Official Title: Validation of RPVi as a Parameter to Predict Fluid Responsiveness

Date of Protocol: February 24, 2022

NCT Number: NCT03706430

Validation of RPVi as a Parameter to Predict Fluid Responsiveness

Sponsor: Masimo
52 Discovery
Irvine, California 92618

[redacted] [redacted]

Study Devices:

Masimo Radical 7 monitoring device

Masimo Root Patient Monitoring and Connectivity Platform

Masimo Rainbow disposable sensor(s) (FDA cleared or investigational devices)

FDA cleared hemodynamic monitor(s) (i.e., Edwards Vigileo/FloTrac or Philips IntelliVue)

Sponsor Protocol Number: CANN0011

IRB: University of California Los Angeles
Institutional Review Board
10889 Wilshire Blvd., Suite 830
Los Angeles, CA 90095-1406

Principal Investigator	Title	Signature	Date
[redacted]	[redacted]		
Sponsor	**Title**	**Signature**	**Date**
[redacted]	[redacted]		

1 INTRODUCTION

This document is a clinical investigational plan for a human research study sponsored by Masimo Corporation. The study will be conducted in compliance with all stipulations of this protocol, ethical principles that have their origin in the Declaration of Helsinki, the conditions of IRB approval, applicable federal and local regulatory requirements, ISO-14155 and International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidance.

1.1 Background and Rationale

The changes in intra-thoracic pressure associated with mechanical ventilation produce fluctuations in the venous return of blood to the heart and consequent changes in stroke volume. (Michard 2005) These dynamic changes can now be tracked by many invasive and non-invasive monitors based upon arterial pressure waveform analysis, ultrasound measurement of arterial flow or vena cava diameters, measurements of thoracic impedance or reactance and analysis of the pulse oximeter plethysmographic waveform. The magnitude of these variations can localize the patient's cardiac function on a classic Frank-Starling curve to guide therapy. Dynamic monitors of cardiac function provide a better prediction of the response of an individual patient to the administration of intravenous fluids when compared to the measurement of pressures within the cardiac chambers. (Marik 2009) Intra-operative optimization of fluid administration and cardiac function using these dynamic monitors decreases post-operative length of stay as well as peri-operative morbidity and mortality. (Gurgel 2011, Hamilton 2011)

Pleth Variability Index (PVi) (Masimo Corp., Irvine, CA, USA) is an algorithm built into the Masimo Radical 7 monitor that determines maximal and minimal plethysmographic waveform amplitudes and then calculates the percentage difference between the two providing a continuous assessment of the respiratory variations in the pulse oximeter waveform amplitude. Recently, Masimo has created a new parameter called RPVi, which is an enhanced version of the currently available PVi parameter. RPVi is available in the multi-wavelength rainbow sensors powered by rainbow® technology. Compared to PVi, RPVi may provide enhanced specificity to changes in fluid volume, a reduction in variability under certain conditions, and fewer post-dropout spikes. Different from other invasive dynamic indices, PVi provides clinicians with a numerical value noninvasively, automatically, and continuously (Sandroni 2012, Vos 2013, Zimmermann 2010). 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 period of time and is calculated as follows:

$$PVi \text{ or } RPVi = [(Pimax - Pimin)/Pimax] \times 100(\%)$$

Multiple studies have demonstrated that PVi can predict fluid responsiveness in mechanically ventilated patients (Desebbe 2010) and can be used to optimize intraoperative fluid therapy (Desebbe 2008). Yin and Ho (2012) and Sandroni (2012) have provided meta-analyses confirming the clinical utility of PVi to guide clinical care. Among the available dynamic monitors of cardiac function in common clinical use (pulse pressure variation PPV, stroke volume variation SVV, corrected esophageal Doppler flow time FTc, etc.) the respiratory variations in the pulse oximeter plethysmographic waveform amplitude (pleth variability index PVi) has the advantage of being completely non-invasive.

The sensitivity of a dynamic monitor of cardiac function is dependent on the magnitude of the swings in the intrathoracic pressure associated with mechanical ventilation. During the introduction of these monitors into daily anesthetic management there has been a concurrent evolution in our intra-operative ventilator management protocols. During the past decade of practice, commonly recommended intraoperative tidal volumes have declined from 10 ml/kg to 8 ml/kg and now down to 6 ml/kg. Recommendations for the use of dynamic monitors as a guide for intraoperative fluid management stress that positive studies were done with controlled tidal volumes of 8 ml/kg and their sensitivity has not been established under conditions

including smaller tidal volumes. There is a pressing need to re-evaluate the performance and utility of these monitors under currently recommended respiratory management practices.

The evolution of the pulse oximetry sensors to incorporate multi-wavelength technologies provided the opportunity to modify the PVi algorithm and improve clinical performance. As a dynamic monitor of cardiac function, PVi/ RPVi is analogous to pulse pressure variation (PPV), which may be derived through minimally-invasive means using beat-to-beat arterial pressure expressed as a percentage by the Philips IntelliVue (Philips Labs, Noord Brabant, NL) or stroke volume variation (SVV), which may be derived through minimally-invasive means using pulse contour analysis of the arterial pressure waveform as done by the Vigileo/Flotrac System (Edwards Labs, Irvine, CA) or Philips IntelliVue (Philips Labs, Noord Brabant, NL). Multiple studies have demonstrated that PPV and/or SVV is a valuable tool in predicting fluid responsiveness in mechanically ventilated patients.

The aim of this study is to test the ability of RPVi to predict fluid responsiveness in mechanically ventilated patients in the operating room and to compare it to other dynamic monitors of cardiac function in this setting.

This study will include patients [redacted] undergoing cardiac surgical procedures in which pulmonary and peripheral arterial catheters are standard monitors used for continuous monitoring of cardiac function and blood pressure, respectively. Patients with cardiac arrhythmias and intracardiac shunts will be excluded. Patients will be assigned to one of the two study groups with different tidal volumes: 6 ml/kg IBW and 8 ml/kg IBW. Both tidal volumes are within the range that is commonly used intra-operatively. In patients without significant pulmonary disease there is no significant risk or benefit associated with either tidal volume, however, there is evidence of decreased utility of the dynamic monitors of cardiac function (PPV/SVV) at lower tidal volumes. Attention to the tidal volume will aid the assessment of the utility of RPVi as a monitor of cardiac response to fluid administration.

1.2 Investigational Device

Masimo Rainbow technology uses a multi-wavelength sensor with various LEDs that pass light through the measurement site to a diode (detector) as shown in the figure below. Signal data is obtained by passing various visible and infrared lights through a capillary bed (for example fingertip) and measuring changes in absorption during the blood pulsatile cycle. The detector receives the light and converts it to an electrical signal which is, in turn, used to predict various parameters.

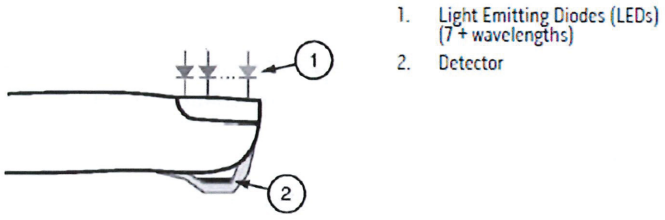

Figure 1: Masimo Rainbow technology overview

Devices used for RPVi evaluation consist of a Masimo Rainbow portable handheld pulse co-oximeter that is docked to a Masimo Root Patient Monitoring and Connectivity Platform and connected to a sensor that can measure SpHb, RPVi, SpO2, pulse rate (PR) and perfusion index (Pi). Masimo Rainbow pulse CO-oximeters are a non-significant risk device that has no additional risks compared to the commercially available pulse CO-oximeter devices.

The Masimo Rainbow sensors are constructed of a soft, flexible polymer in which LED emitters and photodiode detectors are embedded. The sensors, including the LED, photodiodes are the same as that used by commercially available pulse oximeter sensors.

Investigational devices to be used in this study are: Masimo CO-Oximeter devices and non-invasive prototype sensors equivalent to the FDA-cleared sensors; investigational devices and sensors similar in design, material, and risk to Masimo

FDA-cleared products that may be placed on the fingers, shielded from outside light, and attached to the Masimo monitor. The sensors along with its associated devices measure non-invasive physiological parameters like hemoglobin (SpHb), Pulse Rate (PR), Perfusion Index (Pi), Methemoglobin (SpMet), Pleth Variability Index (PVi), RPVi, etc.

1.3 Risk/Benefits

Benefits: There is no specific benefit to the individual subjects for participation in this research protocol.

Sensor risks: As with all optical sensors, the investigational device has the risk of thermal burn. Pulse CO-oximeter noninvasive measurement uses wavelengths in the red and near infrared range like a conventional pulse oximeter used in routine clinical practice for over 15 years. The additional LEDs from Rainbow sensors have been tested and meet the Exempt classification for photo-biological safety of light sources.

All patient-contact materials, including the adhesive used in the design of the Masimo Rainbow sensors, have been subjected to biocompatibility tests per ISO 10993-1 and results demonstrate that the materials are non-toxic, non-irritating, and non-sensitizing. The sensors have been subjected to performance, mechanical, and electrical testing and results demonstrate that the sensors meet the requirements for safety and effectiveness for the intended use of the product.

No other physical, financial, social or psychological risks are anticipated to be associated with participation in this study. Precautions taken to safeguard protected personal health information are described in **section 4.4** on recruitment. The risks associated with the anesthetic and surgical procedure are not discussed in this protocol.

2 STUDY OBJECTIVES

2.1 Primary Objective

This is a prospective, nonrandomized, sequential data collection study to evaluate the ability of RPVi to predict fluid responsiveness in comparison with other dynamic parameters including SVV and/or PPV. Although this is a non-interventional study, focused on data collection, patients will be assigned to one of the two study groups with different tidal volumes: 6 ml/kg IBW and 8 ml/kg IBW. The research data will not be used to modify the subject's standard of care.

Specific aims:

- Evaluate the clinical utility of the RPVi as a predictor of fluid responsiveness in mechanically ventilated patients at two specific tidal volumes (6 ml/kg IBW and 8 ml/kg IBW).

- Characterize the correlations between the RPVi and PPV and/or SVV, as measured by FDA cleared comparator systems, as predictors of fluid responsiveness at two specific tidal volumes (6 ml/kg IBW and 8 ml/kg IBW).

Hypothesis (constructed as the null):

- RPVi as a dynamic monitor of cardiac function will not predict a subsequent increase in cardiac output following the administration of a fluid bolus of a crystalloid solution at a tidal volume of either 6 or 8 ml/kg IBW in intubated, mechanically ventilated patients.

- Changes in RPVi will not differ from concurrent changes in PPV and/or SVV, as measured by FDA cleared comparator systems following the administration of a fluid bolus of a crystalloid solution at a tidal volume of either 6 or 8 ml/kg IBW in intubated, mechanically ventilated patients.

3 CLINICAL TEST SITES

[redacted]

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Number of Subjects

There will be up to 150 subjects enrolled into this study, divided into two groups. There will be no protocol or procedural differences between the groups. The first group of up to 100 subjects will be used to gather data to determine the thresholds for fluid responsiveness that would be used for the second group of 50 subjects. The second group will be the validation set to be used to evaluate study objectives. The anticipated duration of subject participation in this study will not exceed 1 visit. The study enrollment period is expected to be approximately 2 years.

4.2 Inclusion Criteria

- 18-64 years of age at the time of consent
- Scheduled for elective surgery requiring general anesthesia and mechanical ventilation
- Arterial line and other standard of care line placement indicated as part of the scheduled surgical procedure

4.3 Exclusion Criteria

- Patients diagnosed with or history of heart failure, angina, pulmonary heart disease, rheumatic heart disease, cardiomyopathy, congenital heart disease, or valvular heart disease.
- Patients with surgeries at or around site of sensor placement or skin abnormalities affecting the sensor placement area such as psoriasis, eczema, angioma, scar tissue, burn, fungal infection, substantial skin breakdown, nail polish or acrylic nails that would prevent monitoring of pulse-oximeter physiological parameters during the study.
- Patients with cardiac arrhythmias
- Patients with intracardiac shunts
- Patients who live in a nursing home or long-term care facility
- Patients of all ages with underlying medical conditions, particularly if not well controlled, including
    - Patients with chronic lung disease or moderate to severe asthma
    - Patients who are immunocompromised, which may include: patients receiving cancer treatment, smoking, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, and prolonged use of corticosteroids and other immune weakening medications
- Patients with severe obesity body mass index [BMI] of 40 or higher
- Patients with diabetes
- Patients with chronic kidney disease undergoing dialysis
- Patients with liver disease or who have been scheduled for or have had a liver transplant

4.4 Subject Recruitment and Screening

The surgical and interventional schedule at [redacted] Main OR will be screened by the research team to identify the potential candidate(s). The study staff will send an email over the [redacted] server to the the principal investigator or Co-investigator to confirm that the patient is eligible for the study. The email will not contain any PHI. Once confirmed, additional subject screening will be performed through a telephone script to reduce physical contact due to COVID-19 precautions. The study staff will provide information about the study and ask if they are interested in participating. A copy of the consent will be emailed to patients who express interest are found to be eligible for the study. If the patient does not express interest in the study during the phone call, no further communication will be made with the patient. To ensure patient privacy, phone calls to patients will occur in a private room, and screening scripts will be discarded. If the patient is interested in the study, the PI or Co-I will obtain written informed consent on the morning of the subject's surgery. The prospective subject will be given sufficient time to review the consent form and discuss the study with friends and family. A written consent form will be required from all consenting subjects.

The patient's privacy will be protected. Only the information relevant to study will be obtained. The patient's information will be kept confidential; if data is written on paper, the paper will be either kept in the research folder which is kept in the

hospital or shredded when it is not needed. If patient data is kept on a computer, the data will only be stored on hospital computers. All data will be de-identified before (1) the study team conducts any statistical tests and (2) sharing the data to Masimo Corporation. The patient's privacy will be protected such that when we approach the subject, during pre-op, we will do so when they are in a private room with or without their family so that any personal information will be kept among their family or just themselves. The Privacy of the patient will be protected throughout the study and beyond the study.

4.5 Informed Consent Process

The Investigator(s) and/or staff delegated for this task are responsible for conducting the informed consent process and for obtaining written informed consent and the HIPAA/data protection authorization from each potential subject before any study-specific procedures required by the clinical protocol are performed.

Informed consent should be obtained in written format and using a form approved by the local IRB and Sponsor. Written (signed) informed consent will be obtained from subjects or their legally authorized representative (LAR). After a patient is deemed eligible from the screening process using the [redacted] surgical schedule, study team members will call the prospective subject to explain the study the day before their scheduled surgical procedure. A copy of the consent will be emailed to the patients who express interest to allow adequate time to review the consent and consider their participation. On the morning of their surgery, the PI or Co-I will provide the consent form in-person. They will give the prospective subject additional time to review the consent form, discuss the study with family, and ask questions. If the subject is interested in participating in the study, written consent will be obtained on the day of the surgical procedure. . In addition to the full disclosure of the risks and benefits of participating in the study, patients will be informed that their participation is voluntary and their decision will not impact patient care. They will also be give adequate time to ask questions regarding the study and to discuss with family and friends before making the decision.

All signed consent and HIPAA forms will be kept [redacted] and are only accessible to study team members [redacted]. If the patient refuses to participate, we not enroll the patient in this study. The original signed consent should be filed in the hospital/clinical chart or with the subject's study documents. A signed copy of the consent and HIPAA/data protection authorization must be provided to the subject. The Principal Investigator (PI) is responsible for ensuring any new information related to the study will be provided to the subject and/or subject's LAR. Subject may need to be re-consented to continue participation, if required by the IRB.

The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. An interpreter will be involved in the consenting process. **Note:** The IRB must officially stamp the translated consent forms.

4.6 Subject Withdrawal

All enrolled subjects have the right to withdraw their consent at any time during this study. All data collected until the time of subject withdrawal will remain in the study database and will be used for analysis. If a subject is withdrawn from the study, the reason for withdrawal will be recorded in the CRF and in the subject's hospital record.

4.7 Subject Discontinuation by Investigator

An Investigator may discontinue a subject from the study, with or without the subject's consent for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject, subject non-compliance, Sponsor instruction, or if the IRB stops the study for any reason. If a subject is discontinued from the study, the Investigator will promptly inform the subject and Sponsor. The reason for discontinuation will be recorded in the CRF and in the subject's hospital record.

5 RISKS AND BENEFITS

The major risks to the patient are related to the surgical procedure (bleeding, infection, pain, etc.). Participation in this protocol places the patient at minimal if any additional risk. There is theoretical extremely small risk of damage to the subject's fingers from the device including potential temporary redness or skin irritation or discomfort associated with exposure to the sensor.

There is no intervention and no alteration to the patient's surgical procedure. Patient will receive standard patient care. All additional measurements will be done through non-invasive sensors. None of the data recorded through these sensors will be used to make decisions regarding the patient.

Noninvasive measurement with Masimo Corporation Radical 7 pulse oximetry: The risk is minimal since the measurement is noninvasive and uses optical technology similar to conventional pulse oximetry.

Sensor risks: As with all optical sensors, the device has the risk of thermal burn. The design includes safeguards, and this risk is believed to be low. All patient-contact materials, including the adhesive used in the design of the Masimo Rainbow sensors, have been subjected to biocompatibility tests per ISO 10993-1 and results demonstrate that the materials are non-toxic, non-irritating, and non-sensitizing. The sensors have been subjected to performance, mechanical, and electrical testing and results demonstrate that the sensors meet the requirements for safety and effectiveness for the intended use of the product. Pressure damage may occur to the tissue if the sensor is placed too tightly.

Volume expansion risks: Risks of volume expansion with [redacted] can include fluid accumulation in the lungs or tissue, decreased oxygen saturation, and edema.

There will be no direct benefits to the enrolled patients. Future benefits to patients might include a reduction in invasive procedures due to the ability to trend moment-by-moment physiological parameters.

6 STUDY DEVICES

6.1 Investigational Devices

Masimo investigational pulse CO-oximeter devices and/or sensors with the RPVi parameter, are with the same or similar technology and materials as the Masimo FDA cleared devices and sensors, that pose no additional risk to human subjects than the FDA cleared devices and sensors.

- Masimo Radical 7 Rainbow monitoring device
- Masimo Root Patient Monitoring and Connectivity Platform
- Masimo Rainbow disposable sensor(s) (FDA cleared or investigational devices)

[redacted]

6.2 FDA-Cleared Devices

- FDA cleared hemodynamic monitor(s) (i.e., Edwards Vigileo/FloTrac or Philips IntelliVue)
- Laptop with [redacted] software
- Electronic data collection of high speed arterial line waveforms

6.3 Device Accountability

6.3.1 Receipt of Study Device

Masimo may ship or hand-carry devices and sensors to the investigative sites. Upon receipt 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.

6.3.2 Use of Study Device

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

6.3.3 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.

6.3.4 Device Deficiency

Device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling. (ISO 14155:2011 3.15). All Masimo device related deficiencies should be reported to the Sponsor and must be recorded in the CRF in a timely manner. This excludes computer issues. These should be reported to the IRB as required per local requirements. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the Sponsor in a timely manner.

7 STUDY PROCEDURES

- Patients are assigned to be ventilated in a volume controlled mode with a tidal volume of either 6 or 8 $ml.kg^{-1}$ of ideal body weight (Devine formula) at a frequency [redacted]. Positive end-expiratory pressure is to be set [redacted] according to the attending physician.
- Anesthesia is induced as per standard of care. Radial and pulmonary arterial catheters inserted as per standard of care.
- All required sensors are placed as per the corresponding instructions for use for the various measurements
- All patients are to be studied [redacted] with no changes in anaesthetic protocol and no volume expansion. Unless clinically contraindicated, patients will receive an intravenous volume expansion consisting of [redacted] given over [redacted].
- Baseline set of haemodynamic measurements (stroke volume and or cardiac output) are to be performed prior to the intravenous volume expansion.
- A repeat set of hemodynamic measurements are to be performed [redacted] after volume expansion.

8 STATISTICAL PLAN

Prior studies of the predictive abilities of dynamic monitors of cardiac function with respect to cardiac output have established that sample sizes of 50 patients are sufficient to characterize the performance of the monitor. However, based an ongoing Masimo study at another clinical test site, preliminary data received suggests that, of the first 83 subjects enrolled approximately 29% were responders. Therefore, in order to analyze the ability of RPVi, the sample size will be increased to a total of up to 150 patients. The first group of up to 100 subjects will be used to gather data to determine the thresholds for fluid responsiveness that would be used for the second group of 50 subjects. The second group will be the validation set to be used to evaluate study objectives in **section 2.1**. As such, the study will be registered on ClinicalTrials.gov but only results from the validation phase will be posted.

Normality of distribution will be tested before any statistical evaluation by using the Kolmogorov- Smirnov method. Descriptive statistical data will be reported as mean ± SD. Except for the bias between both methods (RPVi vs PPV/SVV and SV/CO measurements). Comparisons between PPV/SVV and RPVi and between CO/SV measurements will be performed with a paired student t test. PPV/SVV and RPVi as well as SV/CO measurements will be compared using Bland and Altman. In order to evaluate the ability of RPVi to reliably detect changes in PPV/SVV and for CO measurements to accurately track Flotrac CO changes we will use a method based on polar plotting of PPV/SVV and RPVi and CO measurements changes over consecutive cycles as described by Critchley et al. We will exclude from this analysis small changes of mean value of

PPV/SVV and RPVi and CO measurements less than 3%. In this method, a good trending ability requires an angular bias no greater than ± 5 degrees and a SD for the polar angle of less than ± 15 degrees. In this method, simultaneous changes of each indices of consecutive validated respiratory cycle will be reported on a polar plot. The polar angle will be derived from the ratio of the changes of the two indices such a ratio close to one led to a null angle with the x axis, this angle approach a 90 degrees angle when the ratio diverges from one. The radius will be the mean of the simultaneous changes of the two indices between two consecutive validated respiratory cycles. In these conditions a mean angle and its SD can be calculated.

The strength of linear dependence between PPV/SVV and RPVi and SV/CO measurements for all patients will be measured by the Pearson coefficient of correlation. The mean of correlation coefficients and comparison between correlation coefficients will be performed after a Fischer's transformation. In order to analyze the ability of RPVi to correctly classify the respiratory cycle as responder or non-responder after a volume loading in respect to a theoretical threshold value of PPV/SVV of 12%, we will measure the area under the curve of a Receiver Operating Characteristic (ROC) curve. Then the selected value of RPVi for each patient will be the one which maximized the Youden index (sensitivity + (specificity -1)). The agreement between the two classifications will be quantified by the Kappa score for each patient, taking as threshold value of RPVi the individual value determined by the ROC curve. The reported mean values of areas under ROC curves and Kappa scores will be therefore calculated from the individual values. Taking the intra patients coefficient of correlation as a dependent variable, we will estimate its relationship with potentially explanatory variables by using univariate analysis, including Student t test for qualitative data and correlation for quantitative data and multivariate analysis by multiple linear regression. Categorical binary variable will be transformed into dummy variables. Other correlations will be evaluated by Pearson coefficient.

For all comparisons, a P value < 0.05 will be considered significant. Statistical analysis will be performed using SPSS software version 13.0 for Windows (SPSS Inc., Chicago, IL).

9 SAFETY AND ADVERSE EVENTS

9.1 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 Risk and Benefit **section 5** for details on anticipated adverse device effects.

9.2 Anticipated Adverse Events

- Mild allergic reaction to sensor material and adhesives.
- Discomfort, redness or skin irritation at site of sensor placement.

9.3 Adverse Event Reporting

The PI must promptly report the following adverse events to the Sponsor through the CRF and Adverse Event Report Form, and follow their IRB policy for safety event reporting:

- All Adverse Events, both anticipated and unanticipated and both serious and non-serious, after the first Masimo sensor is placed and up to the last Masimo sensor is removed
- All Unanticipated Adverse Device Effects after the first Masimo sensor is placed and up to the last Masimo sensor is removed

SAEs and UADEs must be reported to the Sponsor within 48 hours. All other Adverse Events should be reported to the Sponsor within 5 business days.

9.4 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. All deviations must be recorded in the CRF and in the Protocol Deviation Form.

9.5 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.

10 DATA MANAGEMENT

10.1 Provisions to Protect the Privacy Interests of Subjects

All information recorded on CRF will be shared with Masimo electronically via secured, password protected database. [redacted] team members will NOT share any patient identifiable information with Masimo at any time. Each subject receives a case number, which is what [redacted] team members use to keep track of patient enrollment. Only [redacted] team members will have access to the original list linking the case number with patient's identifiable information for research purposes (screening and recruitment process, data collection, and organizational purposes). Once data are completely extracted and recorded for the subjects, [redacted] research team will immediately destroy the list of identifiable information).

10.2 Data Management and Confidentiality

All documents associated with this protocol will be kept in a locked office or on password protected computers. All data will be de-identified before any statistical analysis. Only de-identified data will be shared with Masimo and regulatory authorities 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.

10.3 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 investigator will permit trial-related monitoring, audits, IRB review and regulatory inspection(s), providing direct access to source data/documents.

10.4 Case Report Forms

The Sponsor shall provide a paper Case Report Form (CRF) template to the Site. The Site shall capture study data in the CRFs for each subject enrolled. The CRFs will be completed and 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. Entries and corrections to the CRF will be made following Good Documentation Practices.

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, device readings, and if occurrence of any adverse event, protocol deviation, and device deficiencies, etc. The CRF will be signed by the PI and forwarded to Masimo.

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 case. A copy of the completed and signed CRFs will remain on site.

10.5 Data Transfer and Storage

10.5.1 The information will be stored in a password protected electronic database at the study site. Device data, including extracted high speed arterial line waveform data, along with an electronic copy of the CRF will periodically be securely uploaded to sponsor via Druva.

10.5.2 Only authorized sponsor personnel will have access to the transferred data, and will move it to a secure and backed-up drive at Masimo.

10.5.3 Device data and electronic copy of 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 correction. If the investigator is to correct the CRF, the PI shall follow GDP practices to strike thru old entry, add in new entry, and initial and date it, and resend to Masimo the corrected CRF. 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 data, therefore are unable to unintentionally tamper with the original data files. Raw and processed physiological data will be analyzed by Masimo Engineering team.

10.6 Record Retention

All study information, including but not limited to study correspondence, study logs, device accountability records, consent forms, subject records, and copies of the CRFs should be maintained in the Investigator site files.

Study Records shall be retained during the study and for a minimum of two years following completion of the study or until the research data is not required to support a 510(k) clearance. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

11 MONITORING PLAN

11.1 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.

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

- 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 monitoring visit during initial enrollment, when enrollment reaches about 10-15% and/or every year until completion of the study
- A final close out visit after the last patient has finished the study.

11.3 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.

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

11.5 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.

11.6 After each visit, the monitor will provide a monitoring follow-up letter to the investigator within 4 weeks of visit completion. The monitoring follow-up letter 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 12.3** for details on suspension and termination.

11.7 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.

12 ADMINISTRATIVE ASPECTS

12.1 Confidentiality

All data collected will be kept confidential and de-identified. It can only be accessed by researchers and will be used for research purposes only.

12.2 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 clean version of the new protocol amendment will be kept on file by the PI 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. Both PI and sponsor will retain the IRB approval letter as confirmation that the protocol amendment was approved.

12.3 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 determine that the 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 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 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.

12.4 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.

13 AGREEMENT BETWEEN INVESTIGATOR AND SPONSOR REGARDING RESPONSIBILITIES FOR GOOD CLINICAL PRACTICE

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 protocol.
- 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.

14 REVISION HISTORY:

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