Official Title: Validation of a pulse oximetry based hemoglobin measurement system. Comparison of plethysmographic variability index to standard methods of guiding fluid and transfusion management in the critically ill adult patients. Validation of Clinical Efficacy of ORI for supplemental oxygen titration.

Date of Protocol: August 10, 2016

NCT Number: NCT02841397

Validation of a pulse oximetry based hemoglobin measurement system. Comparison of plethysmographic variability index to standard methods of guiding fluid and transfusion management in the critically ill adult patients. Validation of Clinical Efficacy of ORI for supplemental oxygen titration.

Sponsor: Masimo
52 Discovery
Irvine, California 92618

Principal Investigator: [redacted]

Study Devices:
Masimo Radical 7 Rainbow monitoring device
Masimo Root Patient Monitoring and Connectivity Platform
Masimo Rainbow ReSposable disposable sensor
Masimo Rainbow Disposable optical sensors
Masimo Fourboard
Laptop for Automated Data Collection (ADC) software
Masimo investigational devices and sensors of a similar use and design as FDA-cleared devices and sensors

Sponsor Protocol Number: DORO0001

IRB: Loma Linda University
Office of Sponsored Research
11188 Anderson Street
Loma Linda, California 92350

[redacted]	[redacted]	**Signature**	**Date**
Sponsor	**Title**	**Signature**	**Date**
Vikram Ramakanth	Senior Clinical Program Manager		

1 INTRODUCTION

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

1.1 Background and Rationale

Statement of the Problem:

Many critically ill patients in the ICU present with significant anemia due to blood loss and body compartment fluid shifts after major surgery, trauma, coagulopathic bleeding, pathologic bleeding, or chronic disease. Maintaining euvolemia and preventing anemia by optimization of both fluid and packed red blood cell (PRBC) transfusion management in these patients can be a daunting task. Studies in critically ill adult patients have shown that both anemia and blood transfusion can be associated with increased morbidity and mortality (1-4). Additionally, both hypo and hypervolemia may deleteriously affect organ function. (5-8). Therefore, maintaining patients within a target hemoglobin (Hb) range and rendering euvolemia could result in improved patient outcomes.

Another challenge in the ICU is weaning ventilated patients so they can be eventually extubated or keeping patients from being intubated if they have tenuous respiratory status. The pulse oximeter and abg are currently used for these objectives. When desaturation is noted on a pulse oximeter it is often a late sign and hence limits salvage maneuvers. One of the key lab values to allow weaning of the ventilator and to know that a tenuous patient is adequately oxygenating is PaO2 from an ABG. Unfortunately getting an ABG is invasive. Also even if an arterial line is present the desire to do multiple checks is limited by resources (respiratory staff to run samples, nurse's availability to draw samples and time delay in obtaining results.)

Background Information:

Previous studies have shown that anemia in critically ill adult patients with nadir Hb less than 9 g/dl and baseline Hb less than 10 g/dl is associated with increased morbidity and mortality, even though many healthy patients can tolerate Hb as low as 5 without evidence of inadequate oxygenation (1,2). ICU patients have been shown to safely tolerate Hb levels in the range of 7-9 g/dl with decreased mortality compared to patients who are transfused to keep Hb between 10-12 g/dl. Except in patients with cardiovascular disease, such as unstable angina or myocardial infarction, there is little evidence to support transfusion of patients to Hb greater than 10 g/dl (3,9,10).

Blood transfusion carries a significant risk and critically ill patients who receive transfusions have an increased mortality versus those who do not. Additionally, there is a positive correlation between an increased ICU/hospital length of stay and the number of units of blood transfused (1,4,9). Blood transfusion also carries a risk of infection and immune mediated transfusion reactions. This creates the potential for unnecessary harm to patients if a blood transfusion is administered without a clear medical indication. Currently, blood loss is measured through monitoring drainage catheter outputs and visual inspection of blood on dressings. The patient's Hb can also be measured intermittently by various means such as arterial blood gas (ABG) analysis, or blood samples sent to the lab, which has to be done multiple times in a patient at risk and which also on its own leads occasionally to significant blood loss. The FDA has recently approved a device for use in adults that provides continuous noninvasive measurement of Hb from pulse oximetry sensors (Masimo Rainbow Co-Oximetry, Masimo Corp, Irvine, CA). This measurement is referred to as pulse hemoglobin (SpHb). The device utilizes more than 7 wavelengths of light with processed algorithms to quantify Hb species. [redacted]. Currently there are no studies demonstrating the utility of SpHb as a guide for transfusion management or its validity in the critically ill ICU patient. [redacted]

It may be that continuous Hb assessment could allow more accurate titration of blood transfusion to maintain Hb levels in a target range. This may result in limiting the total number of units transfused to a patient, the amount of time a patient's Hb level is above or below the target range, and the amount of blood draws for Hb lab checks.

[redacted] This information can be characterized as the Oxygen Reserve Index (ORI). This index is presented on a unit-less scale between 0 and 1 that correlates with arterial oxygen concentrations between 100 and 200mmHg. This index is designed to supplement standard arterial hemoglobin saturation monitoring. (12) Preliminary studies have evaluated the relationship between ORI and paO2 in the general surgical population. (11) In addition, the ORI has been demonstrated to provide a clinically useful advanced warning of impending arterial hemoglobin desaturation in pediatric patients. (13) The relationship between ORI and standard saturation monitoring is characterized by this illustration from the above referenced whitepaper:

Oxygen Reserve Index (ORI) is an index measured noninvasively and continuously to provide an earlier indication of impending hypoxia by extending oxygen monitoring of pulse-oximetry to the moderate hyperoxic (100-200 mmHg) regions.

The device also has the capability to continuously measure the plethysmography variability index (PVI). PVI is calculated automatically and represents the variation in amplitude of the pulse oximeter waveform with respiration (22-24). PVI is analogous to stroke volume variation (SVV), which may be derived from arterial waveform, pulmonary artery catheter, esophageal Doppler, echocardiography or other device measured variations with respiration[redacted] Of course use of this device requires an arterial catheter be placed. Multiple studies have demonstrated that SVV is a valuable tool in predicting fluid responsiveness in mechanically ventilated patients. When SVV is elevated, patients are more likely to respond with increased stroke volume and cardiac output when fluid is administered. The threshold SVV of

12% has been defined in several studies as the best cutoff value for predicting an increase in stroke volume index greater than 5% (25-32).

SVV is not the only arterial waveform derived variable that can be used to predict fluid responsiveness. Pulse Pressure Variation (PPV), which is a pressure-based dynamic variable, has been shown to correlate well with SVV in terms of predicting fluid responsiveness (9). Recently, PVI has also been shown to predict fluid responsiveness and to correlate with SVV and PPV (9). The advantage of PVI, however, is its ability to predict fluid responsiveness by non-invasive means (22-24). Improper intraoperative fluid administration has consequences for patients such as tissue hypoperfusion, increased hospital length of stay, and increased morbidity (18-21). Using PVI as an additional tool to guide fluid management may therefore have a positive impact on patient outcomes.

It is logical that Hb determination should be more accurate when the patient has near-normal intravascular volume. As stated previously, an SVV value of 12% or greater is associated with fluid responsiveness, identifying patients who have abnormally low intravascular volume. These patients may need either blood products or other fluids, as guided typically by hemoglobin measurement. When the SVV is 5% or less, the patient is considered to be normovolemic or possibly hypervolemic. The range of SVV between 6-11%, however, is less clearly defined with regards to fluid status. Recent attempts to delineate whether patients in this range would benefit from fluid administration have been successfully demonstrated in both animal and human studies. The temporary addition of PEEP to the ventilation settings and monitoring the effect on SVV can be used to show "near-hypovolemia" in mechanically ventilated patients. The addition of PEEP results in a decrease in venous return to the right heart and a subsequent decrease in left ventricular stroke volume, which may have significant physiologic effects in a borderline hypovolemic patient. When SVV increases to greater than 12% as a result of the addition of PEEP, the patient is likely hypovolemic and would benefit from a fluid bolus (Y-AA). Again, as PVI is analogous to SVV and PPV, fluid therapy has the potential to be guided by non-invasive measurements and may respond similarly to SVV when PEEP is added to patients who are nearly hypovolemic.

In addition, dynamic parameter measurements like the SVV, PVI etc, can be measured by analyzing the waveforms from various sources as listed in the Table 1 below.

Site	Transducer	[redacted]
Finger Tip	Optical	[redacted]
Radial Artery	Pressure/Flow	[redacted]
[redacted]	[redacted]	[redacted]
Finger Digits	Pressure (Penaz Principle)	[redacted]

Table 1: Hemodynamic parameter measurements waveform sources.

These measurements are affected by both volume status changes and vascular tones, although to varying degrees depending on the measurement site. Any measurement of volume status changes or vasomotor tone changes is made difficult because of the challenges in isolating the exact cause of the signal waveform attribute changes. For example the finger-tip pulse-oximeter is affected the most by vasomotor tone changes whereas the nasal alar pulse-oximeter is more effected by changes in volume status and less so by vasomotor tone. This study hypothesizes to compare the fluid status measurements obtained from various sources and measurement sites.

[redacted]

1.2 Study Devices

The Masimo Radical-7 is a noninvasive monitor that measures arterial oxygen saturation (SpO2), pulse rate (PR), and perfusion index (PI), along with optional measurements of hemoglobin (SpHb), carboxyhemoglobin (SpCO®), total oxygen content (SpOC), methemoglobin (SpMet), Pleth Variability Index (PVI®), Oxygen Reserve Index (ORI™), Acoustic Respiration Rate (RRa®), and Pleth Respiration Rate (RRp). Masimo SET® technology is clinically proven to satisfy all sensitivity and specificity requirements for pulse oximetry. Masimo rainbow® technology uses 7+ wavelengths of light to continuously and noninvasively measure carboxyhemoglobin (SpCO), methemoglobin (SpMet), and total hemoglobin (SpHb®), as well as providing a more reliable probe-off detection. Total oxygen content (SpOC) provides a calculated measurement of the amount of oxygen in arterial blood, which may provide useful information about oxygen both dissolved in plasma and combined with hemoglobin. Perfusion Index (PI) with trending capability indicates arterial pulse signal strength and may be used as a diagnostic tool during low perfusion. Pleth Variability Index (PVI) may show changes that reflect physiologic factors such as vascular tone, circulating blood volume, and intrathoracic pressure excursions. [The utility of PVI is unknown at this time and requires further clinical studies. Technical factors that may affect PVI include probe malposition and patient motion.] Oxygen Reserve Index (ORI) is an index measured noninvasively and continuously to provide an earlier indication of impending hypoxia by extending oxygen monitoring of pulse-oximetry to the moderate hyperoxic regions. Respiration rate can be determined by the acoustic (RRa) or plethysmographic waveform (RRp). [redacted]
FastSat® tracks rapid changes in arterial O2. A detailed description of the Masimo Radical-7 can be found in the attached manual.

Masimo Rainbow sensors: a finger probe that consists of a series of light emitting diodes (LEDs) and photodetectors. First, light is emitted through a capillary bed; then, the sensors detect the transmitted light. The signals from the sensor are processed and used to quantify hemoglobin levels noninvasively.

[redacted]
Data acquisition system: consists of a hardware component connected to a laptop with data collection software used to capture wavelength data.

1.3 Risk/Benefits

The major risks to the patient are related to the surgical procedure, prolonged intubation or initial reason for ICU admission (bleeding, infection, pain, etc). Participation in this protocol places the patient at minimal if any additional risk. Additional blood sampling with each ABG analysis or CBC represents only 0.1% of the estimated blood volume of a 15 kg child and a much smaller percentage in larger patients. The maximum additional volume removed for sampling in one subject (40 mL) represents approximately 3.4% of the estimated blood volume of a 15 kg child and a much smaller percentage in larger patients. It is expected that many subjects will have fewer than 10 blood samples ordered by the ICU care team that would be used for data collection in this study. The small additional volume needed for sampling will not adversely impact the patient. The additional blood volume removed for testing purposes will not be large enough to change transfusion decisions. Pulse oximeters are commonly utilized devices that are considered to be minimal risk. There is theoretically an extremely small risk of damage to the subject's fingers from the device including potential mild allergic reaction to sensor material and adhesives, temporary skin irritation or discomfort associated with exposure to the sensor.

There are no direct benefits to the subject from participation in this protocol. Possible future benefits to society or other patients may occur if the system is shown to be accurate enough to be used in place of invasive determination of Hb or PaO2 in critically ill adult patients.

Safety parameters: Case report forms will be analyzed quarterly by the internal review process of the Department of Anesthesiology/Critical Care Center Research Division. Any adverse events related to protocol participation will be reported to the IRB. In addition, all adverse events will be reported to the sponsor.

2 STUDY DESIGN

This is a sponsored, prospective, nonrandomized, sequential data collection study to be performed in anemic adult patients who are admitted into the Surgical Intensive Care Unit (SICU/8100), Cardiothoracic Intensive Care Unit (CTICU/7100) or Neuro-Multidisciplinary Critical Care Services (NMCCS 8100 or 9100). Noninvasive pulse oximetry-determined SpHb will be compared to ABG co-oximetry and research lab equipment-determined Hb values, Oxygen Reserve Index (ORI) will be correlated with paO2 via ABG, PVI and acoustic waveform data will be compared to the arterial waveform extracted SVV or PPV values. The study goal is to establish the correlation of Hb values determined by the SpHb system with Hb as measured by other validated devices, use ORI to correlate with paO2 in the moderate hyperoxic regions and correlation of PVI with SVV or PPV values.

3 CLINICAL TEST SITE

LLUMC University Hospital
11234 Anderson St
Loma Linda, CA 92354
[redacted]

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

- Admitted into the SICU/8100, CTICU/7100, or NMCCS 8100 or 9100
- Aged 18 years or older
- Mechanically ventilated
- Arterial line placed
- Vigileo/Flotrac System being used for guidance of fluid management

4.2 Exclusion Criteria

- Pregnancy
- Prisoner status
- Extreme hemodynamic instability
- Multiple vasopressors in use with questionable peripheral blood flow
- Lack of appropriate sites for sensor placement
- Patient or patient's legal representative refusal

4.3 Subject Recruitment and Screening

The SICU/8100, CTICU/7100 or NMCCS 8100 or 9100 patient census will be screened by the research team to identify the potential candidates. There will potentially be up to 600 patients participating at Loma Linda University in this study.

4.4 Informed Consent Process

Study team members will approach the subject or subject's legally authorized representative to explain the study. Subject or subject's legally authorized representative will be informed about the potential benefits and risks of participation and informed that their participation is voluntary and their decision will not impact patient care. Subject or subject's legally authorized representative will be given adequate time to read the consent form and ask questions. Once the subject or subject's legally authorized representative have had all the questions answered and agreed to participate, the subject or subject's legally authorized representative will be asked to sign the informed consent form and HIPAA form.

5 STUDY DEVICES

The Masimo Radical-7 is a noninvasive monitor that measures arterial oxygen saturation (SpO2), pulse rate (PR), and perfusion index (PI), along with optional measurements of hemoglobin (SpHb), carboxyhemoglobin (SpCO®), total oxygen content (SpOC), methemoglobin (SpMet), Pleth Variability Index (PVI®), Oxygen Reserve Index (ORI™), [redacted] Masimo SET® technology is clinically proven to satisfy all sensitivity and specificity requirements for pulse oximetry. Masimo rainbow® technology uses 7+ wavelengths of light to continuously and noninvasively measure carboxyhemoglobin (SpCO), methemoglobin (SpMet), and total hemoglobin (SpHb®), as well as providing a more reliable probe-off detection. Total oxygen content (SpOC) provides a calculated measurement of the amount of oxygen in arterial blood, which may provide useful information about oxygen both dissolved in plasma and combined with hemoglobin. Perfusion Index (PI) with trending capability indicates arterial pulse signal strength and may be used as a diagnostic tool during low perfusion. Pleth Variability Index (PVI) may show changes that reflect physiologic factors such as vascular tone, circulating blood volume, and intrathoracic pressure excursions. [The utility of PVI is unknown at this time and requires further clinical studies. Technical factors that may affect PVI include probe malposition and patient motion.] Oxygen Reserve Index (ORI) is an index measured noninvasively and continuously to provide an earlier indication of impending hypoxia by extending oxygen monitoring of pulse-oximetry to the moderate hyperoxic regions. [redacted]. A detailed description of the Masimo Radical-7 can be found in the attached manual. The syringes and sample tubes for the additional blood samples will be provided by Masimo.

Investigational devices to be used in this study are non-invasive prototype sensors similar in design, material, and risk to Masimo FDA-cleared products that may be placed on the fingers, hands, ears, forehead, nose (includes placement on or across alar, nasal cartilage, septum, etc), neck, toes, feet, and/or body, shielded from outside light, and attached to the Masimo Rainbow monitor. The energy output and materials used in the investigational sensors are similar to the FDA-cleared models and pose no additional risk to the subjects. Investigational sensors used in the study have been tested and shown to meet electrical, thermal conductivity, and biocompatibility safety standards. [redacted]

5.1 Device Accountability

5.1.1 Receipt of Study Device

Upon receipt of the of the study device supplies, 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.

5.1.2 Use of Study Device

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

5.1.3 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.

6 STUDY PROCEDURES

6.1 Study Procedures

Routine monitors will be used such as pulse oximeter, blood pressure cuff, 5 lead EKG and additional monitors per discretion of the treating physician. Additionally, up to eight Masimo noninvasive sensors will be placed on the fingers, hands, ears, forehead, nose (includes placement on or across alar, nasal cartilages, septum, etc.), neck, toes, feet and/or body, shielded from outside light, and attached to the Masimo Rainbow monitor. Pulse oximeter sensors will be properly aligned to ensure that the emitter and the detector are across from each other. For the sensors placed on the cavity like ala or septum, the site will be cleared of any pre-existing mucus. A standard pulse oximetry sensor will be placed on an appropriate site and attached to the standard ICU monitor. An arterial catheter will be required for enrollment into the study. A study team member will record various measurements of heart rate, arterial blood pressure, cardiac output, SVV, PPV, PVI and PI, etc. from the different devices used for comparison. High speed arterial waveform data will be electronically collected from the arterial line using data acquisition system. Ventilator waveform data may be collected from the ventilator box.

6.2 Study Duration

Patients admitted directly into SICU/8100, CTICU/7100 or NMCCS 8100 or 9100 may be monitored for up to three days.

6.3 Sample Collection

Each patient enrolled in this trial will have Hb measured and recorded prior to data collection. SpHb data will be obtained continuously or via spot check in SICU/8100, CTICU/7100 or NMCCS 8100 or 9100. During spot checks, blood samples must be obtained simultaneously with noninvasive reading and will thus be coordinated. SpHb will be recorded with each blood draw sample. Additional blood sampling is necessary to validate the SpHb system. For patients over 15 kg weight, at each standard of care ABG sampling an additional 4 mL of blood will be collected for patients in the SICU/8100, CTICU/7100 or NMCCS 8100 or 9100and sent for cell count and cyanomethemoglobin determination by Masimo laboratories. These additional samples will be obtained to a maximum of 10 ABG samples per patient, only when ordered by ICU team. Thus up to 40 mL total additional blood volume may be obtained in one subject. Blood samples will be inverted or rolled 10 times to ensure proper mixing to prevent micro clotting. Patients less than 15 kg will not have any additional blood sampling done at the time of ABG analysis. All decisions regarding fluid management and the need for transfusion will be at the discretion of the attending physicians caring for the patient and will be based on the results of the clinical status and Hb measured by CBC as is customary for transfusion. The time of the CBC draw and corresponding blood samples will be noted as part of the data collection for validation of the system.

6.4 Data Collection

Additional data collection for this study will include demographics such as age, height, weight, [redacted] (skin tone), site dimensions (e.g. finger diameter for finger sensor, alar thickness for nose sensor), pre-existing comorbidities, surgical procedures performed[redacted] and ASA status, medications. Volumes of fluid input (blood, albumin, crystalloid) and output (estimated blood loss, urine output) will also be recorded. Other de-identified data such as ventilator settings, may be collected for data analysis. 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 may be accessed to obtain above defined data.

6.5 Data Analysis

Statistical analyses will be performed using statistical analysis software to determine the correlation between changing hemoglobin concentrations determined by the 3 different methods and spectral absorbance. ORI data will also be analyzed to determine any correlation with PaO2 obtained by ABG. PVI data will be correlated to SVV. Outcome data will be analyzed for any relationships between the inciting event, blood loss and outcome markers to evaluate for any predictive value of inciting factors and any correlation between transfusion and fluid management variables on outcome.

6.6 Time Table and Costs

Study will continue until enrollment target has been met and subject data is collected. No inducement for participation is offered to patient's legal representatives. There are no added monetary costs to the patient related to participation in this protocol. It is routine care to place arterial catheters in ventilated critically ill adult patients, especially if they are anemic or require frequent lab checks. Masimo engineers will analyze the data, and aggregate data will be provided to the LLU Anesthesiology Department for analysis, presentation and possible publication.

7 SAFETY AND ADVERSE EVENTS

7.1 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.

7.2 Anticipated Adverse Events:

The risk from the device is minimal since it is non-invasive and uses wavelengths in the red and near infrared range like a conventional pulse oximeter used in routine clinical practice for over 15 years but can include skin irritation and thermal skin burn from the optical sensors.

7.3 Adverse Event Reporting:

- All Adverse Events, both Anticipated and Unanticipated, must be recorded in the CRF and in the Adverse Event Report Form.
- All Adverse Events must be promptly reported to the Sponsor.
- All Unanticipated Adverse Device Effects will be also reported to both the Sponsor and the IRB.
- Both Serious Adverse Events and Unanticipated Adverse Device Effects must be reported to the Sponsor within 48 hours. All other Adverse Events should be reported to the Sponsor within 5 business days.

- All Serious Adverse Events will be also reported to the IRB per IRB reporting requirements. These reports may include, but will not be limited to: date of onset; brief description of the events; their treatment; whether they resulted in death, inpatient hospitalization, severe or permanent disability or were life threatening; their relationship to the study device; and resolution.

Deviations from the study protocol

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. 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.

Withdrawal of IRB approval

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

8 DOCUMENTATION AND DATA MANAGEMENT

8.1 Screening and Enrollment Log

A subject screening and enrollment log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

8.2 Case Report Forms

The site shall contain study data in a Case Report Form for each subject enrolled, completed and the CRF will be signed by principal investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must 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 site staff, authorized by the investigator.

CRF entries will be checked by study monitor 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. The monitor or study manager will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site.

8.3 Data Collection, Transfer and Storage

Device data will be captured through data capture software [redacted] and stored on a laptop. Device data, including arterial waveforms, along with electronic copies of the CRFs will be uploaded to sponsor via secure FTP portal after each study visit completion.

Only authorized sponsor personnel will have access to transferred data. Once data has been transferred via FTP, they are moved from FTP server to a secure and backed drive. [redacted] CRF 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 correction.

8.4 Record Retention

Study data will be retained for the necessary period of time as required by the institution's regulations. Study Records shall be retained for a minimum of two years after study closure. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

9 MONITORING PLAN

9.1 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 a direct employee from the Clinical Research department trained on departmental SOPs on conduct and monitoring of sponsored studies.

9.2 In accordance with good clinical practices guidelines, there will be at least three scheduled monitoring visits to ensure overall regulatory compliance of the study:

[redacted]

9.3 The monitor will contact and visit the investigator and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other GCP-related documents (IRB approvals, IRB correspondences, and ICFs) provided that subject confidentiality is maintained in agreement with HIPAA regulations.

9.4 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.

9.5 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.

9.6 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. 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 16 for details on suspension and termination.

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

10 ADMINISTRATIVE ASPECTS

10.1 Confidentiality

All documents associated with this protocol will be kept in the locked office of the PI 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 protocol. Data collected by data capture software and data entered in case report form will be shared with Masimo via a secure, password protected server that only study staff and Masimo study team members will have access to. Blood specimens will be handled according to standard procedures for biological materials. Data will be retained for up to 2 years following completion of the final analysis.

10.2 Protocol Amendments

Any changes made to the clinical investigational plan/study protocol 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 both the principal

investigator and the sponsor. The protocol amendment will be submitted to the IRB for approval. At a minimum, a redline version and a clean version of the new protocol amendment will be kept on file by the PI and the sponsor. Protocol amendments will need to be version controlled. Both PI and sponsor will retain the IRB approval letter as confirmation that the protocol amendment was approved.

10.3 Suspension or Termination of Study Site

The sponsor can suspend or prematurely terminate the PI's and study 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 the study site's compliance to be inadequate at any point during the study, and sponsor moves to suspend or terminate the study site, the sponsor will provide notification in writing to the principal investigator and IRB as necessary. The study site is eligible for reinstatement upon correction of any findings and any open action items prior to the suspension, and upon provision of 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. The sponsor may resume the terminated clinical investigation with prior IRB approval if the device is non-significant risk.

10.4 Termination of Clinical Investigation/Study 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 not later than 5 working days after the sponsor makes this determination, and not later than 15 working days after the sponsor first received notice of the effect.

The sponsor may resume the terminated clinical investigation with prior IRB approval if the device is non-significant risk.

11 AGREEMENT BETWEEN INVESTIGATOR 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 Investigator 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 insure existence and record of all necessary compliance documents, and will conduct monitoring visits to ensure appropriate conduct of the study.

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13 REVISION HISTORY:

Version Number	Version Date	Summary of Revisions Made:
1	July 17, 2016	Original version