Official Title: Feasibility and Performance Evaluation of INVSENSOR00024

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NCT Number: NCT03831282

Feasibility and Performance Evaluation of INVSENSOR00024

Sponsor: Masimo
52 Discovery
Irvine, CA 92618

Primary Investigator: [redacted]

Study Devices: Masimo Radical 7 Pulse Co-Oximeter
INVSENSOR00024 pulse oximeter sensor

Sponsor Protocol Number: CHOC0004

IRB: CHOC Institutional Review Board –Research Institute
1201 W. La Veta Avenue
Orange, CA 92868

Principal Investigator	Title	Signature	Date
[redacted]	Principal Investigator		
Sponsor	**Title**	**Signature**	**Date**
Cristina Johnson	Sr. Manager, Clinical Research Compliance		

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

Pulse oximetry is commonly used as a standard of care in critically ill patients in the intensive care units and used in surgical operations to monitor oxygen saturation (SO_2) levels. Advantages of this noninvasive technology allows clinicians to detect hypoxia, avoid hyperoxia, and minimize the frequency of blood gas analysis, as well minimizing mortality rates[1]. Oxygen saturation levels represents the ratio between oxyhemoglobin (oxygenated) and deoxyhemoglobin (non-oxygenated) present in the blood[2]. The pulse oximeter works by measuring frequencies of light which correspond to the type of hemoglobin present in the blood. By isolating the pulsatile signal, the oxygen saturation in the arterial blood vessels can be estimated (photoplethysmography).

Masimo Corporation develops noninvasive medical technologies that contain Masimo Signal Extraction Technology (SET®), such as the Masimo SET pulse oximeter adhesive sensors. Masimo SET signal processing overcomes conventional pulse oximetry technology to distinguish between pulsating blood in arterial and venous blood at measurement site. This FDA-cleared technology accurately measures in real-time the oxygen saturation (SpO_2) and pulse rate, in motion and non-motion, with fewer false alarms and more accurate true alarm detection. Advanced algorithms filter out noise, such as venous signals, to help improve clinician judgment and patient survival outcome in adults, pediatrics, and neonatal populations[10].

Masimo recently received FDA-clearance for the single patient adhesive sensor series of pulse oximeters and patient cables called Red Diamond (RD) in the adult population. The RD SET sensors are designed to maximize patient comfort by the lightweight design in the patient cable and connecter, and optimal components in the sensor. This study will be used to evaluate the feasibility of an investigational sensor, called INVSENSOR00024, for the neonatal population. [redacted]

1.2 Investigational Devices

Masimo RD SET pulse oximeter (SpO_2) technology uses a two-wavelength sensor with light-emitting diodes (LEDs) that pass light through the measurement site to a detector as shown in Figure 1. Signal data is obtained by passing [redacted] through a capillary bed, such as the fingertip, hand, or foot shown in Figure 2. This signal measures the changes in the absorption during the blood pulsatile cycle, which the detector receives as variations in light intensity and converts it to an electrical signal and obtains real-time oxygen saturation levels.

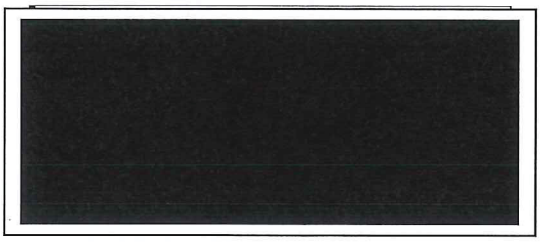

Figure 1. Pulse oximeter sensors

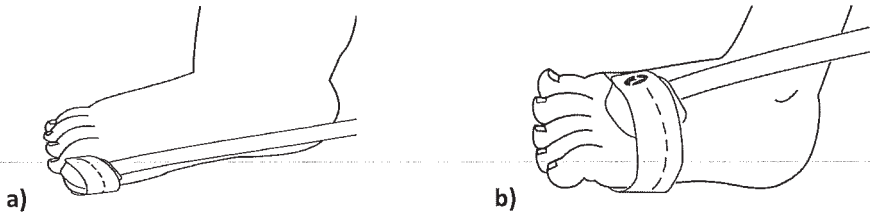

Figure 2. Sensor placement: a) fingertip or big toe and b) foot

Devices to be used in this study maybe United States Food and Drug Administration (FDA) 510(k) cleared devices, and/or investigational. The FDA-cleared device to be used is the Masimo Radical 7® pulse oximeter. The investigational devices to be used in this study is the INVSENSOR00024 sensor [redacted] The INVSENSOR00024 sensors employ identical materials and physical technology as the FDA-cleared devices and 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.

1.3 Risk/Benefits

Benefits: There is no benefit to the individual for participation in this research study. No compensation will be paid to the participants or their families. Future benefits might include a reduction in invasive procedures due to the ability to obtain noninvasive blood parameter measurements.

Pulse oximeter: The Masimo Radical 7 pulse oximeter patient monitor used during this study is FDA-cleared and poses no risk to the subject.

Sensor risks: As with all optical sensors, the INVSENSOR00024 sensors are investigational devices that have risks of thermal burn. The design of these sensors includes safeguards, and this risk is believed to be low.

All patient-contact materials including the adhesive used in the design of the INVSENSOR00024 sensors are biocompatible, compliant with ISO-10993-5 and ISO-10993-10 testing, and the results demonstrate that the materials are non-toxic, and non-irritating, and non-sensitization. The sensors have been subjected to performance, mechanical, and electrical testing, skin surface temperature and results demonstrate that the sensors meet the requirements for safety and effectiveness for intended use of the product, refer to investigational brochure for further details.

Patient cable risk: Entanglement of the sensor cables may occur but the research personnel will be present during the study to avoid such an occurrence.

Ambient light shield risk: Suffocation from the shield may occur but the research personnel will be present during the study to avoid such an occurrence.

2 STUDY OBJECTIVES

The primary objective of this clinical investigation is to evaluate the performance of INVSENSOR00024 in the neonatal population.

3 STUDY DESIGN

This is a prospective, non-randomized, single arm study design to evaluate SpO2 performance of the INVSENSOR00024 sensors in the neonatal population in a clinical environment using convenience sampling.

[redacted]

4 CLINICAL TEST SITE(S)

Children's Hospital of Orange County (CHOC)

1201 W. La Veta Avenue

Orange, CA 92868

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

Subjects will be healthy and non-healthy newborns (1 month old or younger) at CHOC. A convenience sampling with up to 30 subjects with diversified demographics (age, gender, ethnicity, skin tone, comorbidities, etc.) will be recruited and enrolled at this site with the following inclusion and exclusion criteria.

5.2 Inclusion Criteria

- Less than or equal to 1 month (28 days) of age
- Weight ≤ 5 kg at the time of consent or last recorded weight prior to consent.
- Subjects admitted with standard of care (SOC) arterial blood sampling line already in place

5.3 Exclusion Criteria

- Subjects with both significant abnormal aortic arch and radial line in place
- Subjects with suspected or diagnosed critical congenital heart disease (CCHD)
- Subjects with underdeveloped skin
- Subjects with abnormalities at the planned application sites that would interfere with system measurements
- Subjects with known allergic reactions to foam/rubber products and adhesive tape
- Deformities of limbs, absence of feet, severe edema, and other at the discretion of the Principal Investigator

5.4 Study Timelines

The anticipated duration of subject participation in this study will not exceed 1 visit during their stay at CHOC. The sensors may be placed up to 2 (two) times while the arterial line is in place. [redacted]

5.5 Subject Recruitment and Screening

Potential subjects will be recruited from the patient pool at CHOC. Subject screening for the clinical research study will take place during recruitment to determine if an individual is eligible to participate in the study. If the subject is eligible, informed consent and HIPAA be obtained. See Section 7.1 for details on informed consent procedures.

5.6 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. Participant's parent/legal guardian may elect to

withdraw their child at any time without any consequences or loss of benefits to which they are entitled. As the subject, the child may be withdrawn from the study prior to expected completion for reasons such as safety concerns, failure to meet protocol requirements, subject consent withdrawal, etc.

Any data collection, until the time of subject's withdrawal, may be included in the final data analysis unless the subject withdraws their consent. Notification of the subject's withdrawal should be documented in the case report forms (CRFs) and include clear documentation of the reason for withdrawal to the Sponsor.

In case a subject leaves the study prematurely, another subject may be recruited.

6 STUDY DEVICE

6.1 Description

FDA-cleared devices:

Masimo Radical 7 Pulse CO-Oximeter

The Radical 7 pulse CO-oximeter is a noninvasive patient monitor that continuously measures and monitors in real-time the oxygen saturation of arterial hemoglobin (SpO2), and pulse rate (PR), among other parameters, and is for use with adult, pediatric, and neonatal patients during both motion and no motion conditions, and for patients who are well or poorly perfused in hospitals, hospital-type facilities, mobile, and home environments. The patient cable connects the INVSENSOR00024 sensor to the Radical 7.

Masimo RD rainbow M20 patient cable

The FDA-cleared RD M20 patient cable is similar to FDA-cleared RC-12 patient cables, but is only used for RD SET series sensors.

Investigational devices:

INVENSOR00024 sensors

[redacted]

6.2 Device Accountability

6.2.1 Receipt of Study Device

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.

6.2.2 Use of Study Device

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

6.2.3 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.

6.2.4 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 Informed Consent and Screening Procedure

7.1.1 Following identification of a potential eligible subject, as defined by the inclusion and exclusion criteria, the child's parent(s), guardians(s), legally authorized representative, will be approached by the study staff. The study research staff will explain the purpose and procedures of the study in respect to potential risks & benefits, and clarification of subject's rights & privacy and allow ample amount of time for participating in the described study. The research team will emphasize that participation is voluntary, has no monetary compensation, and declining the participation will not affect their child's medical care.

7.1.2 As a subject, the child must meet all the inclusion criteria and none of the exclusion criteria prior to being enrolled in the study.

7.1.3 This protocol requires written informed consent in accordance with applicable federal and state regulations, as well institutional review board (IRB). If the child's parent(s)/legal guardian(s) express interest in participating in the study, they will be asked to read the written informed consent.

7.1.4 Once the parent(s)/legal guardian(s) questions have been answered and the informed consent signed and dated, the Principal Investigator or delegate will also sign the informed consent document, approving that the subject will be enrolled in the study. The Investigator shall retain the original copy of the signed informed consent document in each subject's records and provide a copy to the subject. The investigator shall not enroll any subject to participate in the study or consent any subject prior to receiving IRB approval of the informed consent form.

7.1.5 Subject's demographic information which may include, but is not limited to: gender, age, weight, height, race, ethnicity, [redacted] before/after sensor use will be recorded on the case report form (CRF).

7.2 Noninvasive readings

[redacted] The subject will be fitted with the INVSENSOR00024 sensor on either the hand, foot or toe; whichever fits best following the manufacturer's directions for use (DFU) referenced in the investigator brochure. [redacted]

7.2.3 Record sensor placement location, ID/lot number, and other application information into the case report form (CRF).

7.2.4 Connect the patient cable to the Radical 7 and the investigational sensor.

7.2.5 Ensure that the Radical 7 is docked into the docking station and powered on prior to conducting the noninvasive measurements.

7.2.6 Allow the SpO2 and other vital parameters to appear on the Radical 7 patient monitor then begin noninvasive measurements via [redacted]

7.2.6.1 An additional attempt may be performed if a SpO2 value does not appear on the Radical 7 [redacted] Record any changes to sensor placement and include detailed comments directly in the CRF.

7.2.7 The noninvasive measurement will be initiated approximately [redacted] before standard of care (SOC) blood draw.

7.2.8 Record time of SOC blood draw into [redacted] and case report form (CRF). [redacted]

7.2.9 After the SOC blood draw, continue data collection for an additional [redacted] if this is the last blood draw foreseen for the subject. If data collection is anticipated to continue until the next SOC blood draw, then noninvasive data collection may continue without interruption.

7.2.10 If possible, collect data for up to [redacted] SOC blood draws, however data collection can be concluded after the [redacted] SOC blood draw.

7.2.11 [redacted] will be recorded in the CRF. [redacted]

7.2.13 Study completion is after the noninvasive measurements are complete. The study duration from the time of blood sample is obtained until after the noninvasive data collection is completed will be based on the SOC blood draw scheduling.

8 STATISTICAL ANALYSIS

8.1 Sample Size Determination

8.1.1 [redacted] Feasibility

8.1.1.1 This study will use a convenience sampling of 25 subjects, but up to 35 subjects may be enrolled to account for possible events such as subject withdrawal, device deficiencies, and/or incomplete cases.

8.1.1.2 The initial version of the protocol (version 1.0) was a feasibility study performed, in part, to generate estimates of various statistical parameters required for sample size calculation. As such, there is no formal statistical plan in the neonate population. However, Masimo studies in the adult population have indicated 25 subjects provide sufficient statistical power for most applications. Refined estimates of statistical parameters will be used in the planning of a future validation study.

8.1.2 [redacted] Clinical Environment

8.1.2.1 A variance analysis of the initial subjects (Version 1.0) used in the feasibility phase of this protocol, provided an across subject variance of 3.72 ($\sigma = 1.93$).

8.1.2.2 This value can be used to determine the Number of Subjects needed for a range of effect sizes using the following equation and parameters for a one sided hypothesis test[1]

$$N = \left(t_{\propto} + t_{\beta}\right)^2 * \frac{\sigma^2}{\delta^2}$$

$\alpha = 0.05$

[1] William Diamond, Practical Experiment Designs for Engineers and Scientists (Wiley, 2001), 29

$\beta = 0.20$
$\delta = Minimum\ Required\ Detection\ Limit$
$\sigma^2 =$ Estimated Variance for A_{RMS}
$t_\alpha\ is\ the\ t - distribution\ cumulative\ density\ function\ for\ a\ one\ sided\ hypothesis\ test$

8.1.2.3 As noted in FDA Guidance UCM081352, there will be "inherently greater noise in the measurement of neonatal oxygen saturation." Therefore, an effect size of $\delta = 1.5$ is chosen to allow for additional variation due to use of clinical personnel, clinical pre analytic procedures, and utilizing hospital reference instruments.

8.1.2.4 The equation above can then be solved iteratively. Therefore, the second part of the study will select a minimum of 12 new subjects; up to a maximum of 30 subjects that may be pooled across multiple clinical sites.

8.1.2.5 There are no other acceptance criteria for this study. Bias, Precision and RMS values will be reported but are not required for specification validation as this is a convenience sample study using hospital personnel and reference instruments. Results are intended as an adjunct to the full validation study performed in a controlled clinical laboratory using healthy adult volunteers.

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.

9.2 Anticipated Adverse Events:

Sensor may cause slight, temporary redness, which should fade away shortly after sensor removal.

Sensor may cause thermal burn; however, the design includes safeguards and this risk is believed to be minimal.

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. 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 possible, but no later than 5 working days after the protocol deviation.

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 after the IRB notification of withdrawal of approval.

10 DATA MANAGEMENT

10.1 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.

10.2 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.

10.3 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.

10.4 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 a secure 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. Device data and electronic copy of CRFs will be checked for completeness. If there are inconsistent or missing data points, a data query log 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 through old entry, add in new entry, and initial and date it, and resend the updated corrected CRF copy to Masimo. 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.

10.5 Record Retention

All study records, 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 data will be retained for the necessary period of time as required by the institution's regulations. Study Records shall be retained during the study and for a minimum of two years after study closure 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:

[redacted]

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 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 follow-up letter. 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 13.3 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 VULNERABLE POPULATIONS

12.1 Definition

12.1.1 Vulnerable population are research participants, such as children, prisoners, pregnant women, handicapped, or mentally disable persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion and undue influence. This study will recruit children from either economically or educationally disadvantaged families.

The federal regulations that govern the protection of human subjects (21 CFR Part 50, Subpart D) require additional protection for the vulnerable population.

12.2 Protection of vulnerable subjects

- For children, the Investigator will ensure that parent/legal guardian does not unduly influence subjects to participate (21CFR Part 50). Parents/legal guardian of the participant will have ample time to ask questions and understand the information being presented.
- Participant's parents/legal guardian with limited English skills will be provided translated documents in native language, staff/independent interpreter, and have ample time to ask questions and understand information.
- There is no undue influence to the parent/legal guardian of the participant due to no financial incentive for the economically disadvantaged subjects since there is no compensation for the completion or participation in this study.
- Educationally disadvantaged parent/legal guardian of the participant will be provided ample time to ask questions and comprehend the information.
- 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.

12.3 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.

13 ADMINISTRATIVE ASPECTS

13.1 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.

13.2 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.

13.3 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.

13.4 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.

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:
1.0	October 25, 2017	Original version
2.0	November 28, 2018	Updated title, title for sponsor personnel and name of investigational sensor to "INVSENSOR00024". [redacted] Inclusion criteria updated to clarify 1 month as 28 days and include ≤ 5 kg. Exclusion criteria updated to exclude subjects with both significant abnormal aortic arch and radial line in place, and suspected or diagnosed CCHD. [redacted] Administrative updates and clarifications made to investigational devices, study timelines, subject recruitment and screening, non-invasive readings, data management and confidentiality, data transfer and storage, record retention and monitoring plan.

16 REFERENCES

1. Jubran, A. (2015). Pulse oximetry. *Crit Care*, **19**, 272.
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