Official Title: A Multi-Center Study on the Utility of Non-invasive Carboxyhemoglobin and Total Hemoglobin Measurement in Emergency Department Patients

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A Multi-Center Study on the Utility of Non-invasive Carboxyhemoglobin and Total Hemoglobin Measurement in Emergency Department Patients

Sponsor:
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Study Devices:
Rad-67 Pulse CO-Oximeter

Rainbow DCI Mini Super Sensor

Sponsor Protocol Number: SUNE0002

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1 INTRODUCTION

This document is a protocol for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki. In participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of IRB/IEC approval, ISO-14155, and International Conference on Harmonization Good Clinical Practice guidelines ICH GCP.

1.1 Background and Rationale

Carbon monoxide (CO) is the leading source of poisoning in the US[1] and elsewhere. CO poisoning (COP) can cause severe disability and death[1]. CO is released whenever there is combustion of fossil fuels including wood, oil, kerosene, etc. The diagnosis of COP is made when exposure to CO occurs and there are signs and symptoms consistent with toxicity[2]. Exposure can be determined either with measurement of environmental CO levels or carboxyhemoglobin (COHb) concentrations in the blood. COP can cause headache, nausea, vomiting, dizziness, syncope, loss of consciousness, coma, focal neurological deficits, psychiatric manifestations and cardiac ischemia. Because CO is colorless, tasteless and has no odor, patients may not know if they have been exposed. Universal screening with a blood test is not feasible and not typically performed. Many of the signs and symptoms associated with COP are non-specific and may be attributed to other conditions if CO exposure is not considered. Patients could therefore be released from the hospital to return to an environment with CO potentiating toxicity, leading to death or severe disability. The use of environmental CO detectors has increased in public facilities and private homes in the US, but screening of emergency medicine subjects for CO exposure is not yet a standard practice. A device which estimates COHb concentrations non-invasively using a finger probe has been approved by the FDA and utilized in clinical care. This device passes 8 separate frequencies of light through the fingertip and measures absorbance at those frequencies during pulsatile blood flow, allowing estimation of pulse oximetry (Sp) hemoglobin species (Oxyhemoglobin: SpO2, total hemoglobin: SpHb, carboxyhemoglobin SpCO, and methemoglobin: SpMet). We have used this device at Rhode Island Hospital to screen patients who presented for any complaint and showed that 1-4/10,000 patients had unsuspected (both to the patient and clinician) COP[3,4]. The sources of exposure were often faulty exhaust systems or dysfunctional appliances in the home. Other investigators have replicated these findings in Vermont (unpublished), Europe[5,6] and Turkey[7]. Studies which have evaluated the accuracy of the device when compared to blood COHb measurements have shown variable results[8-10]. Taken together, these studies show that sensitivity of the device has utility for COP screening, but it does not have the accuracy to replace blood COHb.

The device manufacturer has developed a new diagnostic platform that allows for simultaneous measurement of SpO2, SpCO and SpHb, with modifications that may improve diagnostic performance. Most emergency department routinely measure SpO2 during triage, and some (such as Rhode Island Hospital) also measure SpCO. Enhancement of the triage oxyhemoglobin profile to include total Sp CO and SpHb could provide significant benefit in a busy emergency department setting.

Determination of anemia rapidly in the Emergency Department may prevent morbidity and mortality. Patients with traumatic injuries causing hemorrhage, occult internal hemorrhage (GI bleeding, ectopic pregnancy, etc.), hemolysis, or other critical anemias, could be quickly identified. Triage nurses could then expedite physician evaluation and acquisition of blood samples for type and cross. Screening for anemia is subjectively performed by observing for pallor in the skin and mucous membranes (in particular, the palpebral conjunctiva). However, studies have shown that this method is not reliable[11]. Validation of a non-invasive screening method that may be utilized in the pre-hospital setting or in emergency department triage could prevent complications associated with delays in diagnosis of anemia by blood analysis.

References:

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7 Zorbalar N, Yesilaras M, Aksay E. Carbon monoxide poisoning in patients presenting to the emergency department with a headache in winter months. *Emerg Med J*. 2014;31:e66-e70.
8 Touger M, Birnbaum A, Wang J, et al. Performance of the RAD-57 Pulse CO-Oximeter Compared With Standard Laboratory Carboxyhemoglobin Measurement. *Annals of Emergency Medicine*. 2010;56(4):382-388.
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1.2 Study Device

SpHb and SpCO technology uses a multiwavelength sensor with various light emitting diodes (LEDs) that pass light through the measurement site to a detector as shown in the figure below. Signal data is obtained by passing various visible and infrared lights (LEDs, 500 to 1400nm) 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 SpHb and SpCO.

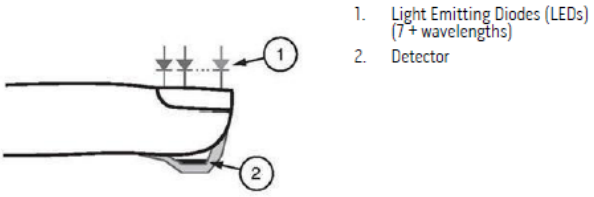

Figure 1 Masimo technology overview

Devices used for SpHb and SpCO measurement evaluation consist of a Masimo Rainbow pulse CO-oximeter (e.g. Masimo Rad-67, investigational) connected to a fingertip sensor (e.g., Masimo DCI Mini Super sensor, investigational). The investigational devices used in this study employ similar material and technology compared to FDA-cleared devices. The investigational devices have undergone risk analysis and safety testing in accordance with applicable safety standards, including electrical safety, current leakage, mechanical safety and biocompatibility testing for patient contacting materials. That risk assessment concluded that the investigational devices do not pose unmitigated risks to operator or subject.

The Rad-67 is a prototype handheld pulse CO-oximeter with Rainbow technology similar to already cleared Masimo noninvasive pulse CO-oximeters and is intended for spot-check measurements on patients in various care area settings (hospitals, hospital-type facilities, and clinics). The device is a more compact version of 510(k) cleared Rad-57 and Pronto devices. The Rad-67 also comes with an upgraded display with touchscreen capabilities. The Masimo Rad-67 is intended to be used with Masimo sensors and patient cables.

The Masimo reusable DCI Mini sensor is intended to measure non-invasive physiological parameters such as SpO2, SpHb, SpCO, SpMet, PR, and PI, similar to the existing FDA cleared Masimo reusable sensors. The DCI Mini sensor has a slimmer and more compact design compared to other Masimo reusable finger sensors. The DCI Mini sensor is intended to be used on adults or pediatric subjects weighing greater than 3 kg.

1.3 Risk/Benefits

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

Sensor risks: 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 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.

2 STUDY OBJECTIVES

The purpose of this study is to determine the clinical utility of triage screening for anemia and COP in the ED setting.

SpCO:

1. Measure extent of agreement between SpCO and COHb determined by co-oximeter measurement of blood in the emergency department.
2. Determine diagnostic performance characteristics of SpCO (sensitivity, specificity, False Positive and False Negative) compared to gold standard of laboratory measurement of COHB in whole blood using a co-oximeter. We will define *a priori* a "true positive" of COHb $\geq$7 for COP.
    a. We will also dichotomize smokers and non-smokers, and perform a post-hoc analysis to determine if the use of an alternate threshold for "true positive" based on smoking history is feasible.
3. Determine utility of SpCO for screening purposes by surveying the provider to determine the impact of screening test. Providers will be asked: Did the patient have a CO poisoning clinical diagnosis? Did SpCO screening lead to identification of occult toxicity?
4. Determination of elimination pharmacokinetics of CO in emergency department patients with CO toxicity as related to method of O_2 administration (nasal cannula, non-rebreather mask, CPAP, or endotracheal intubation). Clinicians will administer O_2 as dictated by patient care, the method and amount of O_2 will be recorded. CO elimination will be evaluated as a function of FiO_2.

SpHb :

Primary objectives

1. Determine diagnostic performance characteristics of SpHb for detecting anemia (Sensitivity, Specificity, False Positive and False Negative) compared to reference hemoglobin measurement by the hospital laboratory, based on WHO criteria for anemia. For comparison, total Hb determined by blood gas analyzer will also be measured and used only related to research. This value will be not recorded in the medical record and will be kept blinded to clinical care team. This will be completed if sufficient number of participants with anemia are enrolled during the study period. (If not, a separate study related to this objective will be designed)
2. Determine utility of SpHb for screening purposes
    a. Establish threshold of SpHb that best predicts the clinical outcome of "acute treatment of anemia", defined as: blood transfusion, admission to hospital for further workup of anemia, or admission to operating room

b. The threshold of SpHb will be determined by receiver operating curve analysis of the pooled results from the first set of 500 subjects for each institution.
c. Validate the SpHb threshold that predicts the outcome of "acute treatment of anemia" using a second set of subjects of 500 subjects from each institution.

Secondary objectives:

1. Measure extent of agreement between SpHb and total Hb determined by central hospital laboratory. Total Hb determined by blood gas analyzer will also be compared to the central laboratory measurement.
2. Survey the provider to determine the impact of the screening test. Providers will be asked: Did SpHb screening expedite care of patients? Did SpHb screening identify occult anemia?

3 STUDY DESIGN

This is a prospective, nonrandomized, multi-center study of the performance of simultaneous non-invasive testing for two common disorders (COP and anemia). We will determine the limits of agreement and performance characteristics of non-invasive SpCO and SpHb values compared to standard blood tests for measurement of COHb and hemoglobin, in the emergency department setting.

4 CLINICAL TEST SITE

Rhode Island Hospital

[redacted]

University of Vermont

[redacted]

Tepecik Training and Research Hospital

[redacted]

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

At least 3000 subjects across three sites may be enrolled onto this study. We expect to enroll approximately 1000 subjects at each site. This sample size is based on previous experience that has have demonstrated: 1) Occult toxicity occurs in approximately 1-3/10,000 ED visits. 2) Higher numbers of CO, needed to determine extent of agreement between non-invasive and laboratory measurements, are infrequent.

5.2 Inclusion Criteria

- Age 1 year or older.
- At least one digit has acceptable width as measured by study-provided digit gauge.
- Presenting to emergency department for any complaint.
- Potential for IV catheter and/or blood draw for CBC as standard of care.

5.3 Exclusion Criteria

- Patients who are unable to consent and also surrogate consent was unable to be obtained.
- Patients with fingernail polish, discoloration or trauma to fingers.

5.4 Study Timelines

Subject participation in this study is not expected to delay any care or prolong their stay in the ED. The study will be conducted approximately between October 1, 2016 and December 31, 2018. We anticipate enrolling an average of 10 patients a day.

Subject Recruitment Patients may be screened at triage with FDA approved oximeter devices as part of standard of care procedures. The results of this screening will be recorded in the chart if performed, by clinical staff as per routine procedure.

A convenience sample of patients aged 1 year and up presenting to the emergency department for any complaint and who have received or will receive a blood test for CBC or an IV catheter during their care (determined by their care provider independently) or will be approached by trained research staff for evaluation for enrollment in the study.

We will also approach patients with known CO exposure or who have anemia to enroll them in this study. The attending emergency physician will conduct usual clinical care; research staff will seek to obtain informed consent for this part of the study.

Research staff will also be notified of any patient presenting to the emergency department with suspected CO exposure (e.g. rescued from fire), toxicity or anemia, or patients with signs and symptoms of CO toxicity (unexplained headache, nausea, vomiting, dizziness or lightheadedness, syncope, neurological deficits, shortness of breath). The treating provider will be notified if the patient has agreed to participate. If the clinician determines an IV is necessary, these patients will also be eligible for inclusion in the study.

Informed Consent:

- Full written informed consent will be obtained for all subjects enrolled in the study.
- Surrogate consent may be obtained if subject is unable to consent due to cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of the research subject.
- In an emergency room setting, the order of priority does not apply, nor does the surrogate have to show reasonable knowledge of the subject. Surrogate consent may be obtained from a surrogate decision maker who is any of the following:
    - The person's agent designated by an advance health care directive.
    - The conservator or guardian of the person having the authority to make health care decisions for the person.
    - The spouse of the person.
    - The domestic partner of the person as defined in Section 297 of the Family Code.
    - An adult son or daughter of the person.
    - A custodial parent of the person.
    - Any adult brother or sister of the person.
- In emergency room research settings, no surrogate consent may be utilized if there is a disagreement whether to consent among any available surrogates.
- If the potential research subject has questionable capacity, the investigator shall proceed with the standard consent process and document the subject's abilities to understand and express a reasoned choice. If there is lack of decisional capacity, the investigator shall inform the subject of the intent to obtain surrogate consent. If the subject expresses resistance, the subject shall be excluded from the research study. If there is no resistance expressed, the investigator will proceed to obtain surrogate consent. Subsequently. the investigator shall describe the consent process to the surrogate.
- A subject who regains the cognitive ability to consent must be re-consented using standard consenting procedures.

HIPAA Waiver for Subject Screening

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.

5.5 Withdrawal of Subjects

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

6 STUDY DEVICE

Masimo Rad-67 pulse co-oximeter

Masimo DCI Mini Super sensors

6.1 Device Accountability

6.1.1 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.

6.1.2 Use of Study Device

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

6.1.3 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.

7 STUDY PROCEDURES

Stage 1: After obtaining informed consent, from the patient (18 y.o. and over) , legal guardian (<18 y.o.) with child assent or patient surrogate, as appropriate, the sensor will be placed as per sensor directions for use (DFU), and the SpCO and SpHb values recorded (this process takes less than 1 minute and is not associated with any pain or discomfort). Near-simultaneously [redacted]), a [redacted] ml vial of blood will be withdrawn from the patient's IV site for analysis. No new needle sticks will be performed. The study will not interfere with any aspects of patient care. The blood analysis for COHb will be performed immediately in the ED using a blood gas analyzer specifically obtained and properly calibrated for this study, by research personnel who will receive a standardized training program on its use. The patients will incur no additional cost and they will experience no delay in care or any prolongation of their stay in the ED stay related to this study. Hospital Laboratory Hemoglobin values, if measured as part of patient care, will be obtained from the patient's chart and

recorded on the case report forms (CRF). Demographic information, height, weight, gender, age, skin color, vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry), presence or absence of jaundice, smoking history will be recorded on CRFs along with the values of SpCO, SpHb, COHb and hemoglobin concentration. If an abnormal COHb (>10%) value is observed, the measurement will be repeated using a Masimo FDA-cleared pulse CO-oximeter (e.g. Rad-57 and DCI sensor). If abnormal values are confirmed, the patient's clinician will be notified by research staff immediately. The clinician will independently determine any course of action related to patient care utilizing this information. CRFs will be kept within a locked filing cabinet in the Emergency Medicine Research Office which is locked. A de-identified data spread sheet will be created and kept on a storage device with encryption.

Stage 2: We will also approach patients with known CO exposure or who have anemia to enroll them in an arm of this study. Research staff will be notified of any patient presenting to the emergency department with suspected CO exposure or toxicity including patients with signs and symptoms of CO toxicity (headache, nausea, vomiting, rescued from fire, unexplained neurological deficits) or who have low hemoglobin values for any reason determined as part of their routine care. The treating provider will be notified if the patient has agreed to participate and if the clinician determines an IV is necessary, these patients will also be eligible for inclusion in the study.

Stage 3: In some cases of confirmed COP, patients will be asked to participate in an arm of the study where elimination pharmacokinetics of CO from the blood is determined. Serial, non-invasive measurements ([redacted]) of SpCO, SpMeth, SpO_2 and SpHb will be obtained from patients with SpCO or COHb concentration of [redacted] or higher. Three additional [redacted] ml. blood samples will be obtained from this selected group for COHb analysis during this hour after the first COHb sample for blood gas analysis. For children under the age of 8, the three additional samples will be no more than [redacted] ml each. We will record the method and amount of O_2 administered during the [redacted] hour of treatment, so that we can analyze the effects of varying FiO_2 on CO elimination kinetics.

For patients ultimately determined to have a CO poisoning or anemia diagnosis, the treating clinicians will be surveyed by the research personnel in real-time to determine if the clinicians thought screening impacted patient care for these patients (the short survey is included below).

At the end of study data analysis, if the clinical utility of the investigational device is demonstrated through this study, the data from the Stage 1 subjects will be unmasked. Study sponsor and/or the investigators will retrospectively analyze the data collected from these subjects to determine if any subjects had high CO readings. Such subjects will be contacted to inform that the Masimo device measured high levels of CO during their ED visit and to consult with their healthcare provider.

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

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

- Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
- Adverse Device Effect (ADE): an adverse device effect is any untoward or unintended response to a medical device which may result from insufficiencies in the instructions for use or deployment of the device, or from use error.
- Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.
- Serious Adverse Device Effect (SADE): a serious adverse device effect is an adverse device effect that results in death, inpatient hospitalization, severe or permanent disability or is life threatening.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life threatening problem or death cause by or associated with, a device, if the effect, problem, or death was not previously identified

in nature, severity or degree of incidence in the investigational plan, or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects. Refer to the Device Risk Analysis and Risk Assessment section for details on anticipated adverse device effects.

8.2 Anticipated Adverse Events:

Mild allergic reaction to sensor material.

8.3 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.

8.4 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.

8.5 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.

9 DATA MANAGEMENT

9.1 Provisions to Protect the Privacy Interests of Subjects

Potential study candidates will be identified in real time, as they arrive and register in the emergency department. Research staff will check with the provider to ensure the subject's appropriateness. Subjects will only be approached about the study in private treatment rooms in the emergency department. The research staff will provide the consent form in person and give the prospective subject sufficient time to review the consent form and discuss the study with friends and family.

9.2 Data Management and Confidentiality

All documents associated with this protocol will be kept in the locked 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.

9.3 Source Documents

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

9.4 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.

9.5 Data Transfer and Storage

9.5.1 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.

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

9.5.3 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.

9.6 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.

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: children,

economically disadvantaged or unemployed, educationally disadvantaged, limited English skills and/or Non-US citizens, pregnant women, and employees/colleagues/students of the Principal Investigator and/or study staff.

10.2 Protection of vulnerable subjects

- For children, assent forms will be required from subjects 7 – 17 years and the Investigator will ensure that parent or legal guardian does not unduly influence subjects to participate. Subjects will have ample time to ask questions and understand the information being presented.
- No compensation will be 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.
- For pregnant women, any anticipated or possible risks to mother or unborn child will be clearly outlined in the informed consent form.
- Medical care will be provided to these subjects after the clinical investigation has been completed 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.
- Surrogates are prohibited from receiving any financial compensation for providing consent.
- A subject who regains the cognitive ability to consent must be re-consented using standard consenting procedures.

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

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 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.

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

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.

14 REVISION HISTORY:

Version Number	Version Date	Summary of Revisions Made:
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]