Official Title: Correlation of Changes in PaO2 and ORi in Adult Patients

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NCT Number: NCT03488238

Correlation of Changes in PaO2 and ORi in Adult Patients

Sponsor: Masimo
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Irvine, California 92618

Principal Investigator: [redacted]

Study Devices: Masimo Radical 7 rainbow pulse oximeter device
Masimo Root Patient Monitoring and Connectivity Platform
Masimo rainbow disposable sensors

Sponsor Protocol Number: FLEM0007

IRB: Office of Research
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Principal Investigator	Title	Signature	Date
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Sponsor	**Title**	**Signature**	**Date**
[redacted]	[redacted]		

1 INTRODUCTION

This document is a clinical investigational plan for a human research study. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. By participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of IRB approval, federal and local regulatory requirements, 21CFR 812, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidance ICH GCP.

1.1 Background and Rationale

Masimo Corporation is the developer of noninvasive technologies for the measurement and monitoring of physiological variables, such as arterial oxygen saturation (SpO_2), total hemoglobin concentration (SpHb), carboxyhemoglobin concentration (SpCO), methemoglobin concentration (SpMet), acoustic respiration rate monitoring (RAM), and cerebral and regional oximetry (rSO2, O3™). These technologies are noninvasive and have a good patient safety record.

A continuous supply of oxygen is essential for normal cell function. Failure of a patient's oxygen supply to meet metabolic needs is common to all forms of circulatory failure, tissue acidosis, and ultimately mortality. Like all essential commodities for body functions, optimal quantities of oxygen are required. A patient's oxygen status can be largely classified into 3 ranges: Hypoxia (less than normal), Normoxia (normal) and Hyperoxia (more than normal). The three states are typically classified using dissolved oxygen levels in the plasma (PaO2), instead of arterial hemoglobin oxygen saturation (SaO2), due to sensitivity of PaO2 in all three states including hyperoxia (unlike SaO2). Figure 1 shows the three oxygen states based on PaO2 values along with the relationship between PaO2 and SaO2.

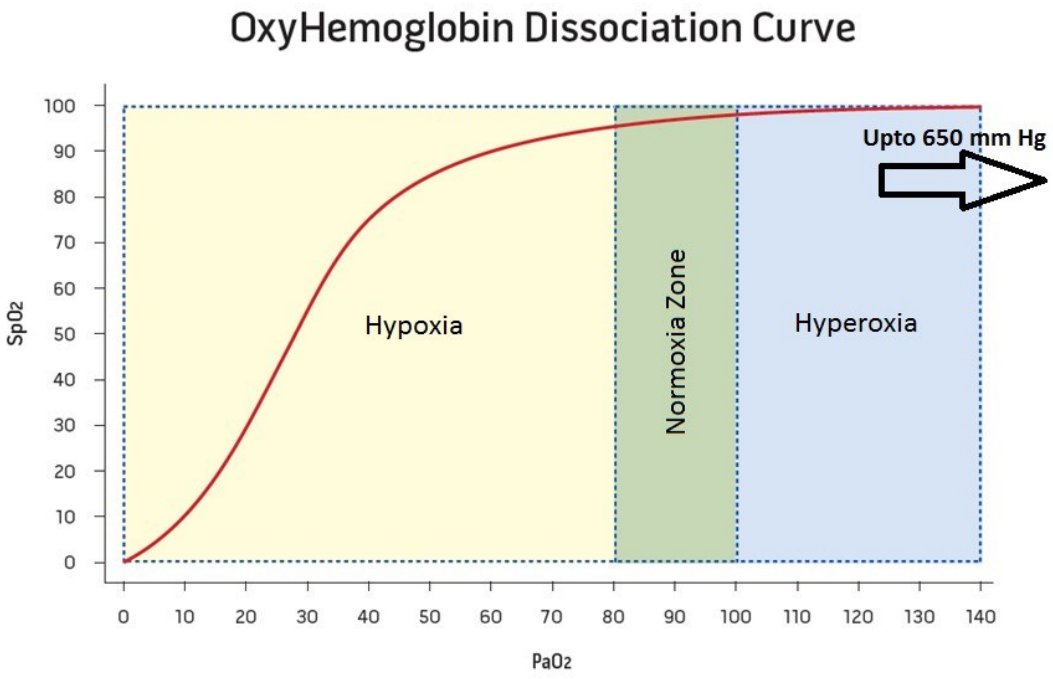


Figure 1: The oxygen dissociation curve with the three oxygen states

In order to prevent episodes of hypoxia, patients in critical care are administered a certain amount of supplemental oxygen to prevent hypoxia and improve safety in situations where the oxygen supply may be lost intermittently. However this excess supply should be in moderation as large amounts of oxygen may result in lung damage or other complications. Hence it becomes imperative to monitor the amount of surplus oxygen in blood.

Currently, clinicians monitor a patient's oxygen status, both continuously and non-invasively, using a pulse oximeter to obtain SpO2 (a proxy for SaO2) levels. However, SpO2 is sensitive in the normoxic and hypoxic regions and largely remains flat in the hyperoxic region (Figure 1). Clinicians consequently must resort to invasive blood sampling to obtain PaO2 values for oxygen status within the hyperoxic zone. This method has multiple drawbacks such as limited information from

intermittent sampling to potential delay due to the time difference between blood draw and when the PaO2 value is obtained through blood gas machines, and potentially significant loss of blood due to multiple blood draws.

The Oxygen Reserve Index (ORi) is a reference that could help clinicians with their assessments of normoxic and hyperoxic states by scaling the measured absorption information between 0.00 and 1.00. [redacted]

While not a direct measurement of PaO2, ORi provides a continuous and non-invasive index which correlates with changes in PaO2 values in the range of 100 to 200mmHg.

ORi together with pulse oximetry may provide useful reference information about a patient's partial pressure of oxygen in arterial blood (PaO2) and the transition between oxygen regions such as moving from normoxic to hypoxic regions. This can be useful during clinical applications such as during endotracheal intubation, in which unintended desaturations may occur. Additionally, ORi may be used as reference information for clinicians when they monitor the patient's reserve oxygen supply.

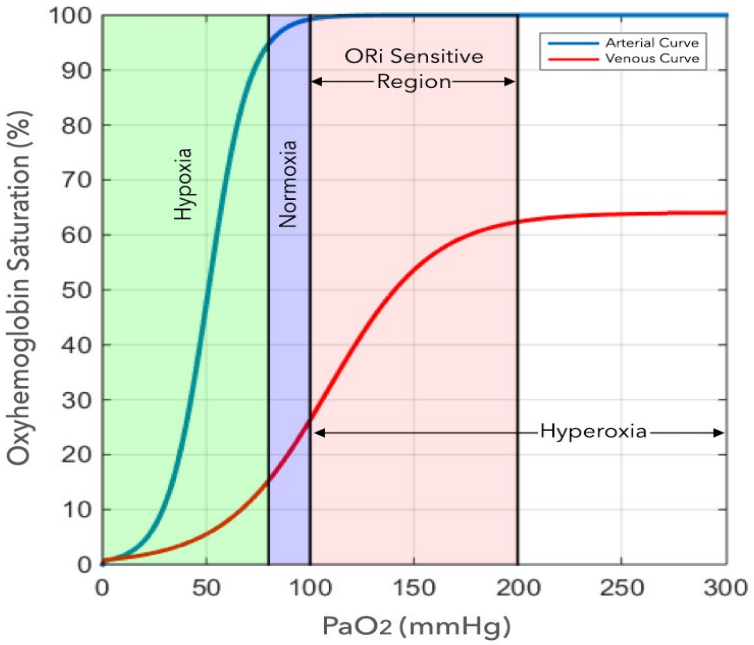


Figure 2: PaO_2 vs SaO_2 and SvO_2

This protocol is designed to evaluate the correlations between ΔORi and ΔPaO2 and the potential use of ORi as an early warning of impending arterial oxygen desaturation.

2 STUDY OBJECTIVES

2.1 Specific aims:

- evaluate the clinical utility of the change in the Oxygen Reserve Index as an early warning of impending arterial oxygen desaturation in adult patients

- characterize the correlations between the Oxygen Reserve Index and the arterial oxygen content during pre-oxygenation and induction of general anesthesia in adult patients

2.2 Hypothesis (constructed as the null):

Intraoperative changes in ORi will not correlate with increases in arterial oxygen content during pre-oxygenation or induction of general anesthesia and ORi will not provide clinically significant additional warning of impending arterial desaturation.

3 STUDY DESIGN

This is a prospective, non-blinded, non-randomized study of the Oxygen Reserve Index (ORi) in a clinical setting. It is designed to evaluate the correlations with ORi and ΔPaO2 and the potential use of ORI as an early warning of impending arterial oxygen desaturation.

3.1 Study Endpoints

This is a prospective clinical study designed with the following endpoints:

- Primary endpoint – measure the ΔPaO2and it's correlation with changes in ORi (ΔORi) during the induction of general anesthesia in patients in whom continuous arterial pressure monitoring is a planned component of the anesthetic monitoring.
- Secondary endpoint – evaluate the potential clinical utility of the ORi as an early warning for impending desaturation.

4 CLINICAL TEST SITE

University of California Davis Medical Center

2315 Stockton Blvd, Sacramento, CA 95817

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

A minimum of 22 completed subjects will be needed for the study with enrollment of a maximum of 100 subjects.

5.2 Inclusion Criteria

- Age greater than 18 years
- ASA physical status III or IV
- Scheduled for an elective surgical procedure requiring endotracheal intubation and the use of an arterial pressure monitoring catheter placed prior to induction of general anesthesia

5.3 Exclusion Criteria

- Age less than 18 years
- Adults unable to give primary consent
- Pregnancy
- Prisoners

5.4 Study Timelines

[redacted]

- This study is anticipated to require up to 3 months for completion of patient enrollment.

- Primary analysis of the data is expected to require an additional 6 months.

5.5 Subject Recruitment and Screening

Patient recruitment and informed consent will be obtained in the UCDMC perioperative suite. Recruitment will be by direct discussion between the prospective candidates and the study investigators prior to their scheduled surgical procedure. The investigators 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.

All items of the Informed Consent will be explained in a way that is easily understandable. 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 is now adequately consented. Now the patient will be enrolled as a study subject, at which time the subject will be assigned a study identification number or enrollment number.

All subjects will have their medical history reviewed at the time of screening by either the PI or the study staff who is 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 a subject is deemed ineligible after screening, the subject will be withdrawn from the study.

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

HIPAA

The screening of patients will require the investigators to access personal health information to identify prospective subjects without HIPAA authorization. The research could not be practicably carried out without this waiver of consent. The risk of harm from contacting the participants is greater than the risk of the study procedures. The research is of minimal risk and does not involve any procedures for which written consent is normally required outside the research setting. The participants' rights and welfare will not be adversely affected by waiving consent. This protected health information will not be inappropriately reused or disclosed to any other person or entity. To further safeguard all protected health information, the data will not be labeled with any personal identifying information, or with a code that this research team can link to personal identifying information. The data will not be stored with any protected health information identifiers.

5.6 Early Withdrawal of Subjects

5.6.1 Withdrawal of Individual Subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences or loss of benefits to which they are otherwise entitled. Subjects may be withdrawn from the study prior to expected completion for reasons such as safety concerns, failure to adhere to protocol requirements, subject consent withdrawal, etc.

Any data collected until the time of subject withdrawal may be included in the final data analysis. Information on the subject's withdrawal should be documented in the case report form and should include clear documentation of the reason for withdrawal to the Sponsor.

5.6.2 Follow-up for subjects withdrawn from study

None. There are no long term effects anticipated from participating in this study.

5.6.3 Data from individual subjects after withdrawal

In case a subject leaves the study prematurely, the data collected may be included in data analysis.

6 STUDY DEVICE

6.1 Study Device

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). Signal IQ is a feature for signal identification and quality indication during excessive motion and low signal to noise situations. FastSat® tracks rapid changes in arterial O2. A detailed description of the Masimo Radical-7 can be found in the attached manual. [redacted]

The Masimo Root System is also being used in this study. The Root System is indicated for use by healthcare professionals for the monitoring of multiple physiological parameters in healthcare environments. The Root works together with the Radical-7 to display data. The Root serves as a convenient alternative user interface to integrate modules to provide health care professionals the ability to access, control and monitor measurement technologies (within the respective modules) that have been previously cleared by the FDA.

Rainbow Adhesive Sensors are FDA cleared for the measurement of functional oxygen saturation of arterial hemoglobin (SpO2), pulse rate (PR), perfusion index (PI), pleth variability index (PVI), carboxyhemoglobin saturation (SpCO), methemoglobin saturation (SpMet), total hemoglobin (SpHb) and total oxygen content (SpOC). Although no modifications are required for the Rainbow Adhesive sensors for the study, the sensors have not been cleared for the indications for use of measuring ORi.

6.2 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 as it only observation with the recording of intraoperative ORI and ABG measurements. Precautions taken to safeguard protected personal health information are described in the section on recruitment. The risks associated with the anesthetic and surgical procedure are not discussed in this proposal.

6.3 Device Accountability

6.3.1 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.

6.3.2 Use of Study Device

Use of devices and sensors will be documented on case report forms for each subject. Any unused devices must be returned to the Sponsor at the end of the study or before product expiration date.

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 Deficiencies

Device deficiencies are defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Record all device deficiencies on the case report form and report to the Sponsor.

7 STUDY PROCEDURES

7.1 Following arrival of the patient in the operating room all standard and planned physiological monitors will be placed. A baseline ORi will be measured and an arterial blood gas (ABG) sample will be collected for measurement of the PaO2.

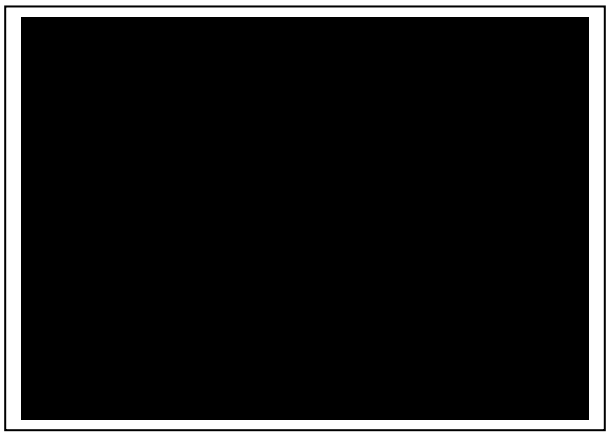
7.2 As per routine, the patient will then be pre-oxygenated with 100% oxygen. [redacted] a second ORI will be recorded and ABG sample collected.

7.3 General anesthesia will be induced with a combination of amnestics, narcotics, intravenous induction agents and muscle relaxants as clinically indicated. With stable mask ventilation, a third ORI will be recorded and ABG sample collected immediately prior to initiating laryngoscopy and endotracheal intubation.

7.4 Intubation will be under direct visualization using a GlideScope. When the arterial hemoglobin saturation reaches [redacted] a fourth ORi will be recorded, an ABG sample will be collected and ventilation will be initiated with 100% oxygen either via the endotracheal tube or resumed mask ventilation.

7.5 A final post-induction ORi measurement and ABG sampling will occur 5 minutes following initiation of controlled ventilation with 100% oxygen.

This planned protocol sequence can be summarized graphically as:



Arterial blood gas measurement: ABG samples will be analyzed using Radiometer's ABL blood gas analysis system. Each sample will use [redacted] of blood for a total blood volume of [redacted] for this study.

8 STATISTICAL PLAN

8.1 Sample Size

The same sample size calculation used for the healthy subjects is used to determine the sample size for this study with sick subjects, which is calculated to be a minimum of 22 subjects. Based on this, the sample size for the study with sick subjects is established as the following for 95% confidence interval:

Number of Subjects	Number of Invasive Measurements per Subject	Number of Noninvasive Sensors Per Subject
22 minimum[4]	4 minimum	1 minimum

8.2 Acceptance criteria

In accordance with ISO-80601-2-61, SpO2 accuracy is determined as accuracy root mean square (A_{RMS}), where SpO2 measurements are compared with reference SaO2 measurements. However unlike SpO2, ORi is an index value without a unit and ORi does not directly measure PaO2. Therefore, sensitivity and specificity analysis is used to evaluate ORI's performance relative to the changes in PaO2.

Although concordance calculation is based on sensitivity and specificity analysis, concordance analysis is not applicable for the sick subjects because of the lack of sample size. Thus the specifications for ORI are the following:

- Specificity of ΔPaO2 vs. ΔORI > 80%
- Sensitivity of ΔPaO2 vs. ΔORI > 85%
- Concordance of ΔPaO2 vs. ΔORI > 80%

Where ΔPaO2 is the change in PaO2 and ΔORi is the change in ORi. These specifications are based on the study by Applegate et al. The Applegate study evaluated the ORI to PaO2 relationship during surgery of 106 patients. The data showed that decreasing ORI had 77.7% sensitivity and 76.7% specificity for detecting decreasing PaO2.

In determining specificity and sensitivity, ΔPaO_2 and ΔORi are defined as:

$$\Delta PaO_2 = PaO_2(t) - PaO_2(t_{ref})$$

$$\Delta ORI = ORI(t) - ORI(t_{ref})$$

Where t_{ref} is the time of the sample closest to $PaO_{2threshold}$ in a [redacted] mmHg window. Thus, a [redacted] mmHg window is used as it is not possible to draw a blood sample at the exact value of $PaO_{2\ threshold.}$

Samples with Δ PaO2 of [redacted] mmHg are ignored.

8.3 Statistical analysis

Similar statistical analysis as described in the study with healthy subjects ([redacted] will be performed on the data for this study with sick subjects. However unlike healthy subjects, the FiO2 levels for sick subjects cannot be easily varied. Therefore, substantially fewer PaO2 samples are available for sick subjects. As a result, all PaO2 samples for sick subjects are accounted for in data analysis even if the PaO2 sample is outside the 100 to 200 mmHg range.

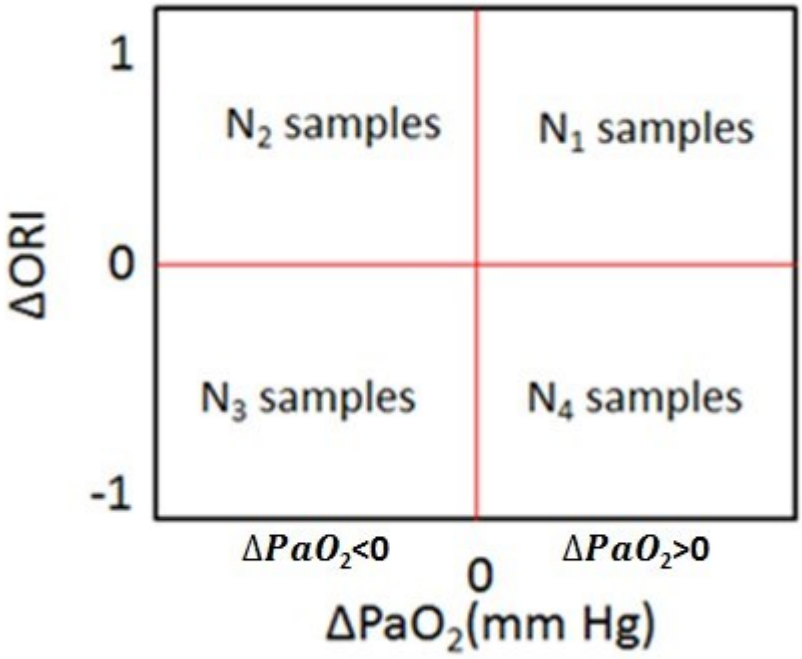


Figure 3: Specificity and Sensitivity Illustration for ΔPaO_2 vs ΔORi

In accordance with Figure 3, the following relationships are defined as:

Specificity = N1 / (N1 + N4), where t_{ref} is the baseline sample time

Sensitivity = N3 / (N2 + N3), where t_{ref} is the sample time at the end of 100% pre-oxygenation.

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 the Device Risk Analysis and Risk Assessment section 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.

9.3 Adverse Event Reporting:

- All Adverse Events, both Anticipated and Unanticipated, must be recorded in the within 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.

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 with the exception that under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor or the EC. 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 documented and 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. If protocol deviations continue to occur frequently at a study site, a corrective and preventive action (CAPA) may be opened by the Sponsor.

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 VULNERABLE POPULATIONS

10.1 Definition

10.1.1 Vulnerable populations are defined as disadvantaged sub-segment of the community requiring utmost care, special considerations and protections in research. This study will recruit subjects from the following: economically disadvantaged or unemployed, educationally disadvantaged, and limited English skills and/or Non-US citizens.

10.2 Protection of vulnerable subjects

- There is no compensation provided for economically disadvantaged subjects to eliminate possibility of undue influence due to financial incentive.
- Educationally disadvantaged subjects will be provided ample time to ask questions and comprehend information.

- Medical care will be provided to these subjects if they are injured as a direct result of participating in this research study. The cost of treatment for any research related injury will be covered by Masimo.

10.3 **Responsible Parties**

- The IRB will review research with vulnerable populations and evaluate consent, level of risk, coercion, and the reason for choosing this particular subject population. The IRB will be responsible for determining what practices will include continuing review for compliance while monitoring these studies.
- The Investigator holds the ultimate responsibility for protecting the rights, safety, and welfare of research subjects by ensuring that all regulations and proper documentation of consent is handled in a compliant and timely manner.

11 DATA MANAGEMENT

11.1 Confidentiality of Records

Information about the patients will be kept confidential. The data will be stored on a password protected database on a secure server, accessible only to the Investigators. Study data that will be released to Masimo and other regulatory authorities will be de-identified and will only pertain to study data collection, demographics, finger location of the sensor, and the recordings from the pulse oximeter.

11.2 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. For this study, the case report forms may also be used as source worksheets.

11.3 Case Report Forms

The Site shall capture study data in the CRFs for each subject enrolled. The CRFs will be completed and initial and dated by the PI or delegated personnel. 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 CRFs will be signed by the PI to attest that the data is complete and accurate and forward a copy to Masimo.

CRF entries will be verified by study monitor and any errors or inconsistencies will be queried to the site on an ongoing basis. Any changes will be made directly on the paper CRFs and re-verified. 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

11.4 Data Transfer and Storage

The information will be stored in a password protected electronic database at the study site. Device data along with an electronic copy of the CRF will periodically be securely uploaded to sponsor via secure FTP portal. Only authorized sponsor personnel will have access to the transferred data, and will move it to a secure and backed-up drive at Masimo.
CRFs will be checked for accuracy and completeness of data. If there are inconsistent or missing data points, a data query list will be generated and submitted to the PI or designee, who shall both follow GDP practices for data correction by striking through the old entry, adding in new entry with initial and date, 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 study data, therefore are unable to unintentionally tamper with the original data files.

11.5 Record Retention

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

Study records shall be retained during the study and for a minimum of two years after date of study closure or date when records are not required to support 510(k) clearance. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

The Sponsor is responsible for verifying study data, retaining records, analyzing data, and authoring study reports.

12 MONITORING PLAN

12.1 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.

12.2 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 enrollment, when about 10-15% done and/or every year
- A final close out visit after the last patient had finished the study.

12.3 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.

12.4 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.

12.5 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.

12.6 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 13 for details on suspension and termination.

12.7 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.

13 ADMINISTRATIVE ASPECTS

13.1 Protection of Human Subjects

Per 21 CRF 50, written consent must be obtained from each subject or from their legal guardian prior to any study procedures in accordance with applicable federal, state, and study site regulations. The Investigator must keep a copy of the signed consent form in each subject's record and provide a copy to the subject as well. The Investigator shall not allow a subject to participate in a study or sign consent prior to IRB approval.

Prior to the start of data collection or subject enrollment, the Investigator must provide documentation of IRB approval of the study protocol and a copy of the approved informed consent form (21 CFR 50).

All subjects will be monitored closely throughout the study. The following measures will be taken to ensure the privacy of subjects:

- A code (unique identification) number for each subject will be kept on file.
- Only their correspondence identification number will identify subjects.
- Access to the documents and data will only be made to the Investigators and study staff in the study.
- The confidentiality of these documents will be protected to the extent provided by the law.

13.2 Institutional Review Boards

The Sponsor and/or Investigator must submit the protocol to the appropriate IRB and obtain a copy of the written and dated approval letter.

The approval letter should state the name of the documents reviewed, date of review, date of approval, and reference the study name (protocol title, study number, and version).

The informed consent used by the Investigator must be reviewed and approved by the Sponsor prior to submission to the IRB. The Investigator cannot enroll subjects until a copy of the approved informed consent is obtained from the IRB.

Any amendments to the protocol or informed consent should be submitted to the IRB for review and approval per 21 CFR 56. The IRB should be notified of any changes that may affect conduct of the study or pose safety risks to the subjects.

13.3 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.

13.4 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 for approval, the protocol amendment must be agreed upon and signed by both the Investigator and the Sponsor. The Investigator shall not make any changes to the protocol without Sponsor approval and documented approval from the IRB. Both PI and Sponsor will retain the IRB approval letter and approved protocol as confirmation that the protocol amendment was approved.

13.5 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 GCP and federal regulations 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 and/or IRB.

13.6 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.

14 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.

15 REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made:
1	14Nov2017	Original version

16 REFERENCES

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