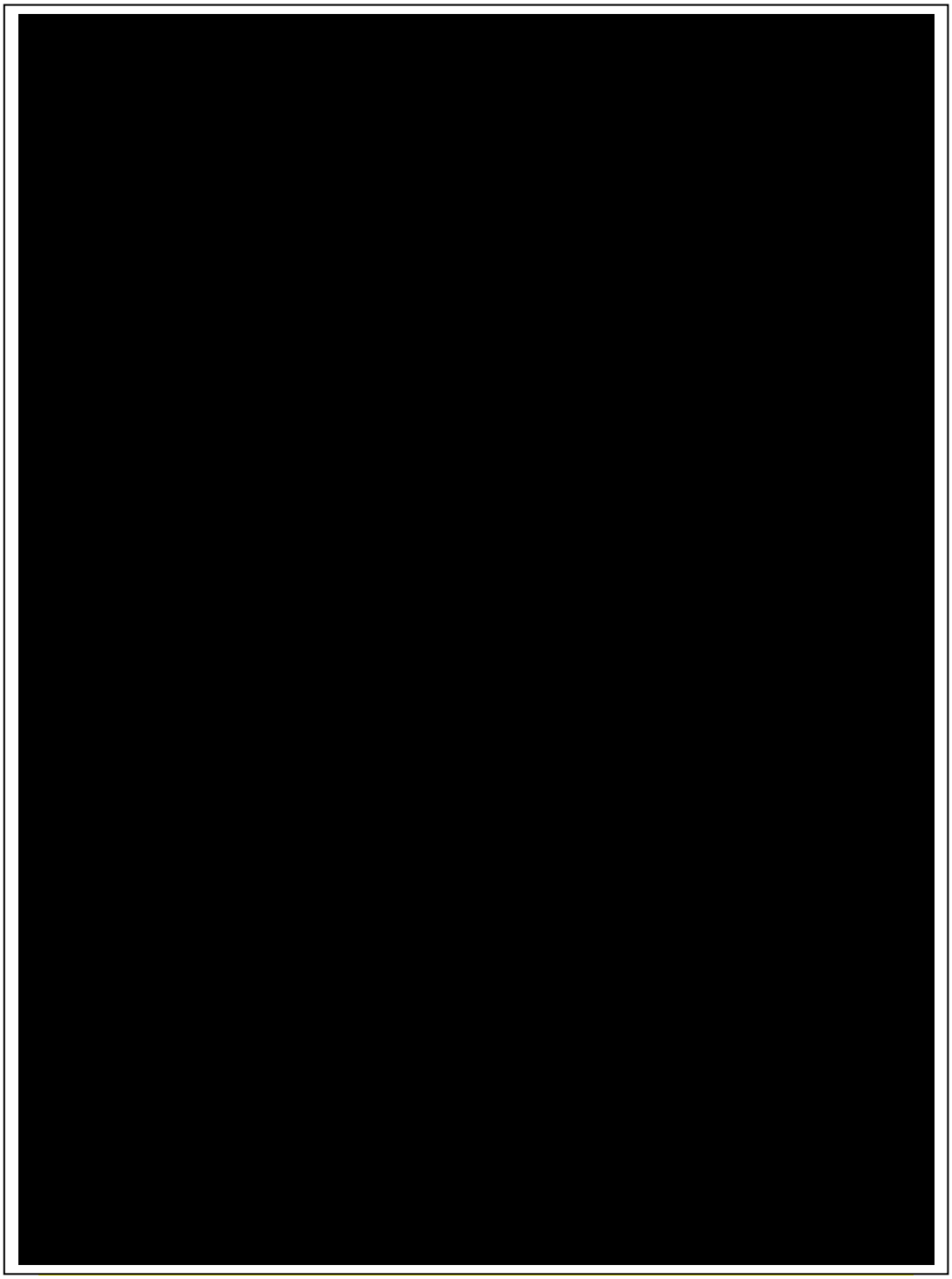
6.2 Intervention Group

Prospective subjects will be enrolled in the intervention group after the control group enrollment phase has been completed. Intervention group subjects will be treated per individual clinical site's SOC procedures during and after surgery. In addition, these subjects will also be monitored with SpHb with In Vivo adjustment and RPVi monitoring devices to trigger confirmatory laboratory blood draws, which will then be used to guide standard of care blood transfusion and fluid infusion decisions. The investigator will make a determination of the threshold for blood transfusion on a case-by-case basis depending on individualized patient clinical conditions. This threshold value will be determined prior to the start of the surgical procedure and it will be recorded in the CRF. Dynamic fluid responsiveness parameters such as RPVi are already in use by many providers to guide fluid infusion decisions, but unlike RPVi, most dynamic fluid responsiveness parameters are often obtained by invasive means, along with other hemodynamic parameters. The procedure for monitoring with In Vivo SpHb and RPVi is illustrated in the

Flow Diagram (Figure 3). The amount of blood transfused, amount of fluid infused, the time of blood draw, the value of tHb, along with other study outcome measures and physiological parameters will be reported on the CRF. In Vivo SpHb and RPVi data will be automatically recorded and stored in data files. All blood transfusion and fluid infusion decisions will be made by clinician's judgment with additional supplemental information provided by In-Vivo SpHb and RPVi parameters. Subjects will receive a phone call from the clinical site staff for a 30-day post-op follow-up on the subject's condition.

In Vivo SpHb and RPVi readings that signal a change in the patient's status shall be confirmed with a confirmatory blood draw, as shown in the Intervention Group Study Procedures Flow Diagram (Figure 3). At all times, anesthesiologists shall use their clinical judgment and standard of care tools to make blood transfusion and fluid infusion decisions.

6.3 Intervention Group Study Procedures Flow Diagram



6.4 SpHb In Vivo Adjustment and RPVi

6.4.1 In Vivo SpHb:

The SpHb In Vivo Adjustment feature allow clinicians to manually adjust the SpHb parameter to match that of a corresponding laboratory reference for continuous trending. In order to utilize the In Vivo Adjustment feature of SpHb, the device requires the user to enable this feature and input an offset value. The offset value is the difference between a laboratory tHb value from analyzing a blood sample and the displayed SpHb value when the blood sample was drawn. After the offset value has been entered, the device will incorporate the offset as it compute SpHb values. [redacted]

6.4.2 RPVi:

[redacted]

6.5 Laboratory Evaluation

Throughout the study procedure, venous or arterial blood draws will be taken at the anesthesiologist's discretion either as confirmatory blood draws based on the triggers from the Masimo monitor or based on standard of care clinical judgment in support of blood transfusion or fluid infusion decisions. [redacted] Blood samples will be analyzed by the local laboratory with a co-oximeter or an arterial blood gas (ABG) machine. Data on any hemoglobin measurements and/or ABG performed during the surgery will be recorded on the CRF.

6.6 Follow-Up Procedures

For each subject, this study consists of only one visit which occurs on the day of surgery. The only follow-up being performed is a phone follow-up 30 days after the day of surgery. Subjects will receive a

phone call from the research staff to check on subjects' condition and gather information as required in the Case Report Form. This follow-up provides information for secondary outcome measures only.

6.7 Schedule of Activities

Table 3. Study activities and relative time for each subject.

Schedule	Study Activities
Day 0 – 1	Screening
Day 1	Informed Consent
Day 1	Enrollment, Study Data Collection
Day 30 - 40	Subject Follow-Up Phone Call, Case Report Form Completion

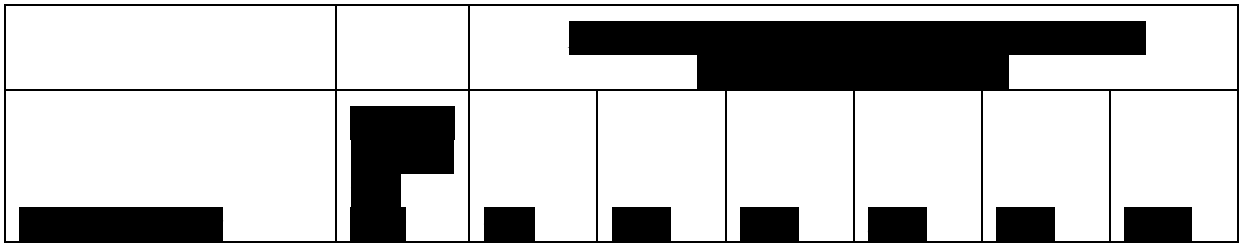
7 SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

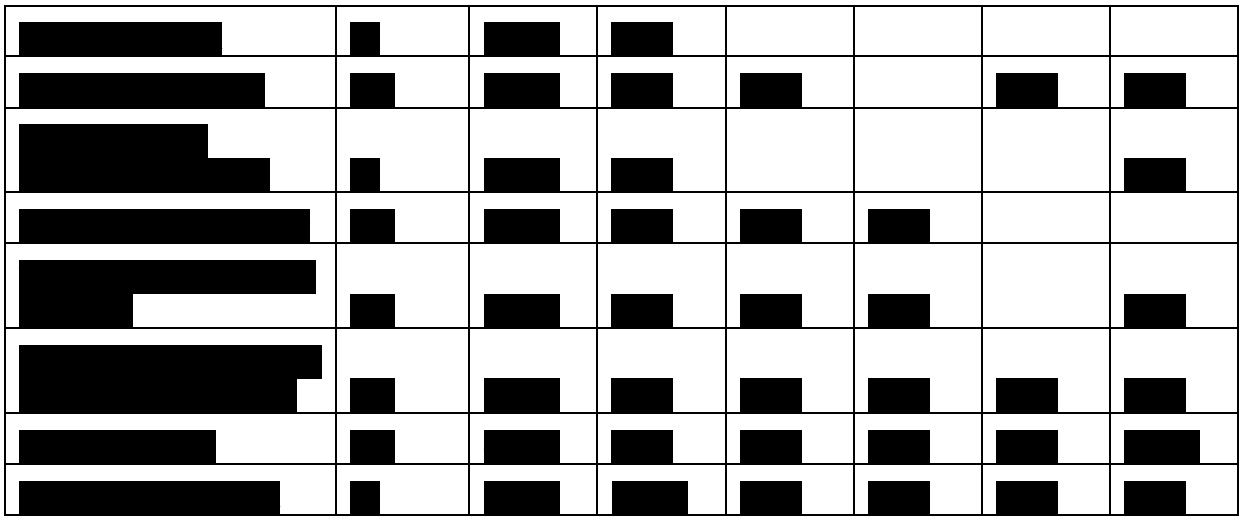
7.1 Power Analysis and Sample Size Determination

[redacted]

7.2 Prior Study Data

[redacted]





[redacted]

7.4 Adjusting For Intra-class Correlation

Assuming that the intra class correlation (ICC = ρ) is 0.001, the estimated sample size from the simulation is adjusted for the design effect (DE) to account for correlation within each Site.

Adjusted Sample Size = Estimated Sample Size x DE

Where DE = 1 + (m – 1)ρ and m equal to the average estimated sample size per site.

[redacted]

Table 5. Sample Size Results

[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
	[redacted]	[redacted]	
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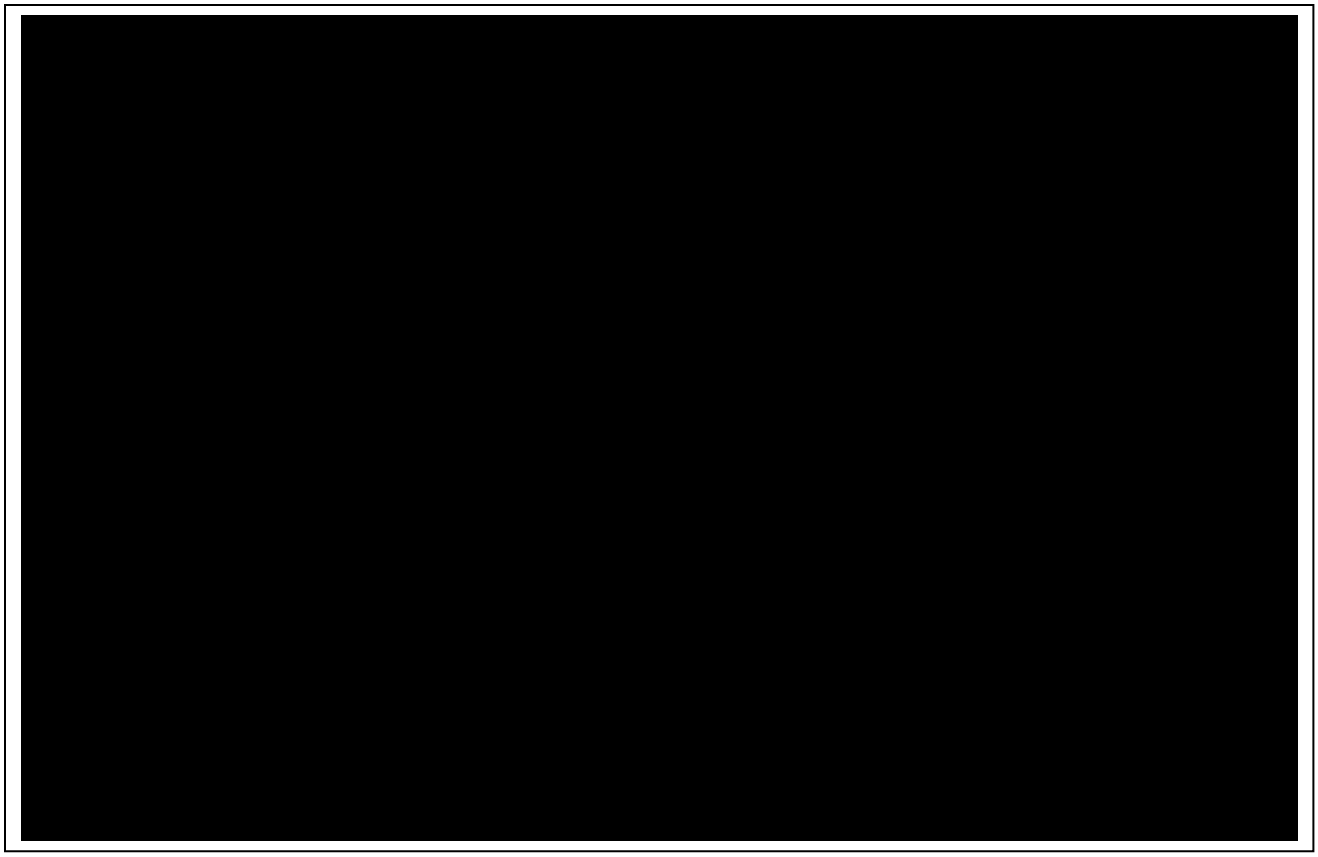

7.6 Data Analysis

7.6.1 Interim Analysis

One interim data analysis and a final analysis will be performed; the interim analysis will be performed after collecting data on 281 subjects in the intervention group and 562 subjects in the control group.

7.6.2 Statistical Analysis

Data from the intervention group will be compared to the control group for statistically significant changes. For those outcome measures that result in statistically significant differences between the intervention and control, study investigators will evaluate the numerical values of the differences for clinical significance. Any study outcome measures determined to be clinically significant are considered successful. All outcome measures will be reported for each site individually and for all sites pooled. Note, exact numerical values for clinical significance are not able to be pre-determined for all outcome measures, as the clinical setting and subject population targeted by this investigation are novel and are difficult to predict.

7.6.2.1 Summary Statistics and Baseline comparisons:

Descriptive statistics will be estimated for each group. Continuous variables will be described by their means, medians, standard deviations, and interquartile ranges. Categorical variables will be described by their frequencies and percentages. Demographics and baseline clinical measurements will be compared

between the groups using ANOVA to compare the means of the continuous variables and Fisher's exact test / Pearson's chi-squared test (χ^2) to compare the rates of the categorical variables.

7.6.2.2 Study Outcomes Statistical Analysis:

Having measurements collected within clusters (clinical site) creates correlated observations. These correlations invalidate the independence assumption in commonly used univariate and multivariate statistical techniques such as t-tests and multiple linear regression. Generalized Linear mixed models (GLMMs) are a flexible class of models that account for correlated observations and thus are a commonly used method for cluster data analysis. This class of model does not require the normality assumption. Generalized linear mixed models will be used for outcomes following a distribution from the exponential family other than normal.

GLMMs will be used to assess the effect of the intervention on continuous and discrete dependent variables. GLMMs differing with respect to their fixed effects, random effects, and residual covariance matrix will be examined. GLMM generally take the form of Equation 1 for baseline observations.

Equation 1. Generalized Linear mixed model assessing intervention effect for a given outcome:

$$y_{ij} = (\beta_0 + \gamma_{0j}) + \beta_1 * \text{int}\,ervention + \sum_{k=2}^{p} \beta_k x_k + \varepsilon_{ij} \qquad (1)$$

The outcome, y_{ij} is the value of a response variable for the i[th] individual of the j[th] cluster (clinical site). The betas represent fixed effects for the intercept (β_0), intervention coefficient (β_1), as well as coefficients (β_2 , …, β_p) for other variables to be included in the model (e.g. demographic and clinical variables). The gamma coefficient (γ_{0j}) represents a cluster-specific random intercept. It is assumed that γ_{0j} has a normal distribution with a mean of zero and a variance of $\sigma^2_{\gamma_0}$.

Type III tests will be used to test the null hypothesis that a specific fixed effect equals zero ($H_0 : \beta_k = 0$). Wald z-tests will be used to test for a significant random intercept ($H_0 : \sigma^2_{\gamma_0} = 0$). Residual and influence diagnostics will be assessed for all models.

Sequential boundary tolerances will be estimated using Lan & DeMets alpha spending function approach.

Statistical analysis will be performed using SAS 9.4 (SAS Institute, Cary, NC)

Table 6. Aims, Outcome Measures and Associated Analysis Planned for those Aims.

Aims/Objectives	Outcome Measures	Planned Statistical Analysis
Reduce overall allogenic transfusion - Volume	Volume of allogenic RBC transfused: Intra operatively	Binomial-Gamma hurdle model. We will include intervention group, demographic and clinical data in the model as progresses.
	Volume of allogenic RBC transfused: Post operatively	

Aims/Objectives	Outcome Measures	Planned Statistical Analysis
	Total Volume of allogenic RBC transfused: Intra and Post	Clinical Site will be the random effect
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Aims/Objectives	Outcome Measures	Planned Statistical Analysis
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Aims/Objectives	Outcome Measures	Planned Statistical Analysis
[redacted]	[redacted]	[redacted]

7.7 Handling Missing Data in Statistical Analysis

Missing data is a potential problem with any study. All efforts will be made to have a complete and valid data set; however, if the situation occurs, where certain data are missing for a particular subject, the following rules shall be followed:

- If volume (mL) of allogenic RBC transfused and total number of units of blood transfused are both missing for a particular subject, and there is indication for blood transfusion, then the subject with the missing data will be excluded from the relevant analysis. If only one value is missing and the other is valid, then estimation for the missing value will be derived from the valid value.
- Missing other outcomes: subjects with missing outcomes data will be excluded from the relevant analysis.
- Missing Covariates: imputations will be used to account for missing covariates; imputation is the substitution of estimate for a missing data point.

7.8 Interim Analysis decisions

The interim analysis will be performed after collecting data on 281 subjects in the intervention group and 562 subjects in the control group.

The Lan-DeMets bounds using O'Brien-Fleming spending function was utilized to calculate the spending alpha. The Overall alpha is 0.05 and One-Sided Bounds

Table 7. Adjusted Alpha and Boundary Results

Analysis	Time	Upper Boundary	Adjusted Alpha	Cumulative Alpha
Interim	0.5	2.5380	**0.0056**	0.0056
Final	1	1.6621	**0.0444**	0.0500

Interim Analysis results will be presented to the principal investigators, the sponsor, and the DSMB for evaluation and decision-making.

7.9 Early Stopping Rules

- Upon review of occurrence of unanticipated adverse device effects and/or other harmful events as a direct result of the clinical investigational procedures, principal investigators, sponsor, and DSMB may decide to terminate the study to safeguard subject safety.
- If the results of the interim analysis show a statistically significant result relating to the outcome measures, then the principal investigators, sponsor, and DSMB may decide to terminate the study.

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, and unanticipated adverse device effect are provided below (ISO 14155:2011, 21 CFR 812.3(s)).

- Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
- Adverse Device Effect (ADE): an adverse device effect is any untoward or unintended response to a medical device which may result from insufficiencies in the instructions for use or deployment of the device, or from use error.
- Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.
- Serious Adverse Device Effect (SADE): a serious adverse device effect is an adverse device effect that results in death, inpatient hospitalization, severe or permanent disability or is life threatening.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life threatening problem or death cause by or associated with, a device, if the effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan, or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects. Refer to the Device Risk Analysis and Risk Assessment section for details on anticipated adverse device effects.

8.2 Anticipated Adverse Events:

- Mild allergic reaction to sensor material and adhesives.
- Low risk of thermal burn from sensor LEDs.
- Low risk of pressure damage if sensors are applied too tightly.

AEs related to surgical procedures are not listed in this CIP.

8.3 Recording and Assessment of Adverse Effects

All adverse events, regardless of treatment group and suspected causal relationship to the investigational device, will be recorded in the sponsor-provided Adverse Event Log at each site. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and, 2) an assessment of the casual relationship between the adverse event and the investigational device.

Adverse event findings associated with the investigational device will be followed until the event (or its sequelae) resolves or stabilizes at a level acceptable to the Principal Investigator.

8.3.1 Causality and severity assessment

The Principal Investigators of each participating clinical site will promptly review adverse events to determine 1) if there is a reasonable possibility that the adverse event was caused by the investigational device and 2) if the adverse event meets the criteria for a serious adverse event.

If the Principal Investigator's final determination of causality is "unknown and of questionable relationship to the investigational device," the adverse event will be classified as "Related" with the use of the investigational device for reporting purposes. If the Principal Investigator's final determination of causality is "unknown but not related to the investigational device," this determination and the rationale for the determination will be documented in the respective subject's sponsor-provided adverse event report form.

8.4 Adverse Event Reporting

8.4.1 Investigator reporting of adverse events to the sponsor

- The investigator must document all adverse events, whether related or unrelated to the study device(s) and/or unanticipated or anticipated in the Adverse Event section of the CRF, and in an Adverse Event Log, which is to be kept in the clinical site's regulatory binder.
- All study device related adverse events and serious adverse events, both anticipated and unanticipated, must be recorded in detail in the sponsor-provided adverse event report form.
- The investigator shall submit to the sponsor a report of any Unanticipated Adverse Device Effect (UADE) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

8.4.2 Investigator reporting of adverse events to the responsible IRB

- The investigator shall submit to the reviewing IRB a report of any UADE as soon as possible, but in no event later than 10 days after the investigator first learns of the effect. These reports shall be submitted according to the local IRB's requirements.

8.4.3 Sponsor reporting of adverse device effects to the FDA

- The Sponsor shall report the results of any evaluation of an observed or volunteered adverse event that is determined to be an UADE. The sponsor shall report the results to FDA, all reviewing IRBs, and investigators as soon as possible, but no later than 10 working days after the sponsor first receives notice of the effect.
- If the results of the Sponsor's follow-up evaluation show that an adverse event that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting, the Sponsor will submit a report of the results of the evaluation to FDA, reviewing IRBs, and investigators as soon as possible, but in no event later than 10 working days, after the determination was made.
- At regular intervals, and at least yearly, the Sponsor shall submit progress reports to all reviewing IRBs and to FDA.

8.5 Additional Reporting Requirements for EU sites

- The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of the Medical Device Directive 90/385/EEC and 93/42/EEC, respectively:
  - Any SAE,
  - Any Investigational Medical Device Deficiency that might have led to a SAE if (a) suitable action had not been taken or (b) intervention had not been made or (c) if circumstances had been less fortunate,
  - New findings/updates in relation to already reported events.
- All reportable events must be reported by the sponsor or the sponsor's authorized representative to the National Competent Authorities (NCAs) where the clinical investigation has commenced at the same time.
- The sponsor or the sponsor's authorized representative must report to the NCAs according to the following timelines:
  - For a SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it, the sponsor or authorized representative must report to the NCAs immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
  - For any other reportable events or a new finding/update to it, the sponsor or authorized representative must report to the NCAs immediately, but not later than 7 calendar days following the date of awareness by the sponsor.
- The clinical site must report the reportable events to the sponsor in a timely manner, but not later than within 3 calendar days after the occurrence of the event. The Principal Investigator of a particular clinical site may delegate the task of reporting to a site staff, but has ultimate responsibility in this matter.
- When providing SAE reports to the NCAs, the sponsor or the sponsor's authorized representatives will use the standardized SAE reporting form provided by the European Commission website.

[redacted]

8.6 Withdrawal of subjects due to Adverse Device Effect

In the event that an Unanticipated Adverse Device Effect occurs, the Principal Investigator may immediately remove the investigational device from the subject and withdraw the subject from the study. The PI will then need to follow any AE reporting guidelines as stated in the CIP.

8.7 Deviations from the study protocol

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated, except for deviations to protect the rights, safety, and well-being of human subjects in an emergency. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects,

must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

All deviations from the protocol will be recorded in a protocol deviation form provided by the sponsor, and will be promptly reported to the sponsor by the clinical site. All protocol deviation forms require signature and date from the Principal Investigator before being send to the sponsor. Upon receipt of the protocol deviation form, the sponsor will make an assessment of the protocol deviation and resolve it in a timely manner. The sponsor will determine the necessary resolution to the protocol deviation and record the resolution in the protocol deviation form.

Corrective and preventive actions and principal investigator disqualification from the study will be determined by the sponsor on a case by case basis as the deviations occur. The sponsor will assess the nature and impact of the deviation in order to take appropriate actions to correct and prevent reoccurrences of the same deviation. The sponsor will assess the frequency and severity of the deviation in order to make a determination for possible PI disqualification from the study.

8.8 Withdrawal of IRB approval

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

8.9 Suspension or Termination of Clinical Site

The sponsor can suspend or prematurely terminate any PI's and site's participation in the study, particularly if sponsor finds serious non-compliance by the PI or site, and if such non-compliance was not resolved in a timely manner. The sponsor will document the decision to suspend or terminate the investigation in writing. A suspended study site cannot enroll new subjects.

If the sponsor determines that any study site's compliance to be inadequate at any point during the study, and sponsor move to suspend or terminate the study site, the sponsor will provide notification in writing to that site's principal investigator. The study site is eligible for reinstatement upon correction of any findings and any open action items prior to the suspension, and provides a written guarantee that the same non-compliance will not reoccur in the future. Site can only resume patient enrollment upon receiving written notification of reinstatement from the sponsor.

If for any GCP and Regulatory non-compliance reasons the study site is prematurely terminated by the sponsor, then the study site is not eligible for reinstatement under the same Clinical Investigational Plan/Study Protocol.

8.10 Termination of Clinical Investigation due to UADE

The clinical investigation may be terminated if sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the subjects. Termination shall occur no later than 5 working days after the sponsor makes this determination, and no later than 15 working days after the sponsor first received notice of the effect. Sponsor shall follow the appropriate reporting guidelines described in earlier section.

Additional European Commission (EC) requirements:

The manufacturer or his authorized representative shall notify the competent authorities of the Member States concerned of the end of the clinical investigation, with a justification in case of early termination.

In the case of early termination of the clinical investigation on safety grounds this notification shall be communicated to all Member States and the European Commission (refer to MDD 93/42/EEC Article 15.7).

[redacted]

9 DATA MANAGEMENT

Study documentation and communication during the study will be centrally managed by the Sponsor. Essential study documents must be version-controlled and reviewed by the Sponsor prior to use at individual sites.

All case report forms and device data files collected will be transmitted securely to the Sponsor via secure file transfer protocol.

9.1 Provisions to Protect the Privacy Interests of Subjects

Potential study candidates will be identified following a review of the surgical schedule. Patient recruitment and informed consent will be obtained when there is sufficient time for a complete discussion between the investigator and the patient. Recruitment will be by direct discussion between the prospective candidates and the study investigators and/or designated study staff prior to their scheduled surgical procedure. The investigators and/or designated study staff will provide the consent form in person and give the prospective subject sufficient time to review the consent form and discuss the study with friends and family.

9.2 Data Management and Confidentiality

All documents associated with this protocol will be kept in the locked offices or on password protected computers. All data will be de-identified before any statistical analysis. Only de-identified data will be shared with Masimo for research purposes stated in this clinical investigation plan. Data collected by data capture software and data entered in case report form will be transferred to Masimo via a secure, password protected server that only study staff and Masimo study team members will have access to. Blood specimens, if any are required per current clinical investigation plan, will be handled according to standard procedures for biological materials. Sponsors and investigators must maintain the required records for a period of two years after the date the investigation is completed or terminated or the records are no longer required to support a regulatory submission, whichever date is later.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, and copies or transcriptions certified after verification as being accurate and complete.

The site is responsible to ensure to remove all PHI from source documents before releasing to the sponsor.

9.4 Screening and Enrollment Logs

A subject screening and enrollment log will be provided to study site by sponsor, and maintained by study site. The screening and enrollment log will document, at a minimum, information such as the number of subjects approached for informed consent, the date of consent, subject eligibility, subject enrollment status, subject withdraw (if applicable) and reason(s) for withdrawal. Screening and enrollment log will not contain identifiable information relating to the subjects; subjects will only be identified by a unique subject ID number.

9.5 Case Report Forms and Data Acquisition

The sponsor shall provide a Case Report Form (CRF) to the Site (See sample CRF in Appendix A1). The site shall capture study data in the CRFs for each subject enrolled.

In Vivo SpHb and RPVi parameters will be captured automatically via data collection software.

[redacted]

9.5.1 The CRFs will be reviewed and signed by principal investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, it is recommended that the reason(s) be noted on the CRF. Case report forms are to be completed on an ongoing

basis. CRF entries and corrections will only be performed by study staffs that are authorized by the investigator. Entries and corrections to the CRF will be made following Good Documentation Practices.

9.5.2 The CRF will include the following information, including but not limited to: inclusion / exclusion criteria, whether patient consent obtained before start of study, demographic information, type and name of surgery, sensor placement, amount of blood transfused, amount of fluid infused, reason for transfusion and/or infusion, amount of blood drawn, timing of blood draws, other event timing, etc.

9.5.3 CRF entries will be checked by Sponsor personnel after receipt and any errors or inconsistencies will be queried to the site on an ongoing basis. Query resolution will be assessed and confirmed by study monitor during site visit.

9.6 Data Transfer and Storage

9.6.1 Device data will be captured through data capture software provided by the Sponsor (e.g. [redacted] on a laptop) or within the study devices directly. Device data along with the CRF will be uploaded to sponsor via secure transfer methods.

9.6.2 Site will upload device data and CRFs on a weekly basis. Site will provide summary details on the data and CRFs being uploaded to Sponsor. Details may include: how many cases collected during the week prior to data transfer, how many files are being transferred in the current iteration, etc.

9.6.3 Only authorized sponsor personnel will have access to the uploaded data on the secure file transfer portal, and will move it to a secure and backed-up drive at Masimo after receiving the upload from study site.

9.6.4 Device data and CRFs will be checked for completeness. If there are inconsistent or missing data points, a data query list will be generated and submitted to the site for corrections. Once all queries have been resolved, Masimo engineers are notified that data is ready for analysis. To ensure data integrity, Masimo engineers will only have read access to the location where data is being securely stored.

9.7 Data Entry Procedures

In the case that paper CRFs are used for the study, study data will be entered into a database by the appropriate Sponsor personnel. Study data for a particular subject will be entered and verified by two different individuals in order to ensure data quality (i.e. the first data entry person enters the initial data, and a different data entry person will verify the first person's work).

9.8 Data Processing and Analysis

[redacted]

9.9 Record Retention

Study data will be retained by each Clinical Site for the necessary period of time as required by the institution's regulations. Sponsors and investigators must maintain the required records for a period of two years after the date the investigation is completed or terminated or the records are no longer required to support a regulatory submission, whichever date is later. The Institution's own retention policies and regulations may apply in addition to the minimal requirement, but no less than 2 years following study closure.

10 MONITORING PLAN

10.1 As the sponsor of this clinical investigation, Masimo Corporation is required by 21 CFR Part 812 of the Food and Drug Administration regulations to monitor and oversee the progress of the investigation. The monitor(s) assigned by Masimo Corporation to this task will be employee(s) from the Clinical Research department who are trained on departmental SOPs and have adequate experience in conducting monitoring visits. Masimo Clinical Research Associates (CRAs) will be responsible for conducting study monitoring activities for this study.

10.2 In accordance with good clinical practices guidelines, the following monitoring visits shall be conducted at each clinical site to ensure overall regulatory compliance of the study:

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment.
- At least one interim monitoring visit during early enrollment for each the control phase and the intervention phase, preferably when site enrollment has reached 10% of subjects for each phase.
- Interim monitoring visits should occur approximately every 90 days. Depending on the outcome of these visits, Sponsor may conduct additional monitoring visits.
- A final close out visit after the last patient had completed the study.

10.3 Prior to the initiation of the clinical investigation at the site, the monitor will conduct a site initiation visit at each clinical site to ensure that the investigator:

- Understands the investigational status of the test article and the requirements for this accountability. · Understands the nature of the protocol or investigational plan.
- Understands the requirements for an adequate and well-controlled study.
- Understands and accepts his or her obligations to obtain informed consent in accordance with 21 CFR Part 50. The monitor should review a specimen of each consent document to be used by the investigator to assure that reasonably foreseeable risks are adequately explained.
- Understands and accepts his or her obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56, and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study.
- Has access to an adequate number of suitable subjects to conduct the investigation.
- Has adequate facilities for conducting the clinical investigation.
- Has sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by applicable regulations

10.4 Study monitor(s) should visit the investigator at each site frequently enough to assure that:

- The facilities used by the investigator continue to be acceptable for purposes of the study.
- The study protocol or investigational plan is being followed.
- Changes to the protocol have been approved by the IRB and/or reported to the sponsor and the IRB.
- Accurate, complete, and current records are being maintained.
- Accurate, complete, and timely reports are being made to the sponsor and IRB.
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

10.5 Study monitor(s) will initiate contact and set up on-site visits with the investigator. Study monitor(s) will be allowed, on request, access to all source documents needed to verify the entries in the CRFs and to all other GCP-related documents (IRB approvals, IRB correspondences, and ICFs) provided that subject confidentiality is maintained in agreement with HIPAA regulations.

10.6 It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency and accuracy of the data being entered on them.

10.7 During each visit, the monitor will also verify presence of informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs/SADEs and protocol deviations/violations, and check CRF against source documentation. During each visit, the monitor should compare a representative number of subject records and other supporting documents with the CRFs to determine that:

- The information recorded in the investigator's report is complete, accurate, and legible.
- Subjects failing to complete the study and the reason for each failure are noted in the reports.
- Informed consent has been documented in accordance with 21 CFR Parts 50 and 56.

10.8 After each visit, the monitor will provide a monitoring report to the investigator within 4 weeks of visit completion. The monitoring report will detail findings and open action items observed during the visit. Each report should include the following information: the date of the visit, the name of the individual who conducted the visit, the name and address of the investigator visited, and a statement of findings, conclusions, and any actions taken to correct deficiencies noted during the visit. It is the responsibility of the Principal Investigator and Study Coordinator(s) to respond to the findings of the monitoring report, and complete any open action items as soon as possible but no later than 60 days of receiving the monitoring report. Any open action items not completed within the time allowed may be sufficient grounds for study site suspension or termination; it will be up to the sponsor to determine whether any incomplete action items are sufficient grounds for suspension or termination. See Section 13 for details on suspension and termination.

10.9 Depending on the quality of the data and/or changes to factors affecting patient safety, additional monitoring visits may be necessary at the sponsor's discretion.

11 DATA SAFETY MONITORING BOARD (DSMB) MONITORING AND REPORTING PROCEDURES

11.1 DSMB Responsibilities

DSMB responsibilities are outlined by the DSMB Charter, which include but are not limited to the following:

- Evaluate the progress of the clinical investigation;
- Review study performance and safety information;
- Protect the safety of the study participants;
- Make recommendations to the Sponsor regarding the continuation, termination or other modifications to the clinical investigation;
- Ensure the confidentiality of the study data and results of monitoring.

11.2 Sponsor Responsibilities

Sponsor responsibilities are outlined by the DSMB Charter, which include but are not limited to the following:

- Assure the proper conduct of the study;
- Assure collection of accurate and timely data;
- Compile and report Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs), and Unanticipated Adverse Device Effects (UADEs) to the DSMB;
- Report safety concern(s) to the DSMB;
- Prepare summary reports of relevant data for the DSMB, if requested;
- Communicate with regulatory authorities, IRB/EC, and investigators, in a manner that maintains integrity of the data, as necessary.

11.3 Frequency of Data and Safety Monitoring by DSMB

Meetings of the DSMB will be held at least every 90 days, or at the request of the DSMB Chairperson. Meetings can be held telephonically, or in person, or a combination of the two methods.

11.4 Content of Data and Safety Monitoring Report

Interim reports to the DSMB shall be prepared by the Sponsor and the Study Biostatistician. Interim reports to the DSMB shall be provided approximately every 90 days after the date of the first official DSMB meeting. The final format of the reports, tables, and listings are to be determined by the Data and Safety Monitoring Board. Data and Safety Monitoring Reports may include, but are not limited, to the following contents:

- Overall study status (e.g. screening, enrollment, and withdraw status)
- Participant descriptive information (e.g. demographic)
- Safety information (e.g. Adverse Events, Serious Adverse Events, UADEs)

- Study quality (e.g. Protocol Deviations, missing variables on CRFs)

11.5 DSMB Membership and Affiliation

The DSMB for the current clinical investigation will consist of 3 voting members. Members will have expertise related to the therapeutic discipline specific to the panel's purpose. DSMB voting members will be from interdisciplinary specialists appropriate to the trial and may include physicians, medical ethicists, biostatisticians, or other specialists as indicated. The members may be recommended by representatives of the Sponsor but will not be affiliated and will be independent of the research under consideration and the investigational product.

11.6 Conflict of Interest for DSMB

Board members should strive to remain free of conflicts of interest after appointment to the DSMB panel and for the duration of their service. Each DSMB member will sign a non-conflict of interest statement in regard to this clinical investigation.

11.7 Protection of Confidentiality

Study data will be presented to the DSMB in a manner that would preserve the confidentiality of the study participants.

All materials, discussions and proceedings of the DSMB are confidential. DSMB members and other participants in DSMB meetings are expected to maintain confidentiality of the study participants, trial data, and the results of the monitoring.

12 BENEFIT / RISK ANALYSIS

The target patient population for the current investigation is adult patients undergoing major surgical procedures associated with the possibility of significant blood loss. A Benefit and Risk Analysis has been performed by the Sponsor, and the Sponsor has concluded that the anticipated benefits outweigh the potential risks in the current investigation/study. Benefits from the use of the information provided by the study devices have the potential to improve the patient's clinical outcomes, while the risks are minimal and are mitigated by study procedures that require for blood draws to confirm device information. Cross reference IDE application Appendix A4, Benefit and Risk Analysis for the BIGT0001 Clinical Investigation for details.

13 ADMINISTRATIVE ASPECTS

13.1 Confidentiality

All data collected will be kept confidential and de-identified. It can only be accessed by site staff assigned to the study and authorized sponsor personnel. All data collected will be used for research purposes only.

13.2 Publication of study results

The principal investigators of this study plan to publish the study data and results in a peer-reviewed journal when the study is completed.

The specific terms and conditions under which the principal investigators may publish the study will be documented in the mutual agreements set between Sponsor and Institutions of the principal investigators; the agreements will be separate documents apart from the CIP.

13.3 Protocol Amendments

Any deviations from the clinical investigational plan/study protocol will require Sponsor and IRB approval and will be documented by way of an amendment. Before submitting protocol amendment to the IRB, the protocol amendment must be agreed upon and signed by the principal investigator and the sponsor. The protocol amendment will be submitted to clinical site IRB for approval. At a minimum, a clean version of the new protocol amendment will be kept on file by the clinical site and the sponsor, but it is recommended to keep both a clean copy and a redline copy of the protocol amendment. Protocol amendments will need to be version controlled. Clinical site PI and sponsor will retain the IRB approval letter as confirmation that the protocol amendment was approved.

Changes to the investigational plan/protocol amendments will also need to be reported to the FDA via a supplemental IDE application (21 CFR 812.35(a)), with the exception of the following situations:

A. Changes effected for emergency use.
   This exception applies in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to the FDA within 5-working days after the sponsor learns of it (812.150(a)(4)).

B. Changes effected with notice to FDA within 5 days.

   The following changes to the protocol do not require prior approval from the FDA, and may be reported in a 5-day notice to the FDA after the changes have been made, if the changes do not affect:

   1. The validity of the data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied up on to approve the protocol;
   2. The scientific soundness of the investigational plan; or
   3. The rights, safety, or welfare of the human subjects involved in the investigation.

   These changes will need to be supported by credible information. Credible information is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the changes does not affect the rights, safety, or welfare of the subjects. Documentation shall include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing. The sponsor is responsible for initially determining if the changes meet the statutory criteria described in 21 CFR 812.35(a)(3).

C. Changes submitted in annual report
   These are minor investigational plan changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect the validity of data/information; patient risk to benefit relationship; scientific soundness of the plan; or rights, safety or welfare of the subjects (21 CFR 812.35(a)(4)).

[redacted]

14 AGREEMENT BETWEEN INVESTIGATORS AND SPONSOR REGARDING RESPONSIBILITIES FOR GOOD CLINICAL PRACTICE

International Conference of Harmonization (ICH) E6 Good Clinical Practice guidance is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

It specifies general requirements intended to:

- Protect the rights, safety and well-being of human subjects,
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- Assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

The Principal Investigators of the clinical investigation shall:

- Obtain and maintain IRB approval of the study.
- Ensure all subjects are consented prior to enrollment, per FDA Code of Federal Regulations titled 21 CFR 50.
- Ensure only appropriately trained personnel will be involved in clinical investigation.
- Maintain study records mentioned in the CIP.
- Maintain logs for study team delegation, site visit/monitoring, equipment disposition, study team training, subject recruitment and enrollment.
- Evaluate all adverse events and adverse device effects and determining whether the study is safe to continue.
- Allow the sponsor to conduct periodic monitoring of study activities to ensure GCP compliance.
- Not promote device prior to clearance by FDA for commercial distribution, except for academic purposes and scientific presentations.

The Sponsor shall ensure existence and record of all necessary compliance documents, and will conduct monitoring visits to ensure appropriate conduct of the study.

Furthermore, the Sponsor and the Principal Investigator shall agree to the following:

- To conduct the clinical investigation outlined in this CIP in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
- To conduct this clinical investigation in compliance with all stipulations of this plan, the conditions of IRB/EC approval, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidelines ICH E6 GCP.
- To not begin the clinical investigation until the required approval/favorable opinion from the IRB/EC or regulatory authority have been obtained, if appropriate.
- To follow any additional requirements imposed by the IRB/EC or regulatory authority, if appropriate.
- To provide adequate insurance to the study subjects, if appropriate.

The Sponsor shall ensure that all study investigators have signed the Investigator Agreement provided by the Sponsor prior to participating in this study (Cross reference IDE application Appendix A5 for a sample copy of the Investigator Agreement).

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16 APPENDICES

16.1 Appendix A1 – Case Report Form sample

17 DOCUMENT REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made:
[redacted]	[redacted]	[redacted]
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