Official Title: Effect of Skin Pigmentation and Race/Ethnicity Factors on the Accuracy of Masimo Pulse Oximeters

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Protocol/Test Procedure Title	Effect of Skin Pigmentation and Race/Ethnicity Factors on the Accuracy of Masimo Pulse Oximeters
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Expected Start Date	TBD
Expected End Date	TBD
IRB	E&I West Coast Board – IRB00007807
Protocol Version Date	TBD

Protocol Test Abstract:

This study is designed to compare the accuracy of a noninvasive measurement of oxygen saturation compared to reference values obtained by a laboratory blood gas analyzer. Subgroups will be analyzed by skin pigmentation and self-identified race/ethnicity information.

Study procedures follow ISO-80601-2-61:2011 standard requirements for basic safety and essential performance of pulse oximeter equipment. Arterial blood samples will be collected from subjects while undergoing a controlled desaturation procedure wherein the concentration of oxygen inhaled is slowly reduced until the subject's arterial oxygen concentration is approximately 70%.

APPROVALS

Author	Date	Engineering	Date
N/A	N/A	N/A	N/A
Quality Assurance	**Date**	**Manufacturing**	**Date**
N/A	N/A	N/A	N/A

Effect of Skin Pigmentation and Race/Ethnicity Factors on the Accuracy of Masimo Pulse Oximeters

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with all stipulations of this protocol, the conditions of IRB approval, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, ISO-14155, International Conference on Harmonisation E6 Good Clinical Practice (ICH GCP), and local regulatory requirements.

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.

1. PURPOSE

The primary objective of this study is to validate the noninvasive oxygen saturation (SpO_2) performance of the Masimo noninvasive MightySat sensor against an arterial blood sample analyzed by a laboratory CO-oximeter reference instrument. Data using the noninvasive devices will be collected from generally healthy volunteers undergoing a desaturation procedure. Study subjects of differing levels of skin pigmentation will be enrolled in the study.

This is a nonrandomized single arm study wherein all subjects are enrolled into the experimental arm and receive the MightySat sensor on one or more fingers. Desaturation will be conducted by reducing the concentration of oxygen the study subject breathes in a controlled manner to obtain noninvasive oxygen saturation readings, SpO_2, at various levels. Reference blood samples will be repeatedly collected from the subject and analyzed using a standard laboratory CO-oximeter. The performance of the sensor will be calculated using Accuracy root mean square (A_{RMS}) analysis of the SpO_2 values and the reference CO-oximeter values.

A secondary objective of this study is to evaluate the performance of the Masimo MightySat and RD SET pulse oximeter sensors in in subgroups based on skin pigmentation and/or self-identified race/ethnicity.

[redacted]

Outcome Measure:

Performance of the sensors will be determined by comparing the noninvasive oxygen saturation measurement (SpO_2) of the pulse oximeter sensors to the arterial oxygen saturation (SaO_2) value obtained from a reference blood sample and calculating the A_{RMS} value.

The primary outcome is to validate that the MightySat meets the acceptance criteria [redacted]

The secondary outcome is to perform equivalence tests between identified subgroups based on skin pigmentation and/or self-identified race/ethnicity. Since the pulse oximeter displays saturation in integer values, equivalence limits will be set to ± 1% SpO2.

2. BACKGROUND AND STUDY DEVICES

An invasive blood sample analyzed by a CO-oximeter reference instrument gives the best measure of arterial oxygen concentration as well as other blood solutes, but cannot measure these parameters continuously and requires skin puncture, arterial line placement and subsequent risk of infection, hematoma, and other physiological damage.

Masimo Corporation develops non-invasive medical technologies. These devices have applications in the operating room, critical care unit, emergency room, emergency transport vehicles, alternative (home) care, as well as physicians' offices. Masimo SET, Masimo rainbow, and other newly-developed Masimo technology allow real-time, non-invasive monitoring of oxygen saturation. Use of monitoring devices on patients has the potential to improve

clinical outcomes while reducing the cost of care and risks to both patients and clinicians associated with arterial and venous punctures.

[redacted] It is a stand-alone fingertip pulse oximeter that combines the functionality of an instrument and sensor into a single portable device that fits on a user's finger. The device is capable of calculating functional oxygen saturation (SpO2) and pulse rate (PR) as well as other pulse oximeter parameters (e.g. perfusion index, waveforms, etc.). The MightySat is used as a spot-checking device.

The FDA-cleared Masimo RD SET sensors used in this study are disposable sensors indicated for the continuous noninvasive monitoring of functional oxygen saturation and pulse rate (PR) as well as other pulse oximeter parameters.

Optional FDA-cleared or other commercially available pulse oximeters may be used for research purposes. See Section 6 for the full list of study equipment and materials.

3. REFERENCE

ISO-80601-2-61:2011 Medical electrical equipment -- Particular requirements for the basic safety and essential performance of pulse oximeter equipment for medical use

4. LOCATION

Masimo Corporation
Clinical Laboratory
52 Discovery
Irvine, CA 92618

[redacted]

5. STUDY POPULATION

5.1. Inclusion Criteria (Eligible Subjects)

- Subject is 18 to 50 years of age.
- Subject weighs a minimum of 110 lbs.
- Subject has a hemoglobin value ≥ 11 g/dL.
- Subject's baseline heart rate is ≥ 45 bpm and ≤ 85 bpm.
- Subject's CO value is ≤ 2.0% FCOHb.
- Subject's blood pressure: Systolic BP ≤ 140 mmHg and ≥ 90 mmHg, Diastolic BP ≤ 90 mmHg and ≥ 50 mmHg, and if systolic BP is lower than 100 mmHg and/or diastolic BP is lower than 60 mmHg, subject passes an orthostatic blood pressure test.
- Subject is able to read and communicate in English and understands the study and the risks involved.

5.2. Exclusion Criteria (Ineligible Subjects) (*= PER PHYSICIAN DISCRETION)

- Subject is pregnant.
- Subject has a BMI > 35.

[redacted]

- Subject has a history of fainting (vasovagal syncope), blacking out or losing consciousness during or after a blood draw, or has a fear of blood draws.
- Subject has open wounds, inflamed tattoos or piercings, and/or has any visible healing wounds that a medical professional determines may place them at an increased risk for participation.*
- Subject has known drug or alcohol abuse.
- Subject uses recreational drugs.*
- Subject experiences frequent or severe headaches and/or migraine headaches, migraine auras, altitude sickness, and/or headaches accompanied by visual changes or sensitivity to light or sound.
- Subject has experienced a concussion or head injury with loss of consciousness within the past 12 months.
- Subject has any history of a stroke, myocardial infarction (heart attack), and/or seizures.
- Subject has any chronic bleeding disorder (e.g. hemophilia).
- Subject has taken anticoagulant medication within the past 30 days (excluding nonsteroidal anti-inflammatory drugs (NSAIDS)).
- Subject has donated blood within the past 4 weeks.
- Subject has Wolff-Parkinson-White Syndrome or Stokes-Adams Syndrome.
- Subject has any symptomatic cardiac dysrhythmia (e.g. atrial fibrillation) and has not received clearance from their physician to participate.
- Subject has a known neurological and/or psychiatric disorder (e.g. schizophrenia, bipolar disorder, multiple sclerosis, Huntington's disease) that interferes with the subject's level of consciousness.*
- Subject has taken opioid pain medication 24 hours before the study.
- Subject has any active signs and/or symptoms of infectious disease (e.g. hepatitis, HIV, tuberculosis, flu, malaria, measles, etc.).*
- Subject is taking medications known to treat any type of infectious disease.
- Subject has either signs or history of peripheral ischemia or carpal tunnel syndrome.
- Subject has had invasive surgery within the past year, including but not limited to major dental surgery, appendectomy, plastic surgery, jaw surgery, major ENT surgery, major abdominal and/or pelvic surgery, heart surgery, or thoracic surgery.*
- Subject has symptoms of congestion, head cold, or other illnesses.
- Subject has been in a severe car accident(s) or a similar type of accident(s) requiring hospitalization within the past 12 months.
- Subject has any cancer or history of cancer (not including skin cancer).*
- Subject has chronic unresolved asthma, lung disease (including COPD) and/or respiratory disease.
- Subject is allergic to lidocaine, chlorhexidine, latex, adhesives, or plastic.
- Subject has a heart condition, insulin-dependent diabetes, or uncontrolled hypertension.
- Subject has delivered vaginally, has had a pregnancy terminated, a miscarriage with hospitalization, or had a C-section within the past 6 months.
- Subject intends on participating in any heavy lifting, repetitive movement of their wrist (including riding a motorcycle, tennis), exercise (working out, riding a bike, riding a skateboard, etc.), or any activity that will put additional stress on the wrist within 24 hours following a study that involves an arterial line.
- Subject has any medical condition which in the judgment of the investigator and/or medical staff, renders them ineligible for participation in this study (Discretion of the investigator/study staff).

5.3. 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.

5.4. Replacement of subjects

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

6. EQUIPMENT AND MATERIALS

Equipment and Materials: All lab analyzers and equipment will be maintained per manufacturer specifications and all study personnel will be trained on the use of relevant equipment. Equivalent equipment and materials to those listed below may be used.

Safety Equipment (FDA-Cleared)

- Blood pressure monitoring system
- A-line pressure transducer
- Electrocardiogram (ECG)
- Masimo Pulse Oximeters (Radical-7)
- Masimo Patient Monitoring Platform (Root®)
- Pulse oximeter sensors and cables (Masimo SET, Masimo rainbow, or comparable)
- Medical-grade oxygen tank, mask, and nasal cannula
- Crash cart

Test Devices

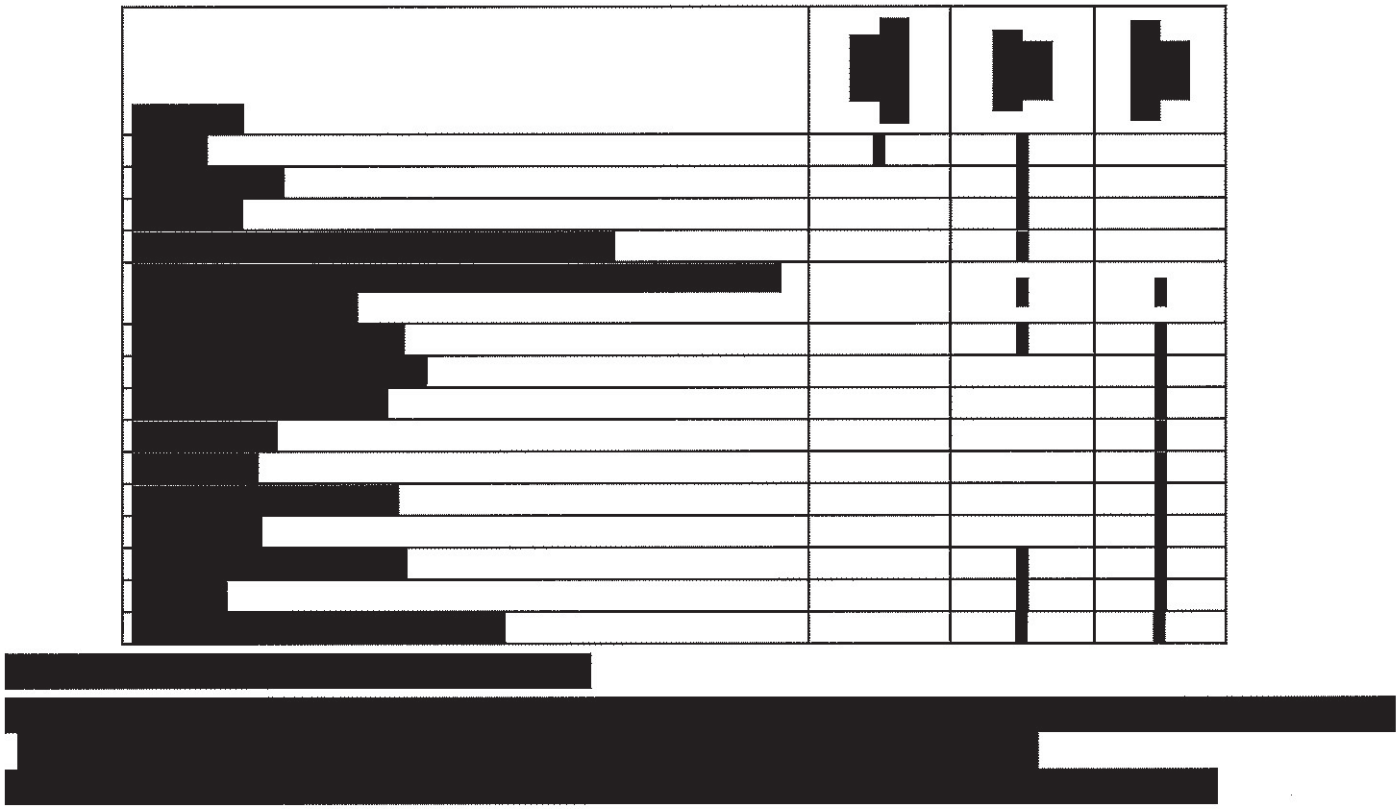
- Masimo MightySat - investigational
- Masimo RD SET SpO2 – FDA-cleared

Research Equipment

- Data Collection Research Equipment
- Laboratory co-oximeters/blood analyzers

7. PROCEDURE

7.1 SCHEDULE OF ACTIVITIES



7.2. RECRUITMENT AND PRESCREENING

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.

7.3 CONSENTING AND SCREENING

Subjects will be asked to provide a copy of their valid government-issued identification. Other information (such as Social Security Number or Tax ID number) will also be collected for tax reporting purposes, as appropriate. Copies of these forms of identification will be stored electronically. The confidentiality and retention of these documents will be protected to the extent provided and required by law.

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, skin tone, ethnicity, height and weight will be collected. These may be recorded for data analysis and/or subject safety monitoring purposes.

Body mass index (BMI) may also be calculated to assess for eligibility for the study.

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 SpO_2, SpCO, and SpHb, may also be recorded.

An orthostatic blood pressure test is **ONLY** required to be performed on subjects that meet the following criteria:

- Initial systolic blood pressure lower than 100 mmHg and greater than or equal to 90 mmHg, and/or
- Initial diastolic blood pressure lower than 60 mmHg and greater than or equal to 50 mmHg.

The following combinations meet the criteria for performing an orthostatic blood pressure measurement. If the criteria are not met, an orthostatic blood pressure test is not required.

Table 1: Criteria for orthostatic blood pressure measurement.

Systolic measurement (mmHg)	Diastolic measurement (mmHg)	Perform orthostatic blood pressure test?
100 or above	50 to 59	YES
90 to 99	60 or above	YES
90 to 99	50 to 59	YES
100 or above	60 or above	NO

The orthostatic blood pressure test will start with the clinician taking the subject's blood pressure while they are lying in supine position. The subject will then stand up for 30 seconds and a second blood pressure measurement will be taken. The subject's blood pressure will need to stay above 90/50 to meet inclusion criteria for the study.

Female subjects will be required to take a pregnancy test. Results will be noted in study documentation. If the pregnancy test is positive, the subject will be notified and removed from the study.

A venous sample will be obtained via needle stick or by placement of an IV and analyzed to verify that the starting hemoglobin level is greater than or equal to 11 g/dL and carboxyhemoglobin (COHb) level is less than or equal to 2.0%. If hemoglobin level is less than 11 g/dL and/or COHb is greater than 2.0%, the subject will be excluded from the study.

7.4. 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, the subject's vitals will be monitored with standard noninvasive monitors, including FDA-cleared pulse oximeters, ECG, and blood pressure cuff. Information from these monitors may optionally be recorded.

Transient increases in blood pressure and heart rate can be expected during line placement, needle sticks, blood draws etc. and may also be attributed to anxiety/nervousness relating to a new environment. For most participants, only the initial recorded blood pressure and/or heart rate determines a subject's qualification for the study. In the case where heart rate and blood pressure

changes suggest participant discomfort or a potential safety concern, the participant will be removed from the study after qualifying, according to the discretion of medical and study staff.

A peripheral venous line will be placed in the subject's hand or arm. This line may be used for the qualifying venous blood draw and for safety or clinical intervention required during the study. The peripheral venous line site will be observed by study staff prior to line placement to ensure no bruising remains from any previous IV placements; if there is bruising the clinician will place the line in another location.

Local anesthetics such as lidocaine, ethyl chloride spray, or Pain Ease skin refrigerant spray may be used in the event that an IV is placed to numb the site. Subjects will be given the option to have lidocaine or numbing spray be used during IV placement for the purpose of making catheter placement more comfortable.

After intravenous access is established, one or more intra-arterial catheter(s) (arterial line or A-line) will be placed in the radial artery of the subject's wrist. Lidocaine will be used to ease discomfort. This study will be done with an arterial line to facilitate continuous blood pressure measurement, and to allow for blood sampling from this site to determine arterial blood gas values (ABG) such as oxygen saturation. Noninvasive ultrasound devices may be used to facilitate line placement.

Upon successful placement of the IV(s), arterial line(s) and the subject's indication that they are comfortable, a minimum of one FDA-cleared pulse oximeter sensor will be placed on the subject for reference values such as oxygen saturation, total hemoglobin, carboxyhemoglobin level, and pulse rate.

[redacted]

After arterial access is established, the study sensor(s) will be placed on the subject's finger(s). Data collection will be initiated using the automated data collection software. Sensors may be repositioned, as needed, to ensure proper placement.

[redacted]

Upon successful placement of the sensors and the subject's indication that they are comfortable, a baseline set of blood samples will be obtained.

A qualified person will complete blood draws. [redacted]

Subjects will wear a nose clip or nose plugs during the desaturation procedure. A mouthpiece will be placed in the subject's mouth. End-tidal and/or partial pressure of carbon dioxide and respiration rate values will be noted after the mouthpiece is placed for subject safety purposes and will be noted again prior to mouthpiece removal. If respiratory rate is greater than 30 breaths per minute at 21% FiO2, the study will be stopped. If respiratory rate is less than or equal to 5 breaths per minute, check blood gas values of first samples after the mouthpiece is placed, then the study will proceed.

Upon indication the subject is comfortable, a gas mixture will be administered through the mouthpiece. The proportion of oxygen in this mixture will be decreased in a controlled manner to lower the subject's blood oxygen saturation. The lowest targeted value will be 70% oxygen

saturation. Readings near 70% will be immediately verified [redacted] to ensure that levels are within the targeted oxygen saturation range and to minimize time that the subject may drop below the targeted range. At any point in the study, if the subject feels uncomfortable, the subject will be given 100% oxygen.

[redacted]

The study will end at a FiO_2 greater than room air (>21%) to help the subject re-saturate after the procedures. If at any point the subject is uncomfortable with the study, the study will be stopped.

Oxygen tank pressure will be checked and noted before the study begins for subject safety purposes.

During the study, subjects may be recorded using photography and/or videography. The recordings may include sound. These recordings may capture identifying features. These recordings may be used in research, product development, product testing, training, and comparison study purposes. Subjects will be given the option to provide consent or opt-out of the recordings

7.5 ENDING PROCEDURE

Study staff may take [redacted], in addition to the blood draws in the procedure section above, to verify the subject's blood values are within normal ranges (e.g. pH, glucose, etc.).

The total overall lab time will be approximately [redacted] In the event that the total lab time exceeds [redacted], subjects will be compensated for the extra time. Subjects will be paid according to the compensation breakdown on the consent form.

At the conclusion of the procedure, the sensor(s)/device(s), IV(s), and arterial line(s) will be removed. A set of pre-discharge vitals, such as heart rate and blood pressure, will be obtained and recorded on the case report form for subject safety purposes. Subjects will be given instructions on post care. All subjects will be instructed to contact the principal investigator or study staff in the event of any potential complication.

Subjects will be offered a snack and water or juice. Subjects are asked to consume food and/or liquid prior to leaving the clinical lab area for their safety due to study procedures such as blood removal and line placement. Subjects may also be asked to wait in the clinical lab or lobby waiting area for up to an additional 30 minutes before leaving to allow for their body to continue adjusting after the study has completed.

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, including subjects that are employees of Masimo, will be advised to take as much time as they need after the study before returning to work.

The subject will be allowed to leave after medical personnel determine it is safe to do so.

7.6 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.

8. ACCEPTANCE CRITERIA

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

9. SAMPLE SIZE JUSTIFICATION AND DATA ANALYSIS PROCEDURE TO BE USED

9.1. Sample size determination

9.2. Statistical Analysis

a. Exclusion

The following data exclusion criteria will be applied before data analysis:

b. Accuracy calculations

Accuracy will be reported as the Bias, Precision and A_{RMS} using the following equations:

$$Bias = \frac{1}{n}\sum_{i=1}^{n}(SpO2 - SaO2)$$

$$\text{Precision} = \sqrt{\frac{\sum_{i=1}^{n}((SpO2 - SaO2) - Bias)^2}{n}}$$

$$A_{RMS} = \sqrt{\frac{\sum_{i=1}^{n}(SpO2 - SaO2)^2}{n}}$$

The A_{RMS} and precision values will be adjusted to account for repeated measurements on each subject.

[redacted]

c. Equivalence Tests

To test the subgroup analysis, an equivalence test between groups will be used.

9.3. Measures taken to minimize/avoid bias:

Subjects are selected from the population surrounding the test site [redacted] Where applicable, subjects with required demographics (skin color, age, gender, etc.) may be preferentially recruited.

Sensors and devices will be provided to operators in a way that minimizes the operator bias. Sensors and devices will be provided at random when deemed necessary.

9.4. Expected Dropout Rates

Subjects may not complete the study for various reasons, such as screen failure, they are unable to complete desaturation criteria, or they are unable to have intravenous or arterial line placed. [redacted]

10. ADVERSE EVENTS

Adverse event: Any untoward medical occurrence in a subjects, users or other persons, whether or not related to the medical device under study.

Device-related adverse event: Adverse event related to, associated with, or caused by, the use of a medical device under study, including but not limited to events that may have been attributed to the device because of device failure or malfunction, improper or inadequate design, manufacture or user error.

Device deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device deficiencies will be reported according to department procedures.

Serious adverse event: Adverse event that: a) led to death, b) led to serious deterioration in the health of the subject, that resulted in: (i) a life-threatening illness or injury, (ii) a persistent or significant impairment of a body structure or a body function, (iii) in-patient or prolonged hospitalization, or (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or c) led to fetal distress, fetal death or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

All adverse events, including inter-current illnesses will be reported and documented as described below.

10.1. Adverse Events

All adverse events that occur during the study shall be recorded on the case report form even if the investigator/study staff assess the adverse event as unlikely to be causally related to the test device or study procedures.

10.2. Serious Adverse Events

The investigator/study staff shall promptly report both serious adverse events and unanticipated adverse device effects to the sponsor within 48 hours. All serious adverse events will also be reported to the IRB per IRB reporting requirements.

At the time of discharge from the study, any unresolved serious adverse event(s) will be followed up by the investigator/study staff until the event(s) are resolved, stabilized or the patient is lost to follow-up or the adverse event is otherwise explained. The investigator and/or study staff will also instruct the subject to report any subsequent events occurring in the next 30 days, which the subject or the subject's physician believes might reasonably be regarded as caused by or have a reasonable possibility of being caused by the test device or procedures involved in the study.

10.3. Unanticipated Problems

Any unanticipated problem involving subjects will be reported to the IRB, such as protocol violations or deviations as required by the IRB reporting procedures.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Measures Taken to Protect the Rights and Welfare of Subjects

All subjects will be monitored closely throughout the study. There will be an ACLS certified medical doctor present in the study area throughout the study.

The following measures will be taken to ensure the confidentiality of the subjects:

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

11.2 Vulnerable Populations

Employees are considered to be a vulnerable population. Participation is not a condition of employment. There will be no repercussions in the workplace in the case that the employee refuses to participate in the study or withdraws at any point during the study. Neither supervisors nor superiors will be involved in the recruitment of employees for participation in the study.

The study may also enroll subjects who are economically disadvantaged, unemployed and/or educationally disadvantaged. 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.

11.3 Documents and Database

Documents will be kept [redacted] after the specific product/tested for is no longer being made. If destroyed, these documents will be shredded and done by a certified company used for destroying medical and clinical data.

[redacted]

12. DEVICE ACCOUNTABILITY

12.1 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 of the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files.

12.2 Use of Study Device

Use of devices and sensors will be documented on case report forms (paper and/or electronic) for each subject.

12.3 Return or Destruction of Study Device

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

13. RISKS AND BENEFITS

13.1. Benefits:

There will be no benefit to the subject. Other possible benefits would be to society as a whole. Evaluation of the accuracy of this new device could enable healthcare workers to more appropriately treat potentially life threatening conditions.

13.2. Device Risks:

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

There is an extremely small risk of damage to the subject's fingers, or other locations where sensors are placed from the device, including temporary skin irritation or discomfort associated with

exposure to the sensor, 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 fingernail, certain types of sensors may not be placed on the particular finger to avoid any discomfort for the subject.

13.3. Venous Cannulation Risks:

Risks associated with venipuncture include discomfort, bruising, bleeding, swelling, infection, hematoma, decreased blood supply, damage to the blood vessel and surrounding nerves, tendons, or tissue, and loss of feeling in the hand and/or arm.

Other anticipated adverse events that may occur, include but are not limited to: vasovagal syncope (fainting), infiltrated IV, blood clot, lightheadedness, feeling flush/warm, feeling nauseated, throwing up, seizures, sudden drop in blood pressure/sudden increase in blood pressure, sudden drop in heart rate/sudden increase in heart rate, tingling sensation of face, arms and/or legs, sweating, and/or mouth dryness.

These anticipated adverse events are expected to be temporary.

13.4. Arterial Cannulation Risks:

Risks include bleeding, decreased blood supply, swelling, infection, hematoma, damage to the blood vessel and surrounding nerves, tendons or tissue. Additional risks include vasovagal syncope (fainting), lightheadedness, feeling flush/warm, embolization (blood clot), feeling nauseated, throwing up, seizures, sudden drop in blood pressure/sudden increase in blood pressure, sudden drop in heart rate/sudden increase in heart rate, tingling sensation of face, arms, and/or legs, sweating, mouth dryness, arterial occlusion, arterial laceration, loss of feeling in the hand and/or arm, and even the loss of the hand due to rare complications of the study.

13.5. Blood Draw Risks:

Discomfort is generally associated with needle puncture. The most common complications associated with blood draws are hematomas or bruising. There is also a possible risk of infection, tendon or tissue damage, damage to the blood vessel and surrounding nerves, and/or loss of feeling in the hand and/or arm.

Other anticipated adverse events that may occur, include but are not limited to: vasovagal syncope (fainting), lightheadedness, feeling flush/warm, feeling nauseated, throwing up, seizures, sudden drop in blood pressure/sudden increase in blood pressure, sudden drop in heart rate/sudden increase in heart rate, tingling sensation of face, arms and/or legs, sweating, and/or mouth dryness. These anticipated adverse events are expected to be temporary.

13.6. Risk From Oxygen Administration:

It is expected that some people may experience feelings of claustrophobia or anxiousness from wearing a mouthpiece, mask, and/or nasal cannula. There are no additional risks associated with high oxygen/oxygen administration for less than 24 hours as long as subjects do not have any cardiac conditions, COPD or any other lung diseases.

Subjects' answers on the health questionnaire will help the medical staff decide if they can safely participate in this study; subjects are encouraged to let the study staff know if they have any concerns.

13.7. Low Oxygen Concentration Risks:

Risks associated with hypoxia include dizziness, shortness of breath, drowsiness, or headache. If or when this occurs, the study can be stopped. There is an extremely small risk of loss of consciousness or death from lack of oxygen. The study shall be stopped by the subject or clinical staff long before this could occur. Breathing a hypoxic (reduced oxygen) mixture has potential risks that include damage to vital organs such as the brain, liver, kidney, and/or heart. Note that several studies have been done with low oxygen using generally healthy subjects without any serious or permanent damage to any of the major organs.

Other anticipated adverse events that may occur, include but are not limited to: vasovagal syncope (fainting), lightheadedness, chest discomfort (e.g. chest tightness, chest pain), feeling flush/warm, feeling of anxiety, feeling nauseated, throwing up, seizures, sudden drop in blood pressure/sudden increase in blood pressure, sudden drop in heart rate/sudden increase in heart rate, tingling sensation of face, arms and/or legs, sweating, mouth dryness, feeling claustrophobic or anxiousness from wearing a mouthpiece and/or mask. These anticipated adverse events are expected to be temporary.

13.8. Risks from Effects of Warming:

Changes in temperature may cause temporary changes in heart rate, or premature ventricular contractions (PVC). The most common discomforts associated with warming may include sweating and/or may cause the subject to feel tired.

In rare instances skin burns may occur when using heating/warming blankets. In the case that this may occur, the blanket will be removed and our medical staff will determine a proper course of action depending on the severity of the burn. Other discomforts may include lightheadedness, dizziness, nausea, clamminess, and/or feeling claustrophobic.

13.9. Nose Clip Risks:

It is expected that some people will have discomfort/pinching/scratches and/or experience symptoms similar to a headache from wearing a nose clip. If this occurs, adjustments can be made and/or the study can be stopped. The nose clip may also leave temporary indentations; these should go away shortly after the nose clip is removed.

13.10. Risk from Inflicted Knowledge:

The risk of inflicted medical knowledge to subjects is negligible since we deidentify all associated sample information including those relevant to our clinical and engineering parameter studies. The monitoring and test results are not examined for diagnostic purposes and do not reflect an attempt to ascertain any subject's medical condition. The attending physician's role during this study is to ensure the safety of the subject during the study.

We will reduce the risk of inflicted knowledge by assuring the subjects that device readings and blood measurements are for research use only. In the case that a subject becomes aware of a condition (e.g. anemia, 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 that particular study.

13.11. Risk 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.

13.12. Risk From Additional Testing:

During the conduct of the study, it is possible, but not likely, that someone could become exposed to the sample of blood drawn from the subject through an inadvertent needle stick or by contact with an open cut. In such circumstances, it will be important to the exposed individual to know whether the blood to which he or she was exposed contained Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV), or Hepatitis C Virus (HCV) and additional testing of the sample will be performed.

Within the consent, subjects will agree to permit a company to test the blood sample(s) by signing the consent. The test results will be maintained as confidential and will only be used by healthcare professionals for the diagnosis and treatment of the exposed individual as appropriate.

In the case that Masimo needs to contact a subject regarding additional testing they will be contacted by a Masimo employee and medical personnel can be available for further counsel if requested.

The cost for the initial testing and compensation for their time/travel to the testing facility will be the only things paid for by Masimo.

13.13. Lidocaine (injection) Risks:

Injection of the Lidocaine may be discomforting and can feel like a slight pinch along with a warm/burning sensation.

Other anticipated adverse events that may occur, include but are not limited to: flushing or redness of the skin, itching skin, small red or purple spots on the skin, unusually warm skin, bruising, bleeding at the application site, swelling, feeling nauseated, dizziness, low blood pressure, and/or tremors.

Although not common, it is also possible to have an allergic reaction to injectable lidocaine (e.g., seizures). Subjects should not take part in this study if they are allergic to lidocaine injection or other types of numbing medicine, or if they have a heart rhythm disorder such as Wolff-Parkinson-White Syndrome or Stokes-Adams Syndrome. Subjects are instructed to tell the study staff right away if they experience hives; difficulty breathing; swelling of the face, lips, tongue or throat.

These adverse events are expected to be temporary.

13.14. Skin Refrigerant (Ethyl Chloride) Risks:

Ethyl Chloride is a topical anesthetic which is used to prevent pain by cooling the skin.

Although unlikely, the anticipated adverse events that may occur, include but are not limited to: changes in skin color (e.g. flushing or redness of the skin), delayed wound healing, rash, itching and swelling. These adverse events are expected to be temporary.

14. EMERGENCY RESPONSE PLAN FOR MEDICAL EMERGENCIES

The physician and nurse present during the study will be ACLS certified and will respond to any medical emergency involving a subject with the ACLS approved protocol for intervention. A crash cart equipped with medications to provide immediate care during emergencies is on site and full emergency services are within 3 miles.

15. MONITORING PLAN

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

16. PROTOCOL DEVIATION AND PROCEDURE TO AMEND PROTOCOL

Modifications to the protocol, informed consent materials, recruitment materials, or any other materials provided to subjects must be reviewed and approved by the IRB prior to implementation.

Deviations to the protocol will be documented on the case report form or a separate document. Protocol deviations will be reported to the sponsor and IRB per IRB reporting guidelines. Deviations from the protocol will be reported in the test report.