Official Title: Rainbow Acoustic Monitoring (RAM) in Patients Weighing up to 10kg Comparison Study

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Rainbow Acoustic Monitoring (RAM) in Patients Weighing up to 10 kg Comparison Study

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Study Device:
INVSENSOR00004
Masimo Radical-7® Pulse Co-Oximeter device with RRa parameter
Masimo SpO_2 Pulse Oximeter Sensor
Capnostream capnograph

Sponsor Protocol Number: SZMU0011

IRB:
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Institutional Review Board
5323 Harry Hines Boulevard
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Loma Linda, CA 92350

Principal Investigator	Title	Signature	Date
[redacted]	Principal Investigator		
Sponsor	**Title**	**Signature**	**Date**
[redacted]	Director of Clinical Research		

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

Recording vital signs (pulse rate, respiratory rate, blood pressure and temperature) is the standard of care for all patients on the hospital ward. However, documentation of vital signs is often poor or inaccurate. Of the four vital signs, respiratory rate is particularly difficult to assess and often not recorded in the patient record. This is in spite of the fact that elevated respiratory rate is one of the best predictors of respiratory deterioration, cardiac arrest and admission to the intensive care unit (ICU)[1].

A simple noninvasive device to continuously monitor respiratory rate is therefore highly desirable. However, existing automated methods have had limited success in broad adoption due to either low accuracy leading to too many false alarms or due to poor patient tolerance for continuous monitoring. These current methods include impedance pneumography (taken from standard ECG electrodes) and end-tidal carbon dioxide monitoring that utilizes a special nasal cannula to sample respiratory gases. The former suffers from low accuracy resulting in high false alarm rates [1,2,3]. In addition, impedance pneumography is a measure of respiratory effort and is known not to detect obstructive apneas, a major requirement for continuous surveillance monitoring of at risk patients. Capnography (ETCO2) monitoring is commonly used in the operating room/anesthesia setting but is not well tolerated in other patient care areas due to patient wearability issues that have resulted in limited compliance[3].

These limitations led Masimo Corporation to develop the rainbow Acoustic Monitoring (RAM) system with Masimo's Signal Extraction Technology (SET®). RAM noninvasively and continuously monitors and measures the acoustic respiration rates (RRa) and waveforms using an adhesive sensor with an integrated acoustic transducer converting acoustical airflow patterns to respiration rates. The RRa has shown to be accurate and reliable in offering clinical facilitations in early detection of respiratory compromise and patient distress in comparison to capnography monitoring [2,3].

The rainbow acoustic respiration sensor (RAS)-125c, is a FDA-cleared RAM sensor which can be applied to adult and pediatric patients weighing greater than 10 kg. The investigational RAM sensor is smaller in design compared to RAS-125c to facilitate sensor placement and improve attachment to the patient's neck with a transparent adhesive to allow flexibility upon sensor placement. The investigational RAM sensor is similar to the RAS-125c in performance parameters but differs in shape and size. In this study, the investigational RAM sensor is being evaluated for use in subjects up to 10 kg.

1.2 Investigational Devices

Masimo's RRa is a parameter that uses an integrated acoustic transducer to convert the acoustical airflow patterns and waveforms from the rainbow® Acoustic Respiration Sensors (RAS), also known as RAM sensors, to calculate respiration rates. Disposable single-use investigational RAM sensors will be evaluated in subjects up to 10 kg and is intended to measure non-invasive acoustic respiration rates. [redacted]

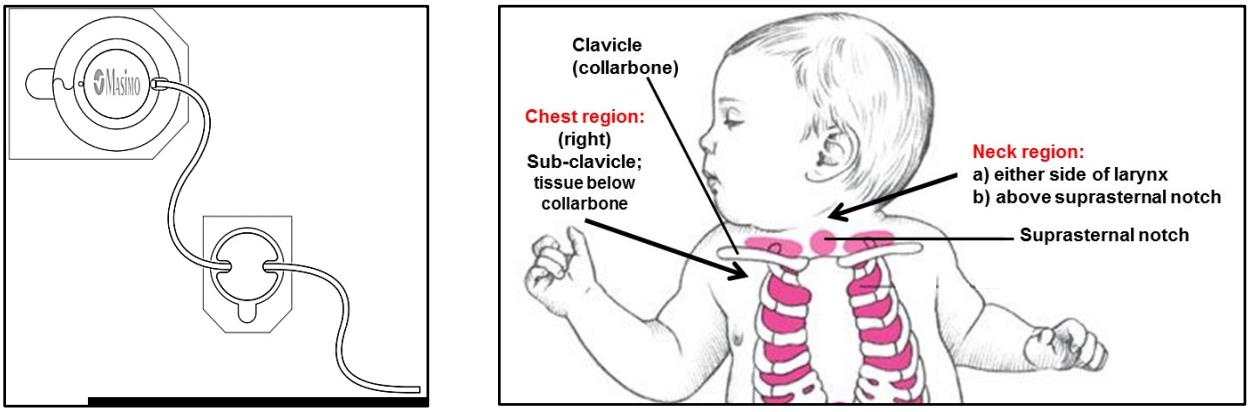


Figure 1. The small and round INVSESNOR00004 sensor (left) and the corresponding sensor placements around neck and chest regions (right).

The investigational use of the investigational RAM sensor for subjects up to 10 kg has 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. The risk analysis conducted resulted in the investigational sensor being classified as a low risk device.

2 STUDY DEVICES

2.1 Description

Investigational Devices:

INVSENSOR00004:

The investigational INVSENSOR00004 rainbow acoustic monitoring (RAM) acoustic respiration sensor is designed to noninvasively convert acoustical airflow patterns into respiratory rate (RRa). [redacted] The investigational sensor is a single patient use adhesive sensor [redacted] which includes biocompatible materials suitable for continuous skin contact.

Masimo Radical 7 pulse co-oximeter:

The Radical-7 is an FDA-cleared device, however [redacted] that enables the use of the investigational sensor for monitoring on the pediatric population, changing its status to an investigational device. No new patient risks will be introduced by the addition of the new software.

FDA-cleared:

Masimo pulse oximeter sensor and RAM Dual patient cable:

The pulse oximetry sensor is FDA-cleared and will be used along with the investigational RAM sensor. Pulse oximetry sensors function by shining light through the fingers or toes of the patient per manufacturer's directions for use to detect pulsation in the capillaries. The RAM dual patient cable joins connection to the investigational RAM sensor.

Capnostream capnography:

The Capnostream capnography is FDA-cleared device that monitors concentration of carbon dioxide (CO_2) in exhaled air to determine end-tidal CO_2 ($EtCO_2$) during anesthesia and intensive care. The capnography utilizes a mask or nasal cannula that is placed at the nostrils of the patient to detect breathing and airflow.

Reference analyzers/methods:

The acoustic raw data collected by the INVSENSOR00004 sensor and Radical 7 pulse co-oximeter will be manually annotated to obtain the inspirations and expirations by sound and visual measurements. The reference (RR_{ref}) will be obtained by measuring respiration rate based on the manual annotations of respiratory inspirations and expirations.

2.2 Device Accountability

2.2.1 Receipt of Study Device

Masimo may ship or hand-carry devices and sensors to the investigative sites. Upon receipt of the of the study device supplies, an inventory must be performed and the Equipment Shipment Check Form (FRM-2713) and the device accountability log (FRM-3407) will be completed for each device and signed by the receiver. 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.

2.2.2 Use of Study Device

Use of devices and sensors will be documented on case report forms (CRF) for each subject. Any unused devices must be returned to the Sponsor at the end of the study.

2.2.3 Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices. 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.

2.3 Risk/Benefits

Benefits: There will be no direct benefits to the enrolled subjects. Future benefits of continuous noninvasive respiration rate monitoring may aid clinicians to predict respiration deterioration in pediatric population in hospitals, hospital-type facilities, mobile, and home environments.

Sensor risks: As with all RAM sensors and pulse oximeter sensors there is risk of thermal burn and skin irritation, discomfort, and redness due to the sensor adhesive. The design includes safeguards, and this risk is believed to be low.

All patient-contacting materials, including the adhesive used in the design of the Masimo Rainbow sensors, have been subjected to biocompatibility tests per ISO 10993-1, ISO 10993-5, ISO 10993-10 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. The modifications to the sensor are specifically designed so as not to introduce any new risks to the subject, and have been developed pursuant to the design control regulations per ISO 14971.

3 STUDY OBJECTIVES

The objective of this clinical investigational study is to compare the acoustic respiration rates (RRa) obtained using the INVSENSOR0004 sensor in the subjects up to 10 kg with the respiration rates determined by manual annotations (RR_{ref}), and when applicable with capnography respiration rate (RR_{cap}).

4 STUDY DESIGN

4.1 General Design

This is a multi-center, prospective and nonrandomized study design. RRa measurements will be compared to measurements of actual respiration rates as determined by manual annotation of recorded respiration data, and when applicable to capnography data.

4.2 Study Outcome and Measurement

Evaluation on the comparison of RRa measurements will be reported as a bias of between the acoustic respiration rate (RRa) parameter and the manual annotation (RR_{ref}).

5 CLINICAL SITES

This is a multicenter study that may enroll up to 100 total subjects. The subjects enrolled in this study may be recruited from the following sites:

Site	Site Name and PI	Site Description
1	Children's Medical Center Dallas (CMCD) [redacted] Dallas, TX	Children's Hospital (Pediatric Anesthesiology)
2	Loma Linda University (LLU) [redacted] Loma Linda, CA	Department of Anesthesiology

6 SUBJECT SELECTION AND WITHDRAWAL

6.1 Population Base

Subjects will be healthy and non-healthy subjects. Subjects will be recruited from diversified demographics (age, gender, ethnicity, skin tone, comorbidities, etc).

6.2 Inclusion Criteria

- Subject weighing up to 10 kg
- Subjects will be inpatients and/or outpatients admitted in the NICU or PICU or PACU
- The parent/legal guardian has given written informed consent/assent to participate in the study

6.3 Exclusion Criteria

- Subjects with underdeveloped skin
- Subjects with skin abnormalities at the planned application sites that may interfere with sensor application, per directions-for-use (DFU) or trans-illumination of the site, such as burns, scar tissue, infections, abnormalities, etc.
- Subjects deemed not suitable for the study at the discretion of the investigator

6.4 Subject Recruitment and Screening

Following identification of a potential subject, the patient will be approached by either the principal investigator or a designated research study staff (co-investigator and/or study coordinator), who will explain the purpose and procedures of the study. If the patient expresses an interest in participating in the study, they will be asked to read the Informed Consent Form.

All subjects will have their medical history reviewed at the time of screening, after informed consent has been obtained, 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 not be enrolled in the study. If the subject meets all of the inclusion and none of the exclusion criteria, the subject will be enrolled into the study.

Information regarding the subject's demographics (including, but not limited to age, weight, race, ethnicity, comorbidities, medications, etc.), preexisting allergies, skin abnormalities and other preexisting diseases/conditions that may be relevant to the study will be recorded within the CRF.

6.4.1 HIPAA

The pre-screening of patients will require the investigators to access personal health information to identify prospective subjects without HIPAA authorization prior to obtaining written informed consent for the study. Informed consent and HIPAA authorization will be obtained during recruitment and screening procedures as described in previous sections of this clinical investigation plan; however, pre-screening process would require a waiver of HIPAA authorization, as the research study could not be practicably carried out without this implied waiver of consent. The participants' rights and welfare will not be adversely affected by waiving consent. Patients' protected health information (PHI) will not be inappropriately reused or disclosed to any other person or entity. To further safeguard all protected health information, the data collected during the study 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.

6.4.2 Withdrawal of Individual Subjects

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

Any data collected until the time of subject withdrawal may not be included in the final data analysis.

Information on the subject's withdrawal will be clearly documented in the case report forms along with reason of the withdrawal and will be notified to the Sponsor, as well as providing documentation in the medical records.

6.4.3 Follow-up for subjects withdrawn from study

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

6.4.4 Replacement of individual subjects after withdrawal
In case a subject leaves the study prematurely, another volunteer may be recruited.

7 STUDY PROCEDURES

7.1 Informed Consent and Screening Procedure

Following identification of a potential eligible subject as defined by the inclusion and exclusion criteria, the child's parent(s), guardian(s), legally authorized representative, and/or the subject (when age appropriate) will be approached by the study staff, who will explain the purpose and procedures of the study in respect to potential risks & benefits, and clarification of subjects rights & privacy information.

7.1.1 Once all their questions have been answered and the informed consent signed, they will be enrolled in the study. The Investigator shall retain a copy of the signed informed consent document in each subject's record and provide a copy to the subject. The Investigator shall not allow subjects to participate in the study or consent any subjects prior to receiving IRB approval of the informed consent form.

7.1.2 Subject's demographic information (including, but not limited to, age, weight, height, race, ethnicity, skin tone pigmentation via Massey Scale, fingertip diameter, etc.) and subject's medical history will be recorded on CRF.

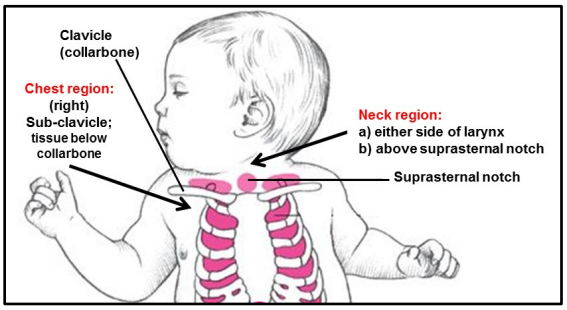
7.1.3 The point of enrollment is defined as the time at which a patient has signed and dated the consent form.

7.1.4 Study exit is defined as when the subject has completed the noninvasive device readings.

7.2 Noninvasive readings:

7.2.1 Subject will be fitted with the FDA-cleared pulse oximeter sensor at respective finger or toe location per manufacturer's Directions for Use (DFU) for the sensor (refer to Investigator Brochure).

7.2.2 Subject will be fitted with the investigational INVSENSOR00004 sensor per manufacturer's DFU. The INVSENSOR0004 sensor may be placed at the following locations depending on the subject's accessibility:



- Neck region: either side of larynx or suprasternal notch
- Chest region: sub-clavicle tissue below collarbone

7.2.3 As an additional piece of information for the study, a photo of the INVSENSOR00004, while it is attached to the subject, may be taken by the study staff. The study staff will notify the subject and/or subject's parent/guardian prior to taking the photo. The photograph will be taken so that no facial features of the subject are captured to protect the subject's privacy and confidentiality.

7.2.4 The investigational INVSENSOR00004 sensor and pulse oximeter sensor will both be connected to the RAM Dual patient cable. The patient cable is connected into the Radical 7 pulse co-oximeter.

7.2.5 Research study staff will assess if the subject can tolerate the capnography mask or nose sensor prior to recording data. The capnography sensor is connected into the Capnostream capnography.

7.2.5.1 If the subject is not able to tolerate with the capnography sensor then the capnography data will not be recorded.

7.2.6 Data will be recorded using laptop with the [redacted]

7.2.7 Periodic checks will be made to ensure subject's well-being and tolerance of the sensors, and to check that sensors are connected. Refer to Procedure Manual for data collection details.

7.2.8 Periodic checks are to be performed at a frequency that is determined to be suitable by the PI and designated study staff.

7.2.9 A minimum of [redacted] manual breath-counts with the duration of [redacted] each count will be performed at the start and towards the end of data collection. All measurements will be recorded in the CRF.

7.2.9.1 Additional manual breath counts ([redacted] duration) may be obtained depending on the length of the data collection period.

7.2.10 The length of the noninvasive INVSENSOR00004 sensor and pulse oximeter sensor readings will be a minimum of [redacted]

7.2.11 Once the subject completes data collection or if the subject withdraws early prior to study completion, the sensors will be removed and the skin will be inspected for signs of redness or irritation. Any skin irritations will be recorded in the CRF and/or adverse event (AE) form.

8 STATISTICAL PLAN

8.1 Sample Size Determination

8.1.1 For equivalence study the sample size is given by[1] $N = \left(\frac{(z_{\alpha/2}+z_{\beta})\cdot\sigma}{\delta}\right)^2$ where

$z_{\alpha/2}$ is the standard normal distribution z-score with tail area α/2

z_{β} is the standard normal distribution z-score with tail area β

δ is the limit of equivalence

σ is the a-priori estimate of standard deviation (precision)

For Type I error rate or α = 5%, $z_{\alpha/2} = 1.96$

For Type II error rate or β = 20% or power = 80%, $z_{\beta} = 0.85$

δ = 2.0 RPM

σ = 3.0 RPM

$N = \left(\frac{(1.96+0.85)\cdot 3}{2}\right)^2 = 18$

This study will use a minimum of 18 subjects with up to 100 subjects to account for possible events such as subject withdrawal, device deficiencies, and/or incomplete cases.

8.2 Statistical Methods

8.2.1 The reference (RR_{ref}) will be obtained by measuring respiration rate based on manual annotations of respiratory inspirations and expirations. Bias will be reported using the following equation and will be used for each site, subject, and for all data combined:

$$Bias = \frac{1}{n}\sum_{i=1}^{n}\left(RR_a - RR_{ref}\right)$$

8.2.1.1 Optional analysis may be performed based on the available capnography data collected from subjects who could tolerate the device. The statistical formula for calculating bias for the capnography results will be similar to the above equation but with RRa replaced by respiratory rate from capnography (RR_{cap}).

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.

[1] Sample Size Calculations, Practical Methods for Engineer and Scientists, Paul Mathews ISBN 978-0-615-32461-6

- 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:

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 (FRM-3391).
- 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

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.

10.2 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 to the completion or participation to 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.

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 EC/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

11.4.1 Training on CRF completion will be provided to study personnel prior to data collection.

11.4.2 Original CRFs will be stored in a secure location at site and scanned copies will be sent to sponsor.

11.4.3 Only authorized sponsor personnel will have access to study data and will move all data related contents and CRF scans to a secure FTP. Masimo Clinical Research will have access to the FTP transferred data.

11.4.4 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 trained on Clinical Research 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 10-15% of initial subject enrollment.
- A final close out visit after the last patient had finished the study.

12.3 The Investigator shall allow 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 medical records and real-time data stored from Radical-7 device/ADC program.

12.6 After each visit, the monitor will provide a monitoring follow-up letter to the investigator within 4 weeks of visit completion. The follow-up 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.

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.

12.8 The Investigator will provide the monitor access to all necessary records to ensure the integrity of the data (21 CRF 812).

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).

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.
- Conduct the clinical investigation in accordance with the protocol, all applicable laws and federal regulations, and conditions or restrictions implemented by the governing IRB.
- 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 ensure 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	7/11/2017	Original version
2.0	1/11/2018	Added Radical-7 as an investigational device Updated details for the INVSENSOR00004.
3.0	04/05/2018	Adjusted the minimum and maximum time limits for the noninvasive readings/recordings. Adding the option of taking a photo of the INVSENSOR00004 while the sensor is placed on the subject.

16 REFERENCES:

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2) The accuracy, precision and reliability of measuring ventilator rate and detecting ventilatory pause by rainbow acoustic monitoring and capnometry. Ramsay MA, Usman M, Lagow E, Mendoza M, Untalan E, De Vol E. Anesth Analg. 2013 Jul; 117(1):69-75.

3) Comparison of Acoustic Respiration Rate, Impedance Pneumography and Capnometry Monitors for Respiration Rate Accuracy and Apnea Detection during GI Endoscopy Anesthesia . Goudra B.G., Penugonda L. C., Speck R.M., Sinha A.C. Open J Anesthesiol. 2013; 3:74-79

4) Accuracy of Respiratory Rate Monitoring using a Non-Invasive Acoustic Method after General Anesthesia. Mimoz O., Benard T., Gaucher A., Frasca D., Debaene B. *Br J Anesth*. 2012 Feb 8.