Official Title: Repeatability and Reproducibility of Oxygen Reserve Index (ORi)

Date of Protocol: October 03, 2022

NCT Number: NCT05636098

CLINICAL INVESTIGATION PLAN

[redacted]

REPEATABILITY AND REPRODUCIBILITY OF OXYGEN RESERVE INDEX (ORi)

Clinical Investigation Title: Repeatability and Reproducibility of Oxygen Reserve Index (ORi)

Clinical Investigation Number, Version: [redacted]

Other Study Identifier: N/A

Study Device(s): Masimo Rainbow Sensors

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

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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 to prior to enrollment, per FDA (Food & Drugs Administration) 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 determine 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 the 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:	Repeatability and Reproducibility of Oxygen Reserve Index (ORi)
Study objective(s):	To evaluate repeatability and reproducibility of Oxygen Reserve Index (ORi)
Investigational device(s):	Masimo Rainbow Sensors
Number of subjects:	Minimum 20 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 180 minutes.
Study endpoint(s):	Repeatability of ORi at different time points will be reported. Reproducibility of ORi across different sensors will be reported.

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1. Technology Background

Pulse oximetry technologies

Pulse oximetry is governed by the following principles:

Oxyhemoglobin (oxygenated blood) and deoxyhemoglobin (non-oxygenated blood) differ in their absorption of red and infrared light (spectrophotometry).

The amount of arterial blood in tissue changes with arterial pulses (photoplethysmography). Therefore, the amount of light absorbed by the varying quantities of arterial blood changes as well.

More generally, Masimo Pulse CO-Oximeters use a multi-wavelength sensor to distinguish between not only oxygenated blood and deoxygenated blood, but also blood with carbon monoxide, oxidized blood and blood plasma. The CO-Oximeter utilizes a sensor with various light-emitting diodes (LEDs) that pass light through the site to a photodiode (detector). See figure below.

Figure 1: CO-Oximeter LED and Detector locations.

Parameter Background

A continuous supply of oxygen is essential for normal cell function. Failure of a patient's oxygen supply to meet metabolic needs is common to all forms of circulatory failure, tissue acidosis, and ultimately mortality. Like all essential commodities for body functions, optimal quantities of oxygen are required. A patient's oxygen status can be largely classified into 3 ranges: Hypoxia (less than normal), Normoxia (normal) and Hyperoxia (more than normal). The three states are typically classified using dissolved oxygen levels in the plasma (PaO_2), instead of arterial hemoglobin oxygen

saturation (SaO_2), due to sensitivity of PaO_2 in all three states including hyperoxia (unlike SaO_2). Figure 2[1]. shows the three oxygen states based on PaO_2 values along with the relationship between PaO_2 and SpO_2 (which is a proxy for SaO_2).

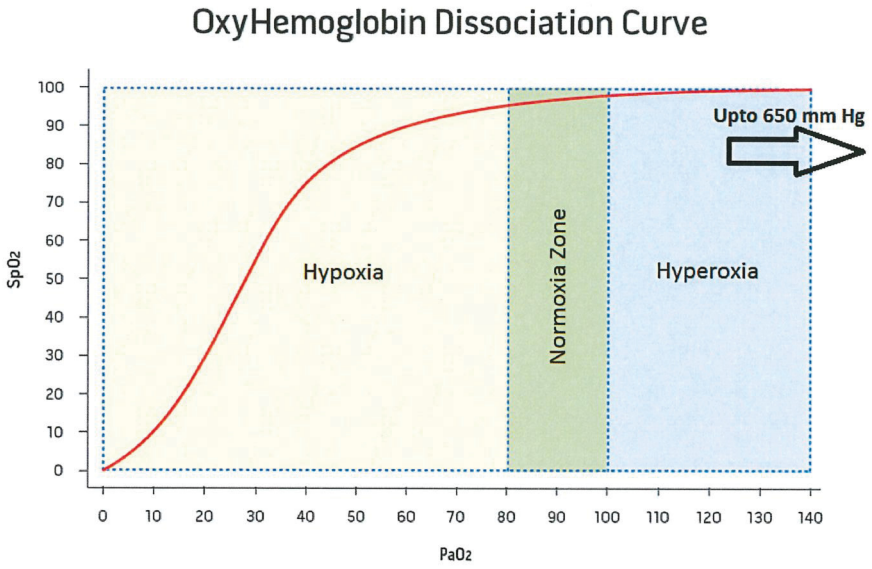


Figure 2: The oxygen dissociation curve with the three oxygen states.

Currently, for clinicians to monitor a patient's oxygen status, both continuously and non-invasively, they utilize a pulse oximeter to obtain SpO2 (a proxy for SaO2) levels. However, SpO2 is sensitive in the normoxic and hypoxic regions and largely remains flat in the hyperoxic region (Figure 2). As a result, clinicians generally resort to invasive blood draws to obtain PaO2 values to provide oxygenation status within the hyperoxic zone. This method has multiple drawbacks such as intermittent samples creating potential delays between time of blood draw and the time when the PaO2 value is finally obtained through the analysis on a blood gas machine.

The ORi parameter is intended to provide clinicians with a convenient noninvasive method for monitoring oxygenation status in the moderate hyperoxic range to be used in conjunction with SpO2 and reference PaO2 measurements. While not a direct measurement of PaO2, ORi is intended to provide a continuous and non-invasive index which can reflect directional changes in oxygenation. The concordance of directional changes to PaO2 from blood samples is used to validate the ability of ORi to monitor oxygenation status in the moderate hyperoxic range.

2.2. Investigational Devices

Pulse Oximeter Sensors and Cables (Masimo Rainbow®)

The investigational devices to be used in this study are Masimo Rainbow sensors. The investigational sensors are produced with the same or similar technology and materials as the Masimo FDA-cleared Rainbow sensors that measure already cleared non-invasive physiological parameters such as SpO2, SpHb, PR, PI, SpMet, and PVi. [redacted] They do not pose any additional risk to patients as compared to the similar FDA cleared sensors.

Masimo Patient Monitoring Platform (Root® or comparable)

The Masimo Root Patient Monitoring Platform is an FDA-cleared patient monitoring and connectivity platform that offers rainbow® and Masimo SET® measurements with other parameters in an integrated platform. With docking capabilities for the Radical-7® handheld monitor and multiple networking/connectivity options, Root integrates multiple streams of data into one display monitor. The software in the Root has been modified to enable the display of the Oxygen Reserve Index (ORi). This modified software has not been cleared by the FDA, which renders the parameter, ORi, on the Root device to be used in this study as investigational. The ORi measurement calculated by the study devices is provided as an output from the serial port on the Root monitor. The output data stream is then captured via a study computer equipped with an automated data collection software (ADC).

Masimo Pulse Oximeters (Radical-7® or comparable)

The Masimo Radical-7 pulse oximeter is an FDA-cleared noninvasive monitoring platform featuring Masimo SET Measure-through Motion and Low Perfusion™ pulse oximetry with the option to measure multiple additional blood constituents and physiologic parameters. The software in the Radical-7 has been modified to enable the display of the Oxygen Reserve Index (ORi). This modified software has not been cleared by the FDA, which renders the parameter, ORi, on the Radical-7 to be used in this study as investigational. The ORi measurement calculated by the study devices is provided as an output from the serial port on the Root monitor. The output data stream is then captured via a study computer equipped with an automated data collection software (ADC).

2.3. FDA Cleared Sensors and Devices

Masimo Patient Monitoring Platform (Root® or comparable)

Root is a patient monitoring and connectivity platform that offers rainbow® and Masimo SET® measurements with other parameters in an integrated platform. With docking capabilities for the Radical-7® handheld monitor and Radius-7™ patient-worn monitor and multiple networking/connectivity options, Root integrates multiple streams of data into one display monitor. The Patient Monitoring Platform, Root, has been modified to enable the investigational ORi parameter, but will have no change in the FDA-cleared Rainbow parameters available for monitoring purposes.

Masimo Pulse Oximeters (Radical-7®, Rad-97®, Radius-7® or comparable)

Masimo rainbow SET pulse oximeters are noninvasive monitoring platforms featuring Masimo SET Measure-through Motion and Low Perfusion™ pulse oximetry with the option to measure multiple additional blood constituents and physiologic parameters. Masimo rainbow and SET technology describes a line of sensors that all use the same type of pulse oximetry technological concepts to read physiological parameters such as:

- Oxygen Saturation (SpO2)
- Pulse Rate (PR)
- Perfusion Index (Pi)
- Total Hemoglobin (SpHb®)
- Oxygen Content (SpOC™)
- Pleth Variability Index (PVi®)
- Methemoglobin (SpMet®)
- Carboxyhemoglobin (SpCO®)
- Acoustic Respiration Rate (RRa®)
- Respiration Rate from the Photoplethysmograph (RRp®)

[redacted]

2.4. 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 study is designed to evaluate the repeatability and reproducibility of ORi using an investigational Masimo rainbow sensors and FDA cleared rainbow sensors connected to the Masimo Radical-7 pulse oximeter and Masimo Root monitor in healthy volunteers as the subjects undergo a controlled hyperoxygenation protocol. The changes in ORi measurements may also be compared to changes in PaO2 values obtained from arterial blood samples analyzed by a laboratory CO-oximeter reference instrument.

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. Benefits would be to society as a whole. Evaluation of the performance of this new device could enable users to monitor and identify potentially life-threatening conditions more appropriately.

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

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

Risks can be categorized into the following categories:

- Those associated with the device
- Those associated with venous blood draws
- Those associated with the placement of venous cannulation
- Those associated with placement of the arterial cannulation
- Those associated with the lidocaine injection
- Those associated with the skin refrigerant (e.g., Pain Ease, Ethyl Chloride)
- Those associated with oxygen administration
- Those associated with low oxygen administration(desaturation)
- Those associated with carbon dioxide administration
- Those associated with mask application
- Those associated with shaving
- Those associated with skin preparation

- Those associated with a nose clip
- Those associated with inflicted knowledge
- Those associated with loss of confidentiality
- Those associated with additional testing

- **Risks Associated with the Device**

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

  There is a risk of discomfort to the subject's finger, or other locations where devices are placed. The application could include 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 be disqualified from the study to avoid any discomfort.

- **Risks Associated with Venous Blood Draw Risks**

  Discomfort is generally associated with needle punctures. 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, inadvertent arterial puncture, 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 pain, 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.

- **Risks Associated with Venous Cannulation**

  Risks associated with venipuncture include discomfort, pain, 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.

- **Risks Associated with Arterial Cannulation**

  The radial artery is the most common site for invasive blood pressure monitoring in anesthesia and critical care medicine because it is technically easy to cannulate and complications are uncommon, in part owing to the good collateral circulation of the hand. The widespread application of invasive arterial pressure monitoring in anesthesia and intensive care is related to the extremely good safety record of this technique.

  Risks include bleeding, decreased blood supply, swelling, infection, bruising, hematoma, damage to the blood vessel and surrounding nerves, tendons, or tissue. Additional risks include pain, 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, irregular heart rate (PAC, PVC, ECG abnormalities, etc.), 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 and/or arm due to rare complications of the study.

- **Risks Associated with the Lidocaine Injection**

  Injection of 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 pain, 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; or swelling of their face, lips, tongue, or throat.

  These adverse events are expected to be temporary.

- **Risks Associated with the Skin Refrigerant (e.g., Pain Ease, Ethyl Chloride)**

  Ethyl chloride and Pain Ease are topical anesthetics 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/or swelling.

  These adverse events are expected to be temporary.

- **Risks Associated with Oxygen Administration**

  It is expected that some people may experience feelings of claustrophobia or anxiousness from wearing a mouthpiece, nasal cannula, and/or mask.

  Subject's will not be exposed to high oxygen for more than 1 hour.

  There are no risks associated with high oxygen/oxygen administration for less than 24 hours if 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.

- **Risks Associated with Low Oxygen Administration (Desaturation)**

  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, irregular heart rate (PAC, PVC, ECG abnormalities, etc.), 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.

- **Risks Associated with Carbon Dioxide Administration**

  Risks associated with carbon dioxide administration include dizziness, shortness of breath, drowsiness, or headache. If or when this occurs, the study can be stopped.

  Other anticipated adverse events that may occur, include but are not limited to tingling, prickling sensations ("pins and needles" feeling), restlessness, sudden drop in blood pressure/sudden increase in blood pressure, sudden drop in heart rate/sudden increase in heart rate, irregular heart rate (PAC, PVC, ECG abnormalities, etc.), sweating, and/or feeling claustrophobic or anxiousness from wearing a mouthpiece and/or mask.

  These anticipated adverse events are expected to be temporary.

- **Risks Associated with Mask Application**

  A mask may be applied to the subject's face using an adhesive dressing or using straps. Risks associated with mask adherence include skin irritation, redness of the skin, itchiness, tingling sensation, rash, changes in skin color, and/or headache. It is expected that some people may experience feelings of claustrophobia or anxiousness from wearing a mask.

  It is expected that some people may experience increased pressure around the area of the mask, this is expected to be temporary and resolve once mask is removed.

  Subjects should not take part in this study if they are allergic to adhesives. 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.

- **Risks Associated with Shaving**

  Subjects may be asked to shave the area of sensor and/or mask application to allow the sensors and/or mask to stick 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 and side effects are temporary and should fade over time. Some of these symptoms may last up to several days after shaving.

  If there are any cuts and/or abrasions near the area of sensor and/or mask application, certain types of sensors or masks may not be placed on the particular location to avoid any discomfort for the subject.

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

- **Risks Associated with Skin Preparation**

  Subjects may be asked to use an alcohol pad, fingertip abrasive pad or comparable on the area of sensor application to allow the sensors 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 and side effects are temporary and should fade over time.

  If there are any cuts and/or abrasions near the area of sensor application, certain types of skin preparation materials may not be used on the particular location to avoid any discomfort for the subject.

- **Risks Associated with Nose Clip**

  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 or when 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.

- **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 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.

- **Risks from Additional Testing**

  During the conduct of the study, it is possible, but not likely, that someone could become exposed to a 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), Hepatitis C Virus (HCV), or Human Immunodeficiency Virus (HIV).

  In the case that an individual becomes exposed to a sample of blood from the subject, the subject will be requested to go to an outside facility (e.g., urgent care clinic, outside laboratory) and have an additional sample(s) taken for additional testing. 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.

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 objective of this study is to evaluate the repeatability and reproducibility of ORi using Masimo Rainbow sensors compatible with Oxygen Reserve Index (ORi) on healthy volunteers. The changes in ORi measurements are compared to changes in PaO2 values obtained from arterial blood samples analyzed by a laboratory CO-oximeter reference instrument.

The study endpoints are to compute repeatability of ORi at two different time points at the same relative oxygenation state and compute the reproducibility of ORi across different sensors on a per subject basis.

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 Masimo Rainbow sensors on their fingers.

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 in the use of relevant equipment.

Safety Equipment (FDA-Cleared)

- Blood pressure monitoring system
- Masimo Patient Monitoring Platform (Root® or comparable)
- Masimo Pulse Oximeters (Radical-7®, Rad-87™, Radius-7®, Rad-97® or comparable)
- Medical-grade oxygen tank, mask, and nasal cannula
- Crash cart

Test Devices (FDA-cleared, consumer products, or investigational)

- Masimo Rainbow sensors – investigational parameter
- Masimo Patient Monitoring Platform (Root®)
- Masimo Pulse Oximeters (Radical-7, Optional: Rad-97®)

Research Equipment

[redacted]

- Laboratory CO-oximeters/blood analyzers
- Laboratory hematology analyzers

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 50 years of age.
- Subject weighs a minimum of 110 lbs.
- Hemoglobin value ≥ 11 g/dL.
- Baseline heart rate ≥ 45 bpm and ≤ 85 bpm.
- 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.
- CO value ≤ 3.0% FCOHb.
- Subject is able to read and communicate in English and understands the study and the risks involved

6.3.2. Exclusion Criteria (Ineligible Subjects)

- Subject has a positive hCG test.
- Subject has a BMI > 35.
- 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 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 or subject is deemed ineligible by the discretion of 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 180 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 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 (including skin tone)	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	
Orthostatic Blood Pressure Test*		X	
Pregnancy test[2]		X	
Allen's Test*		X	
Venous sample (via needle stick or IV placement)		X	
Local anesthetics (lidocaine, ethyl chloride spray, or pain ease skin refrigerant) as needed[3]		X	X

[2] hCG (urine) pregnancy test (all subjects with childbearing potential)
*At the discretion of the study staff

Procedures	Phone Pre-Screen	Baseline Visit 1	Procedure Visit 1
Peripheral Venous Line (IV)[3]		X	X
Intra-arterial catheter (A-line)			X
Placement of test sensors			X
Data collection			X
Hyper-saturation			X
Desaturation**			X
Continuous A-line sampling			X
Line Removal			X
Post Care Instructions Given		X	X
Discharge		X	X
Adverse Event Review and Evaluation[4]		X	X

6.4.2. Recruitment and Pre-Screening

6.4.2.1. Advertisement and Recruitment

Recruitment materials are posted publicly in local newspapers, advertisement websites (e.g., craigslist), schools/universities, social media platforms (e.g., Facebook), bulletins, flyers, handouts, etc. We will recruit human subjects, which will include members of the general public [redacted]

6.4.2.2. Phone Screening

Once the potential subject sees the recruitment material (e.g., advertisement) they can contact us to inquire more details about the study. The recruitment process is managed by the designated person(s) who is trained for phone screening/scheduling.

Appointments are made once the phone screening process is completed and the person screening the subject determines if they qualify or not for the study based on inclusion/exclusion criteria.

Information from the screening will be kept in a database located within the firewall protected Masimo internal network with user level access control enforced domain log in. Additionally, the database is encrypted, and password protected. The information is kept to contact subjects for other studies they may qualify for or for instance, to track subjects who call in and provide false information only to qualify.

6.4.3. Consenting and Screening

Subjects may be asked to provide a copy of their valid government photo ID and/or Social Security Number card (SSN) to verify subject information in our scheduling database and/or to verify the subject's identity. A W-9 form may need to be completed to report earnings to the Internal Revenue Service (IRS).

Foreign persons (a foreign person includes a nonresident alien individual and certain foreign entities that are not U.S. persons) may be asked to provide a copy of U.S. immigration documents/Tax ID Number (TIN) or equivalent, and to complete a W-8BEN form to report earnings to the Internal Revenue Service (IRS).

Copies of these forms of identification may be stored electronically. The confidentiality and retention of these documents will be protected to the extent provided and required by the law.

[3] IV may be placed during screening/baseline, medical staff will offer to use local anesthetics.
[4] Adverse events may be reported by the subject after their visit. See section 10 for additional details.
** Per engineering request

Copies of the SSN and ID card are kept to verify subjects' identities or for instance, to track subjects who provide false identification.

Subjects must read and sign the consent document, using our informed consent process. The paper consent form must be stamped with a current IRB approval. Due to the limitations of the electronic consent form, it may not be stamped with a current IRB approval; however, the IRB will review and approve the electronic document prior to implementation. The electronic consent form will contain indicators that show the version of the consent form. 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 or refuse to answer questions will not be eligible to participate in the study.

Subject demographic information such as age, sex, skin tone, ethnicity, height, and weight will be collected. These may be recorded for data analysis and/or subject safety monitoring purposes. [redacted]

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

Female subjects/subjects with childbearing potential will be required to take a pregnancy test. Results will be noted. If the pregnancy test is positive, the subject will be removed from the study and notified of their pregnancy test results. An Allen's test may be performed at the discretion of the study staff.

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.

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

6.4.3.1. Initial systolic blood pressure lower than 100 mmHg and greater than or equal to 90 mmHg, and/or

6.4.3.2. 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 2: 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.

A venous blood sample will be obtained and analyzed to verify that the starting hemoglobin level is greater than or equal to 11.0 g/dL and carboxyhemoglobin (COHb) level is less than or equal to 3.0%. If hemoglobin level is less than 11.0 g/dL and/or COHb is greater than 3.0%, the subject will be excluded from the study.

After testing, blood samples will be de-identified and discarded in the appropriate biohazard waste

bins.

Subjects may have a blanket placed on them and/or hot water bottles placed under their hands (per request of subject).

Subjects may be offered a snack (e.g., granola bar) and/or beverage (e.g., water, juice) due to the amount of time their involvement in this study may take.

6.4.4. Line Placement Sensor Placement Procedure

If accepted into the study, standard noninvasive monitors may be placed on the subject, which may include FDA-cleared pulse oximeters, ECG, and blood pressure cuff(s) (may not be recorded automatically depending on the protocol, this may be recorded manually for monitoring by medical staff). This is assessed for subject monitoring only. Blood pressure may be obtained from arm cuffs, leg cuffs, finger cuffs, or equivalent devices. Blood pressure may be taken manually or automatically depending on the device used. For data collection purposes blood pressure measurements may be obtained various ways.

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 may be placed in the subject's hand or arm for safety purposes. One or more venous sampling catheters may be used during the study for removal of samples of blood to allow for determination of venous oxygen saturation as well as other non-infectious blood solutes. This line may be used for a qualifying blood draw to verify that the participant meets inclusion criteria. 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 for the subjects.

After intravenous access (if necessary) is established, one or more intra-arterial catheter(s) (arterial line or A-line) may be placed in the radial artery of the subject's wrist. This study is being done with an arterial line to facilitate continuous blood sampling to determine arterial blood gas values (ABG), such as oxygen saturation. Noninvasive ultrasound devices may be used to facilitate line placement and/or for data collection purposes. Examples of how these devices may be used include image capture, continuous noninvasive monitoring of blood velocity in a vessel, etc.

- When used, these noninvasive devices may be secured to the body for continuous measurements and imaging. For instance, an ultrasound probe may be placed on various areas of the body using a strap or other type of apparatus (e.g., headset) to hold the probe in place

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 ox sensor may be placed on the subject for reference values such as, but not limited to, oxygen saturation, total hemoglobin, carbon monoxide, and pulse rate.

Optical sensors for the noninvasive measurement(s) may be placed on the subject's fingers. Other non-

invasive sensors/devices may also be placed on the skin, toes, feet, neck, clavicle, face, chest, forehead, wrist, arms, legs, nose, nostrils, back, abdomen and/or ears. These sensors may be placed and removed by several operators several times during the study.

Non-invasive devices may be placed and/or used.

Subjects may be asked to shave the area of application to allow the sensors and/or mask to stick to the skin.

Raw device data from the noninvasive device(s) may be collected from the sensors/devices and stored.

Other standard output parameters may also be recorded from the device(s) (e.g., SpO2, SpMet, SpCO, PVI, PI, pulse rate, temperature, blood pressure).

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

Subjects may wear a mask or mouthpiece and nose clip/nose plugs during the preoxygenation. End-tidal and/or partial pressure of carbon dioxide and respiration rate values will be noted after the mask or mouthpiece and nose clip/nose plugs is placed for subject safety purposes and will be noted again prior to removal. If respiratory rate is greater than 30 breaths per minute at 21% FiO2 do not proceed with the study. 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 proceed.

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.

In studies with photography, videography, subjects will give consent for the recordings and/or observational group prior to the start of any study-related activities.

Masimo Rainbow sensors will be placed on the subject's fingers. Sensors may be repositioned, as needed, to ensure proper placement. The site of sensor placement should be assessed throughout the duration of the study. If there are any signs of loss of skin integrity and/or loss of circulation or perfusion, the device should be repositioned.

6.4.5. Hyperoxygenation Procedure

Oxygen tank pressure will be checked and noted before the study begins for subject safety purposes. Upon successful placement of the safety monitors 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. These blood draws may occur at various points during the length of the study.

A set of blood samples of approximately 4cc each will be drawn at selected time intervals throughout the study for laboratory analysis of oxygen saturation. Up to 100 samples of blood may be collected and analyzed. [redacted]

The total amount of blood drawn will not exceed 400mL.

Subjects will be given supplemental oxygen through a nasal cannula, mouthpiece, or mask during some portion of the study. This is to simulate the high oxygen environments during surgeries and test our sensors performance during oxygen administration. The FiO2 may be between 21%-100%.

After reaching the desired targeted FiO2 levels during hyper-saturation, the proportion of inspired oxygen (FiO2) may be decreased in specified targeted increments until reaching room air; samples should be drawn at each targeted saturation level. After reaching an FiO2 at approximately room air,

the mouthpiece may be removed, and the subject may be allowed to breathe room air without the mouthpiece.

The timing of all the blood draws will be entered into the data collection software.

Subjects may undergo the hyper-saturation procedure up to 2 times.

It is normal for subjects to feel as though they have to concentrate on their breathing more than they would normally. This is due to the fact that their nose may be plugged, and most subjects are not used to breathing with a mouthpiece. The gas flow rate may be increased to help subjects to feel less like their breathing is restricted.

The process will be stopped if there is any evidence of subject stress or distress. These signs include but are not limited to complaints of feeling faint, chest discomfort, GI distress, urinary discomfort or feelings of a bloated bladder, altered mental status, or significant elevation in heart rate (per physician's discretion).

High oxygen administration should not exceed one hour.

6.4.6. Desaturation Procedure

Subjects may wear a nose clip or nose plugs and use a mouthpiece, or wear a mask, during the desaturation procedure. The mask may be secured to the subject's face by securing adjustable straps and/or Tegaderm adhesive (or equivalent) to secure the mask to the skin. Subjects may be asked to shave the area of application to allow the mask to adhere to the skin. The area of application may also be wiped to remove facial oils, make-up, or any other skin products.

End-tidal and/or partial pressure of carbon dioxide and respiration rate values will be noted at the beginning of the desaturation portion of the study for subject safety purposes and will be noted again at the end of the desaturation portion of the study. If respiratory rate is greater than 30 breaths per minute at room air (21% FiO2), the study will be stopped. If respiratory rate is less than or equal to 5 breaths per minute at room air (21% FiO2), check blood gas values of first samples after the mouthpiece or mask is placed, then the study will proceed.

The subject may participate in slow desaturations, a series of quick desaturations, or a combination of both. These desaturations may occur prior to, after, or in sequence with the hyperoxygenation procedure. Upon indication that the subject is comfortable, a gas mixture will be administered. The gas mixture may include varying proportions of oxygen, carbon dioxide, and nitrogen. The proportion of oxygen in this mixture will be decreased to lower the subject's blood oxygen saturation. The lowest targeted value will be approximately 90% oxygen saturation. Readings near 90% will be immediately verified by the reference CO-oximeter to ensure we are within the targeted oxygen saturation range and to minimize time that subject may drop below the targeted range. Note: At any point in the study, if the subject feels uncomfortable, the subject will be given oxygen through a mouthpiece, mask, or nasal cannula.

A qualified person will complete blood draws. Arterial and/or venous blood samples may be drawn consecutively during the procedure at different saturation levels. No more than 100 samples of approximately 1-4cc each may be drawn. Including blood drawn to flush the line and prepare for new samples.

The points of the blood samples will be noted into the data collection software. Based on data collection requirements, sample timing and timing for saturation changes may vary.

Subject's blood pressure and/or temperature may be monitored throughout the study; these values may be recorded for subject safety or data collection purposes as indicated in the clinical study request.

The study will end with an FiO2 greater than or equal to room air (21%) to help the subject re-saturate

after the procedure. If at any point the subject is uncomfortable with the study, the study will be stopped.

6.4.7. Ending Procedure

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

Study staff may take one final blood draw of 1-4cc, 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.).

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 studying before returning to work.

Subjects will be given instructions on post care. All subjects will be instructed to contact the principal investigator and/or study staff in the event of any potential complication.

After the study has ended subjects will be offered a snack (e.g., granola bar) and something to drink (e.g. water or juice). Subjects are asked to consume the 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 an additional 30 minutes (estimate) before leaving to allow for their body to continue adjusting after the study has completed.

The total overall lab time will be approximately 180 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

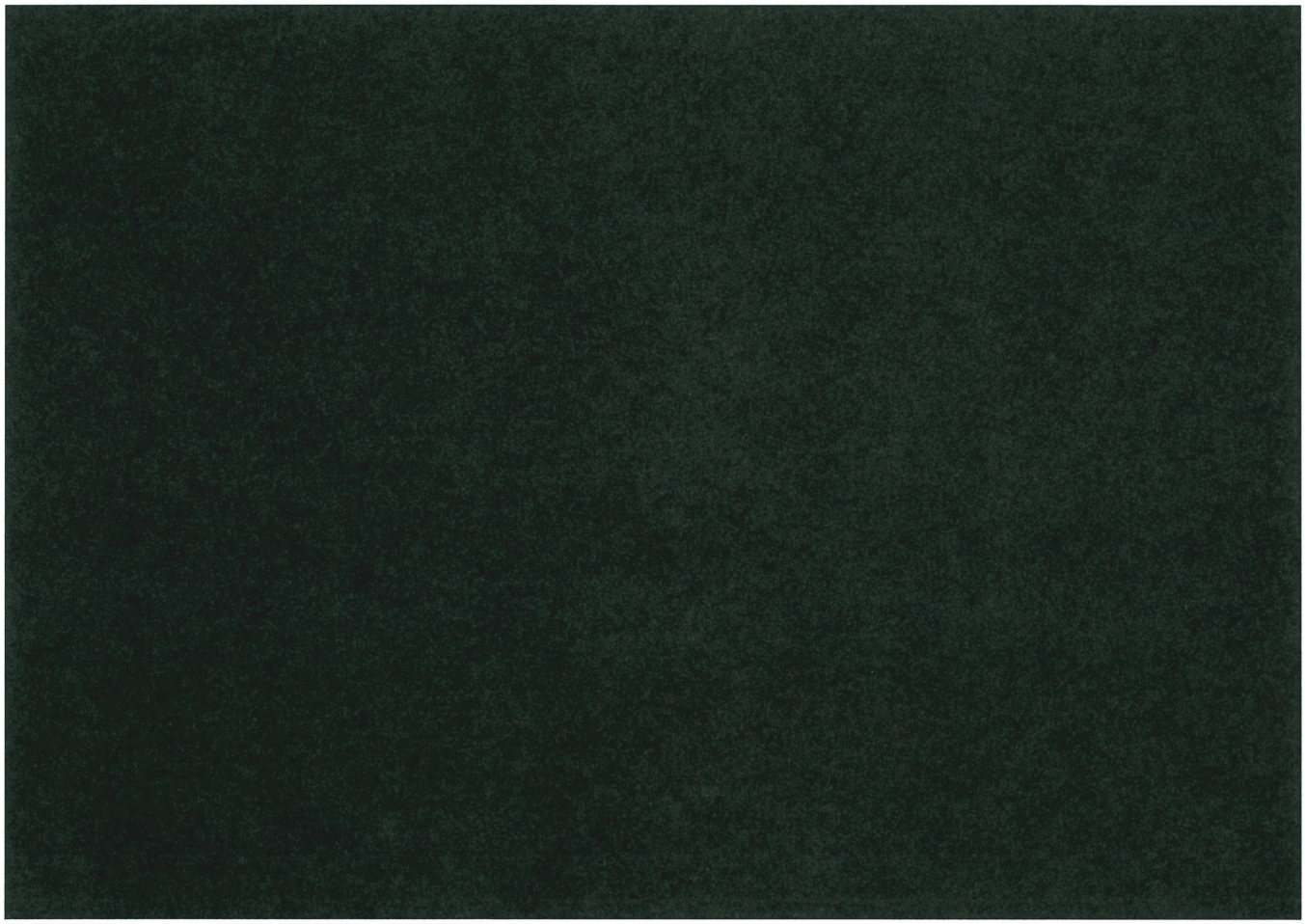
7.1. Acceptance Criteria

N/A

7.2. Sample Size

[redacted]

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



[redacted] minimum of 20 subjects is required for the variation of error to be stable.

7.3. Statistical Analysis

7.3.1. Repeatability variance of ORi will be computed across two different time points per subject.

7.3.2. Reproducibility variance of ORi will be computed across sensors per subject.

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.

However, the sample size per group may be increased to account for dropout rates during the study.

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 of 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 include / 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 the study monitors during site visits.

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 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 each 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 the product's 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 the 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 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 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 (about 2 days). 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 the possibility of undue influence due to financial incentive.
- Educationally disadvantaged subjects will be provided with 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 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 determines that the study site's compliance to be inadequate at any point during the study, and sponsor moves 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 recur in the future. The 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]