Official Title: Clinical Performance of Masimo INVSENSOR00057 for Heart Rate Measurements

Date of Protocol: April 04, 2022

NCT Number: NCT05462886

CLINICAL INVESTIGATION PLAN

[redacted]

Clinical Performance of Masimo INVSENSOR00057 for Heart Rate Measurements

Clinical Investigation Title: Clinical Performance of Masimo INVSENSOR00057 for Heart Rate Measurements

Clinical Investigation Number, Version: [redacted]

Other Study Identifier: N/A

Study Device(s): Masimo INVSENSOR00057 – Investigational

Sponsor: Masimo Corporation
52 Discovery
Irvine, California 92618 USA

[redacted]

Investigator Page

Principal Investigator (s): [redacted]

Investigation Site(s): Clinical Laboratory, Masimo Corporation

Address: 52 Discovery
Irvine, CA 92618

IRB: E&I West Coast Board – IRB00007807

Address: 304 SE 3rd Street
Lee's Summit, MO 64063

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 Clinical Investigation Plan.
- 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.

The principal investigator's signature on this page constitutes the investigator's affirmation that he or she is qualified to conduct the clinical investigation, agreement to adhere to all stipulations of this clinical investigation plan, the conditions of the Institutional Review Board (IRB) or Research Ethics Committee approval, federal and local regulatory requirements, 21 CFR 812, ISO 14155, and International Conference on Harmonization Good Clinical Practice (ICH GCP) guidance.

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

1. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical investigation title:	Clinical Performance of Masimo INVSENSOR00057 for Heart Rate Measurements
Study objective(s):	To validate the performance of the Masimo INVSENSOR00057 ECG heart rate (HR) measurement
Investigational device(s):	Masimo INVSENSOR00057
Number of subjects:	Approximately 50 subjects.
Inclusion criteria:	Refer to section 6.3.1.
Exclusion criteria:	Refer to section 6.3.2.
Duration of the clinical investigation:	Expected duration of study enrollment is 1 to 3 months. Subject participation in the study will be approximately 90 minutes.
Study endpoint(s):	Masimo INVSENSOR00057 ECG heart rate (HR) measurement shall meet its specification.

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1. Background and Study Devices

Masimo Corporation develops noninvasive medical technologies. These devices may have applications in the operating room, critical care unit, emergency room, emergency transport vehicles, alternative (home) care, as well as physician's offices.

Masimo SET, Masimo rainbow, and other newly-developed Masimo technology allow real-time, non-invasive monitoring of patient physiological conditions, such as hemoglobin levels, blood pressure, and body temperature. Use of monitoring devices in patients has the potential to improve clinical outcomes while reducing the cost of care and risks to both patients and clinicians associated with invasive procedures.

Masimo INVSENSOR00057 is a stand-alone wearable health monitor that combines the functionality of a pulse oximeter monitor and sensor into a single portable device that fits on a user's wrist. The device is capable of calculating oxygen saturation (SpO2), heart rate (HR), and pulse rate (PR), as well as other pulse oximeter parameters (e.g. perfusion index, respiration rate, etc.).

FDA-cleared Masimo SET pulse oximeter sensors and/or FDA-cleared electrocardiogram (ECG) electrodes may be used in this study for research purposes.

2.2. Site Information

The Masimo Clinical Laboratory facility is designed as a Phase 1 clinical study research center. The laboratory is staffed by physicians, anesthesiologists, certified registered nurse anesthetists, registered nurses, medical assistants, and clinical research staff. All personnel undergo routine required training on GCP and human research subject protections. The laboratory is equipped with standard FDA-approved medical monitoring equipment including ECG monitors, blood pressure monitors, pulse oximeters, standard hematology analyzers, and has emergency crash carts available. Hospitals and urgent care facilities are within three miles of the Masimo Clinical Laboratory.

3. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

This is a nonrandomized single arm study wherein all subjects are enrolled into the experimental arm and will receive the

INVSENSOR00057 on one wrist. This study is designed to compare the clinical performance of the INVSENSOR00057 ECG HR compared to HR from the FDA-approved electrocardiogram (ECG) monitor.

4. BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

4.1. Anticipated Benefits

There will be no benefit to the subject. Possible benefits would be to society as a whole. Evaluation of the accuracy of this new device could enable users to more appropriately monitor and identify potentially life-threatening conditions.

4.2. Risks/Discomforts Associated with Participation in the Clinical Investigation

The following risks/discomforts associated with study procedures are anticipated adverse events. All adverse events will be documented and reported according to section 14.3.

- **Risks Associated with the Device**

  The noninvasive devices used in this study are similar in technology and design to some commercially available pulse oximeters and other noninvasive devices and hence have the same risks. Pulse oximeters and other noninvasive devices are commonly used and are considered to be minimal risk.

  There is a risk of discomfort to the subject's wrist, or other locations where devices are placed, from the device, including temporary skin irritation, skin inflammation, itching skin, or discomfort associated with exposure to the device, as well as potential temporary mechanical irritation or discomfort.

  There is a remote, yet possible, risk of a burn from the sensor. In the case of a sensor burn, there is the potential for permanent skin damage (scar/discoloration).

  If there are any cuts and/or abrasions near the application site, the subject will disqualified from the study to avoid any discomfort.

- **Risks Associated with Skin Preparation**

  Subjects may be asked to use an alcohol pad or fingertip abrasive pad on the area of the FDA-cleared ECG electrode application to allow the electrodes to adhere to the skin. Risks associated with the skin preparation include cuts and/or abrasions, rash, itching skin, flushing or redness of the skin, unusually warm skin, skin inflammation, and/or skin irritation. Each of these discomforts are temporary and should fade over time.

- **Risks Associated with Shaving**

  Subjects may be asked to shave the area of the FDA-cleared ECG electrode application to allow the sensors to adhere to the skin. Risks associated with shaving include cuts and/or abrasions, bleeding, infection, razor burn, rash, itching skin, flushing or redness of the skin, unusually warm skin, skin inflammation, skin irritation, ingrown hairs, and/or inflamed hair follicles. Each of these discomforts are temporary and should fade over time. Some of these symptoms may last up to several days after shaving.

  Within the consent form, subjects will agree to have ECG electrode adhesion sites shaved or not. Subjects can stop these measures at any time if they feel uncomfortable.

- **Risks from Inflicted Knowledge**

  We will reduce the risk of inflicted knowledge by assuring the subjects that device readings are for

research use only. In the case that a subject becomes aware of a condition (hypertension, arrhythmia, etc.) they have during the course of our study, our study staff will recommend that they contact their primary care physician and we will document this recommendation. As part of that process, we will follow up with these individuals prior to enrollment if their condition meets exclusion criteria for a study.

- **Risks from Loss of Confidentiality**

  Masimo upholds the highest standards to protect hard and electronic data, however, a complete promise for confidentiality cannot be guaranteed due to unforeseeable events.

4.3. Emergency Response Plan for Medical Emergencies

A crash cart equipped with medications to provide immediate care during emergencies is on site and full emergency services are within 3 miles.

Study staff will dial 911 for medical emergencies that require emergency medical services (EMS) to be contacted.

4.4. Alternatives

The alternative is for the subject to not participate in the study.

5. OBJECTIVES OF THE CLINICAL INVESTIGATION

The primary objective of this study is to validate the performance of the Masimo INVSENSOR00057 ECG heart rate (HR) measurement.

Data using the noninvasive devices will be collected from generally healthy male and female volunteers.

HR performance will be calculated using Accuracy root mean square (ARMS) analysis of the HR values from reference ECG monitor HR values.

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1. General

6.1.1. Clinical Investigation Design

This is a nonrandomized single arm study wherein all subjects are enrolled into the experimental arm and receive the INVSENSOR00057 on one wrist.

6.1.2. Measures Taken to Minimize/Avoid Bias

Subjects are selected from the population surrounding the test site (including employees). Where applicable, subjects with required demographics (skin pigmentation, race/ethnicity, age, gender, etc.) may be preferentially recruited.

6.1.3. Equipment and Materials

Equipment and materials are to be used as required. All lab equipment will be maintained per manufacturer specifications and all study personnel will be trained on the use of relevant equipment.

Safety Equipment (FDA-Cleared)

- Blood pressure monitoring system
- Medical-grade oxygen tank, mask, and nasal cannula
- Crash cart

Test Devices [redacted]

- Masimo INVSENSOR00057 – investigational

Research Equipment

[redacted]

- FDA-approved Electrocardiogram (ECG) Electrodes and Monitors

[redacted]

6.1.4. Standard Safety Precautions

Any emergency drug deliveries in the case that a subject loses consciousness or has another emergency arise shall be recorded. This individual will be monitored and this information will be recorded and submitted to the IRB if necessary, as outlined in section 14.3. The subject will be given the option to follow up with a local urgent care facility.

The subject will be monitored through observation by clinical study staff throughout the study procedure.

An additional pulse oximeter may occasionally be used for the duration of the study to monitor subjects' vital parameters to ensure their safety.

All adverse events will be recorded.

6.2. Investigational device(s) and comparator(s)

Refer to section 2 for the description of devices that may be used in this investigation.

6.3. Subjects

Potential subjects may be recruited and enrolled according to the criteria below.

6.3.1. Inclusion Criteria (Eligible Subjects)

- Subject is 18 to 80 years of age.
- Subject is able to read and communicate in English.

6.3.2. Exclusion Criteria (Ineligible Subjects)

- Subject has open wounds, inflamed tattoos or piercings on the area of device placement, and/or has any visible healing wounds that the investigator and/or medical professional determines may place them at an increased risk for participation.
- Subject has any medical condition which in the judgment of the investigator and/or study staff, renders them ineligible for participation in this study or subject is deemed ineligible by the discretion of the investigator/study staff.

6.3.3. Expected Duration of Each Subject's Participation

Expected duration of study enrollment is 1 to 3 months. The expected duration of each subject's participation in the lab will be approximately 90 minutes.

6.3.4. Withdrawal of Subjects

Subjects must be withdrawn under the following circumstances: the subject withdraws consent, or at the discretion of investigator/study staff for subject safety and welfare.

6.3.5. Replacement of Subjects

In case a subject is withdrawn from the study, another subject may be recruited.

6.3.6. Re-contacting Subjects

If the subject fails to provide proper documentation on their individual consent form or other study documents, Masimo may re-contact the subject and ask them to return to the clinical lab in order to properly complete these documents. The subject will be re-contacted via phone or email and be asked to return as soon as possible. The subject will be compensated for travel as outlined in the consent form.

6.4. Procedures

6.4.1. Schedule of Activities

Procedures	Phone Pre-Screen	Baseline Visit 1	Procedure Visit 1
Brief Study Procedure Description	X		
Informed consent		X	
Demographics	X	X	
Medical history (subject-reported)	X	X	
Concomitant medication review	X	X	
Vital Signs (ECG, Blood Pressure Cuff, Pulse Ox)		X	X
Height	X	X	
Weight	X	X	
Placement of test sensor(s)			X
Data collection			X
Discharge		X	X
Adverse Event Review and Evaluation[1]		X	X

1 Adverse events may be reported by the subject after their visit. See section 14 for additional details.

6.4.2. Recruitment and Pre-Screening

Subjects will be recruited using IRB-approved advertisements. Subjects may be referred to the study by previous subjects. Subjects are contacted via phone call to conduct a prescreening interview to determine their initial eligibility for the study. Potential eligible subjects are scheduled for a study visit to the clinical laboratory.

6.4.3. Consenting and Screening

Subjects will be asked to provide a copy of their valid government-issued identification such as driver's license and/or Social Security card. Copies of these forms of identification will be stored electronically. Subjects must read and sign the IRB-approved informed consent document. No study related activities will be conducted until the consent form is signed.

After informed consent is obtained, subjects will be asked a brief series of health questions to ensure their eligibility for this study. Subjects who do not meet the inclusion criteria and/or meet exclusion criteria will not be eligible to participate in the study.

Subject demographic information including age, sex, pigmentation, ethnicity, height and weight will be collected. These may be recorded for data analysis and/or subject safety monitoring purposes.

In addition, a medical history will be recorded after the initial screening questionnaire. Vital signs, such as blood pressure and heart rate, will be recorded for subject safety monitoring. Pulse oximetry measurements, such as SpO2, SpCO, and SpHb, may also be recorded.

6.4.4. Sensor Placement Procedure

The subject will be seated and/or lying in supine position and should refrain from excessive movement during the study.

If accepted into the study, sensors for the noninvasive measurement(s) may be placed on the subject's finger(s), wrist, and/or chest, which may include Masimo SET pulse oximeters and/or commercially-available ECG electrodes. Subjects may be asked to remove their shirt and/or use skin preparation materials on the area of ECG electrode application.

Subjects may be asked to use an alcohol pad or fingertip abrasive pad on the area of ECG electrode application, and/or shave the area of application to allow the sensors to adhere to the skin. Study staff should visually inspect the area that skin preparation materials will be used.

The INVSENSOR00057 will be placed on the subject's wrist. [redacted] In the event of emergency defibrillation, the device must be removed prior to defibrillation.

6.4.5. Data Collection Procedure

Upon successful placement of the sensor(s) and the subject's indication that they are comfortable, data collection will be initiated using the data collection software. Pulse oximeter output values (e.g., SpO2, pulse rate) will be recorded using the data collection software. [redacted]

The subject will be requested to take manual ECG measurements on the INVSENSOR00057 device by holding their finger on the bezel of the device. [redacted]

6.4.6. Ending Procedure

At the conclusion of the procedure, the sensor(s)/device(s) will be removed.

All subjects will be encouraged to remain in the study area until they feel fit to leave. Subjects should feel safe and able before returning to work directly after participation in the study. All subjects, [redacted] will be advised to take as much time as they need after the study before returning to work.

The total overall lab time will be approximately 90 minutes. Subjects will be paid according to the compensation breakdown on the consent form.

6.5. Monitoring plan

A separate document for the study monitoring plan will be developed and followed to ensure subject safety and GCP compliance.

7. STATISTICAL DESIGN AND ANALYSIS

7.1. Acceptance Criteria

For validation studies, acceptance criteria are determined by Masimo specifications for each design.

7.2. Sample Size

[redacted] These records provide hand annotated reference annotations for multiple cardiac conditions on different subjects in a clinical environment. A bootstrap analysis of the prior device data using different Numbers of Subjects and Number of Points per Subject was performed. [redacted] In order to allow for subject dropout and data acceptance criteria for analysis, this protocol will plan on approximately 50 subjects [redacted]

7.3. Statistical Analysis

7.3.1. Exclusion

We exclude points where reference ECG or test ECG is not providing any HR values.

7.3.2. Accuracy calculations

$$Bias = \frac{1}{N}\sum_{i=1}^{N} TestHR_i - RefHR_i$$

$$Precision = \sqrt{\frac{\sum_{i=1}^{N}\left((TestHR_i - RefHR_i) - Bias\right)^2}{N}}$$

$$Arms = \sqrt{\frac{\sum_{i=1}^{N}(TestHR_i - RefHR_i)^2}{N}}$$

$$\text{Arms} = \sqrt{Bias^2 + Precision^2}$$

where N is the total number of measurement, and i is a single measurement.

7.4. Expected Dropout Rates

Subjects may not complete the study for various reasons, such as a clinical screening test failure, at the investigator's or study staff's discretion, or because the subject does not want to continue the study. Due to the short duration and simple, noninvasive procedures of this study, there are limited expected dropouts.

8. DATA MANAGEMENT

8.1. Data Management and Confidentiality

All documents associated with this protocol will be securely stored in a physical location or on password-protected computers. The confidentiality and retention of these documents will be protected to the extent provided and required by the law. 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. Data will be retained for a minimum to 2 years following completion of the final analysis.

8.2. 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: clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, and copies or transcriptions certified after verification as being accurate and complete.

8.3. Case Report Forms

The site shall capture study data in case report forms (CRFs) for each subject enrolled, to be provided to the sponsor. CRFs may be in paper or electronic format through electronic data capture (EDC) software. Masimo shall ensure that systems used for electronic CRFs are compliant with the requirements of 21 CFR Part 11 and ISO / IEC 27001 Certification. The CRFs will be completed and signed by the principal investigator or delegate. 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. For paper CRFs, entries and corrections to the CRF will be made following Good Documentation Practices.

The CRF may include the following information, including but not limited to: inclusion / exclusion criteria, whether subject consent was 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 or delegate to attest that the data are complete and accurate.

CRF entries will be checked by the study monitor and any errors or inconsistencies will be queried to the site on an ongoing basis. Any changes made within an electronic CRF will be tracked by audit trail. Any changes on a paper CRF will be made directly on the CRF and will be initialed and dated by the person making the change. Query resolution will be assessed and confirmed by study monitor during site visit.

8.4. Data Transfer and Storage

8.4.1. Original paper CRFs will be stored in a secure location at the site. Copy of the original paper CRFs may be scanned and sent to sponsor. If using electronic CRFs, the site staff will be assigned unique usernames and passwords for data security. Final copies of the electronic CRFs in EDC are stored on a secure server.

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

8.4.3. CRFs will be checked for completeness and if there are inconsistent or missing data points, queries will be generated. If delegated study staff are to correct the paper CRF, they shall follow GDP practices to strike through old entry, add in new entry, and initial and date it, and provide the corrected information to sponsor. Corrections made to electronic CRFs will be tracked by audit trail and require PI or delegate sign-off.

8.5. 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.

9. AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

Any changes made to the clinical investigational plan/study protocol will be documented by way of an amendment. Before submitting a 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.

10. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Deviations from the protocol must receive both Sponsor and the investigator's IRB/ethics committee approval before they are initiated, with the exception that under emergency circumstances, deviations from the Clinical Investigation Plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor or the IRB/ethics committee. Any protocol deviations initiated without Sponsor and the investigator's IRB/ethics committee 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/ethics committee as soon as a possible, but no later than 5 working days after the occurrence of the protocol deviation. In addition to documenting deviations on the CRF, the Protocol Deviation Form may also be used. If protocol deviations continue to occur frequently at a study site, a corrective and preventive action (CAPA) may be opened by the Sponsor.

Withdrawal of IRB approval: An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

11. DEVICE ACCOUNTABILITY

11.1. 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.

11.2. Use of Study Device

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

11.3. Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices shipped, devices used, and devices 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. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the Sponsor in a timely manner.

12. STATEMENTS OF COMPLIANCE

This document is a clinical investigational plan for a human research study sponsored by Masimo Corporation. 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 the Institutional Review Board (IRB) or Research Ethics Committee approval, federal and local regulatory requirements, 21 CFR 812, ISO-14155, International Conference on Harmonization Good Clinical Practice (ICH GCP) guidance.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

13. INFORMED CONSENT PROCESS

Subjects must read and sign the consent document using the informed consent process as outlined in FRM-3451 Informed Consent Process. No study-related activities will take place prior to informed consent.

14. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

14.1. Definitions

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

- adverse event: untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated (ISO 14155)
- adverse device effect: adverse event related to the use of an investigational medical device
- serious adverse event: adverse event that led to any of the following:
  - a) death
  - b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - 1) a life-threatening illness or injury, or
    - 2) a permanent impairment of a body structure or a body function including chronic diseases, or
    - 3) in-patient or prolonged hospitalization, or
    - 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
  - c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

  Note: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.
- serious health threat: signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

- serious adverse device effect: adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
- unanticipated serious adverse device effect: serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

  Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
- device deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance

  Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

  Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

14.2. List of non-reportable adverse events

All adverse events will be reported and documented as described below.

Refer to section 4.2 for the description of anticipated adverse events.

14.3. 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.

14.4. Device Deficiencies Reporting

All Masimo device related deficiencies should be reported to the Sponsor and must be recorded in the CRF in a timely manner. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the Sponsor in a timely manner.

15. VULNERABLE POPULATION

15.1. Definition

Vulnerable population are research participants, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, who are likely to be vulnerable to coercion and undue influence.

The federal regulations that govern the protection of human subjects require additional protection for the vulnerable population.

15.2. Protection of vulnerable subjects

[redacted]

- Pregnant women may participate in this study. Due to the short duration and simple, noninvasive procedures of this study, the risk to pregnant women and fetus is minimal.
- Reasonable 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.
- 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.

15.3. Responsible Parties

- The EC/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.

16. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1. 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 subject 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.

16.2. 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.

17. PUBLICATION POLICY

In compliance with 42 CFR Part 11, a study that meets the definition of an Applicable Clinical Trial (ACT) and that is initiated after September 27, 2007 must be registered on ClinicalTrials.gov. Results of the clinical investigation will be made publicly available.

18. BIBLIOGRAPHY

N/A

19. REVISION HISTORY

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]