Official Title: Performance Comparison Between Masimo W1™ and Apple Watch Series 8

Date of Protocol: 29Jun2023

NCT Number: NCT05968079

Clinical Investigation Title: Performance Comparison between Masimo W1™ and Apple Watch Series 8

Clinical Investigation Number, Version: CIP-1082A

Other Study Identifier: MACL0003

Study Device(s): Masimo W1™
Apple Watch Series 8
Masimo RD SET Adt

Sponsor: Masimo Corporation
52 Discovery
Irvine, California 92618 USA

1. INVESTIGATOR PAGE

[redacted]

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:**

2. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical investigation title:	Performance Comparison between Masimo W1™ and Apple Watch Series 8
Study objective(s):	Primary Objective: Evaluate the performance of Masimo W1™ against FDA cleared hospital grade pulse oximetry technology under desaturation conditions. Secondary Objective: Compare the performance of Masimo W1™ and Apple Watch Series 8 against FDA cleared hospital grade pulse oximetry technology under desaturation conditions.
Study device(s):	Masimo W1™ Apple Watch Series 8 Masimo RD SET Adt
Number of subjects:	Up to 40 subjects.
Inclusion criteria:	• Subject is 18 to 55 years of age. • Subject is American Society Anesthesiologist status 1 (ASA I) • Subject has a BMI between 18 and 35. • Subject is able to read and communicate in English and understands the study and the risks involved.
Exclusion criteria:	• Subject is currently taking any medications which in the opinion of the principal investigator would not be suitable for participation in the study. • Subject is wearing nail polish that cannot be removed, gel nails, and/or acrylic nails that can interfere with study device's placement. • Participants with conditions or skin abnormalities at or around site of sensor placement that could affect the placement on the sensor or prevent monitoring of physiological parameters during the study, such as psoriasis, eczema, angioma, scar tissue, burn, fungal infection, substantial skin breakdown. • Subject has participated in an investigational drug study within one month prior to the start of the study. • Subject has failed the Allen's Test to confirm patency of the collateral artery. • Subject is female with a positive pregnancy test, or is female and is unwilling to use effective birth control between the time of screening and study termination. • Subject has a positive urine cotinine or drug test. • Subject has a reported allergy to Lidocaine. • Subject has clinically significant anemia or other hemoglobinopathy. • Subject has a room air saturation of less than 95% by pulse oximetry. • Subject has a clinically significant abnormal EKG. • Subject has a clinically significant abnormal pulmonary function test via spirometry. • Subject is intolerant to a breathing mask apparatus. • Subject has a COHb greater than 3%, or MetHb greater than 2% verified by laboratory co-oximeter. • Subject has another condition, which in the opinion of the principal investigator would not be suitable for participation in the study. • Subject is unwilling or unable to provide informed consent or comply with the study procedures.
Duration of the clinical investigation:	Expected duration of study enrollment is 1 to 3 months. Subject participation in the study will be approximately 6 hours (approx. 2 hours for the screening phase and 4 hours for the data collection phase)

Study endpoint(s):	Primary endpoint: Performance of oxygen saturation (SpO2) measurements reported by Masimo W1™. Secondary endpoint: Performance of oxygen saturation (SpO_2) measurements reported by Masimo W1™ watch and Apple watch series 8.

3. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Masimo Corporation is the developer of noninvasive technologies for the measurement and monitoring of physiological variables, such as arterial oxygen saturation (SpO2), total hemoglobin concentration (SpHb), carboxyhemoglobin concentration (SpCO), methemoglobin concentration (SpMet), and other physiological variables to improve patient outcomes and reduce cost of care.

The Masimo W1™ is a watch that provides spot-check ECG measurements and continuous measurements of functional oxygen saturation of arterial hemoglobin (SpO_2), pulse rate (PR), and respiration rate from the pleth (RRp®). The watch has a touchscreen display, a rechargeable battery, and Bluetooth® connectivity to pair to a smartphone App.

Figure 1: Masimo W1™

Additional study devices that will be used in this study include the Apple Series 8 watch, the Masimo Rad-97 Pulse CO-Oximeter and the Masimo RD SET Adt sensor. The Rad-97 and Masimo RD SET are indicated for the continuous non-invasive monitoring of functional oxygen saturation (SpO2), pulse rate (PR), respiratory rate (RRa), and Pleth Variability index (PVi) for adult populations.

The Apple Series 8 watch will be connected to an iPhone, results from the spot check measurements on the Apple Watch will also be manually recorded in the comments portion of a data collection software on a laptop. The Rad-97/RD SET pulse oximeter will be connected to a data collection software on a laptop.

Figure 2: Masimo Rad-97 Pulse CO-Oximeter

Figure 3: Masimo RD SET Adt Sensor

4. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

This study is designed to compare the performance of Masimo W1™ and Apple Watch Series 8 to FDA-cleared RD SET Adt for SpO2 as the subjects undergo a controlled desaturation protocol. This type of study design is required to evaluate the performance of pulse oximeters based upon the ISO 80601-2-61 standard which is also adopted and referenced by the FDA.

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

5.1. Anticipated Clinical Benefits

There will be no benefit to the subject. Benefits would be to society as a whole. Equivalence of the accuracy of this pulse oximetry device could enable users to monitor and identify potentially life-threatening conditions more appropriately.

5.2. Anticipated Adverse Device Effects

See *List of Anticipated Adverse Effects* under section 17.2.

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

The following risks/discomforts associated with study procedures are anticipated adverse events. These anticipated adverse events are expected to be temporary.

All adverse events will be documented and reported following procedures outlined in this document.

Risks Associated with the Device

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

There is a small risk of damage to the subject's wrist(s) and/or finger(s), from the device, including temporary skin irritation, skin inflammation, itching skin, or discomfort associated with exposure to the sensor, as well as potential temporary mechanical irritation or discomfort.

If there are any cuts and/or abrasions near the sensor application site, sensors may not be placed on the particular wrist to avoid any discomfort for the subject.

Risks of Colorimeter

The light is cold to the touch and does not pose any burn risk to the skin.

Risks of Blood Pressure Cuff

The reported risks associated with non-invasive blood pressure (NIBP) cuff measurement include discomfort upon inflation of the cuff, possible bruising, rash (small red or purple spots on the skin, caused by a minor bleed from broken capillary blood vessels), and discoloration of the skin beneath the cuff. Risks may also include nerve injuries (impaired movement, sensation, or function), skin tear, and compartment syndrome.

Risks Associated with Venous 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, 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.

Risks Associated with 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. 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.

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 can 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.

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.

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 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 pads, in the case that this may occur, the warming pad will be removed and our medical staff will determine proper course of action depending on the severity of the burn. Other discomforts may include lightheadedness, dizziness, nausea, clamminess, and/or feeling claustrophobic.

Reproductive Risks

Low oxygen levels may affect normal development of a fetus, so women who are pregnant or planning a pregnancy are not allowed to participate in this research study.

6. OBJECTIVES OF THE CLINICAL INVESTIGATION

Primary Objective: Evaluate the performance of Masimo W1™ against FDA-cleared hospital grade pulse oximetry technology under desaturation conditions.

Secondary Objective: Compare the performance of Masimo W1™ and Apple Watch Series 8 against FDA-cleared hospital grade pulse oximetry technology under desaturation conditions.

7. DESIGN OF THE CLINICAL INVESTIGATION

7.1. General

Data using the noninvasive devices will be collected from generally healthy male and female 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 Masimo W1™ and Apple Watch Series 8 on their wrist(s) and FDA-cleared RD SET Adt on at least one finger. Desaturation will be conducted by reducing the concentration of oxygen the study subject breathes in a controlled manner to obtain noninvasive oxygen saturation readings, SpO2, at various levels.

SpO2 performance will be calculated using Accuracy Root Mean Square (A_{RMS}) analysis of the SpO2 values and the reference FDA-cleared RD SET Adt values.

Outcome Measure:

SpO2 equivalence will be determined by calculating the A_{RMS} value through the comparison of the noninvasive oxygen saturation measurement (SpO2) to the noninvasive oxygen saturation measurement (SpO2) value obtained from the FDA-cleared hospital grade pulse oximetry technology.

7.2. Investigation Site(s)

[redacted]

[redacted]

7.3. Definition of Completion of the Clinical Investigation

The study will be considered as complete when 20 subjects have been evaluated and a final clinical study report is complete, excluding those who have been withdrawn.

7.4. Study Devices and Comparators

Study Devices and Technologies

- Masimo W1™ – Test
- Apple Watch Series 8 – Test
- RD SET® Adt - Control

FDA-Cleared Safety Equipment

- Capnostream 20
- Nexfin bmeye
- ECG Module

Research Equipment (as needed)

- Masimo Pulse Co-Oximeter (Rad-97 or comparable)
- Data Collection Research Equipment (e.g[redacted] Lab Chart, smart phone with data collection application or comparable)
- Colorimeter (e.g., Delfin SkinColorCatch or comparable)
- Warm water bottle, heating pad or Comparable
- [redacted]
- Laboratory CO-oximeters/blood analyzers (e.g. Radiometer ABL90 Flex or comparable)

7.5. Subjects

7.5.1. Inclusion Criteria

- Subject is 18 to 55 years of age.
- Subject is American Society Anesthesiologist status 1(ASA1)
- Subject has a BMI between 18 and 35.
- Subject is able to read and communicate in English and understands the study and the risks involved.

7.5.2. Exclusion Criteria (Ineligible Subjects)

- Subject is currently taking any medications which in the opinion of the principal investigator would not be suitable for participation in the study.
- Subject is wearing nail polish that cannot be removed, gel nails, and/or acrylic nails that can interfere with study device's placement.
- Participants with conditions or skin abnormalities at or around site of sensor placement that could affect the placement on the sensor or prevent monitoring of physiological parameters during the study, such as psoriasis, eczema, angioma, scar tissue, burn, fungal infection, substantial skin breakdown.
- Subject has participated in an investigational drug study within one month prior to the start of the study.
- Subject has failed the Allen's Test to confirm patency of the collateral artery.

- Subject is female with a positive pregnancy test, or is female and is unwilling to use effective birth control between the time of screening and study termination.
- Subject has a positive urine cotinine or drug test.
- Subject has a reported allergy to Lidocaine.
- Subject has clinically significant anemia or other hemoglobinopathy.
- Subject has a room air saturation of less than 95% by pulse oximetry.
- Subject has a clinically significant abnormal EKG.
- Subject has a clinically significant abnormal pulmonary function test via spirometry.
- Subject is intolerant to a breathing mask apparatus.
- Subject has a COHb greater than 3%, or MetHb greater than 2%.
- Subject has another condition, which in the opinion of the principal investigator would not be suitable for participation in the study.
- Subject is unwilling or unable to provide informed consent or comply with the study procedures.

7.5.3. Number of Subjects

Up to 40 subjects will be enrolled in the study.

7.5.4. Subject Classification

Subjects will be classified according to the criteria below:

- **Screened** – Subjects who are assessed for study eligibility, after the they have signed the informed consent form (ICF).
- **Enrolled** – Subjects who have met all the inclusion criteria, do not meet any exclusion criteria and have been assigned a subject identification number.
- **Screen Failure** – Subjects who do not meet all the eligibility criteria. (Reason for the subject's ineligibility will be documented on a *Screening and Enrollment Log*).
- **Withdrawn** – Subjects who do not complete the study due to reasons listed below:
  - Subject voluntarily withdrew their consent.
  - Subject was discontinued from study at the discretion of the principal investigator (PI).
- **Completed** – Subjects will be considered complete if an SpO2 value below 80% is achieved.

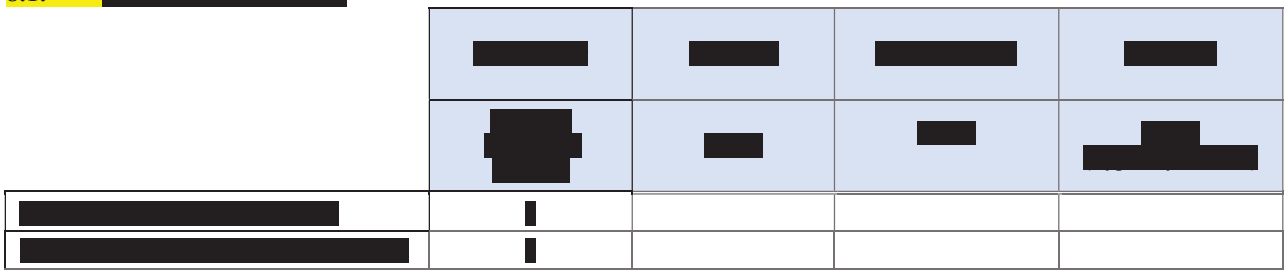
7.5.5. Study Duration

Expected duration of study enrollment is 1 to 3 months. The expected duration of each subject's participation in the lab will be approximately 6 hours (approx. 2 hours for the screening phase and 4 hours for the data collection phase).

8. STUDY PROCEDURES

This study will be conducted in four phases: recruitment phase, screening phase, data collection phase and follow-up phase. Each phase includes one visit; these visits will either be remote or in-person depending on the scheduled activities. Multiple phases/visits may be combined into the same day (as applicable).

8.1. [redacted]



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8.2. Recruitment Phase (Pre-Screening)

Subjects will be recruited using IRB-approved advertisements. Subjects may also be referred to the study by previous subjects. Subjects who are interested in participating will complete an online screening survey via REDcap. At this time interested subjects will have an opportunity to read the IRB-approved Informed Consent Form (ICF). After the screening survey is completed the study staff will review and subjects who qualify based on the survey will be asked to participate in the screening phase and come on-site for Visit 1. Study staff have the option of remotely consenting qualified subjects who have a pre-existing Electronic Medical Record (EMR) at Duke prior to Visit 1. Remote consent will follow the same informed consent process as outlined in Section 8.3.1.

8.3. Screening Phase (Visit 1)

8.3.1. Informed Consent Process

The investigator shall not enroll any subject to participate in the study or consent any subject prior to receiving IRB approval of the ICF. No study related activities will be conducted until consent is signed.

Study staff will discuss the purpose and procedures of the study, risks and benefits, clarify subject's rights and privacy.

The subjects will be provided with enough time to read and understand the informed consent document and their questions will be answered by study staff prior to the subject signing the informed consent form. The research team will emphasize that participation is voluntary.

Once the subjects' questions have been answered and the informed consent is signed and dated, the Principal Investigator or delegate will also sign the informed consent document, approving that the subject will be enrolled in the study. The investigator shall retain the original copy of the informed consent document in each subjects records and provide a copy to the subject.

The point of enrollment is defined as the time at which the assent, consent and/or parental consent is signed and dated. The informed consent will be valid for 45 days from when the informed consent has been fully executed. The subject may withdraw from the study at any time. The subject may withdraw from the study at any time.

8.3.2. Screening

After the informed consent form has been signed by both the subject and the Principal Investigator or delegate the following information, but not limited to, will be recorded on the case report form (CRF):

Inclusion/Exclusion Criteria Assessment: Refer to criteria above in Sections 7.5.1 and 7.5.2.

Medical and surgical history: Current medical conditions, recent medical history including surgeries and concurrent medications within the last 90 days will be collected. Subjects ASA status will also be assessed.

Demographic information: Such as age, gender, skin pigmentation (see assessment details below), self-identified race/ethnicity etc.

Skin Pigmentation Screening:
Study subjects of differing levels of skin pigmentation will be enrolled in the study.

Subjects will be pre-screened for skin pigmentation (dorsal side of the hand) using the *Delfin SkinColor Catch* device, *Monk* scale, [1] and *Massey-Martin* scale [2]. Delfin SkinColor Catch will be the primary stratification method to classify subjects into two groups of light and dark, and Monk and Massey-Martin scales will be used for data collection purposes.

[1] Massey, DS, Martin, JA. The NIS Skin Color Scale. 2003.
[2] Monk, E. Monk Skin Tone Scale. 2019. https://skintone.google.

Delfin SkinColor Catch provides a colorimetric measure of melanin and erythema and automatically calculates the individual typology angle (ITA, - 90° to 90°) degree, which classifies the skin tone. Delfin SkinColor Catch measurements will be taken on the dorsal side of the hand, following the manufacturer's recommendations provided in Delfin SkinColor Catch User Manual. Notably, three measurements (one measurement between thumb and index finger, upper chest, and forehead) will be taken on a dry, smooth region, free of hair, scars, folds, and hyperpigmentation (i.e., area should be representative of subject's overall skin tone). The following parameters will be recorded: ITA, L, A, B values on the CIE-LAB color space, M and E.

Massey-Martin and Monk are two skin-typing scales, with various shades of skin color corresponding to numeric points 1 to 10. Using a mapped pictorial guide the staff will record the respondent's skin color. Values will be recorded for two sites: dorsal side of the hand and the forehead.

To ensure equal representation of light- and dark- skinned subjects, the collected skin pigmentation data will be reviewed where applicable to ensure recruited subjects represents adequate spread for both light- and dark-skin groups and are not concentrated near the ITA cutoff of 10.

Sensor site screening: Sensor application sites (e.g., wrist) will be screened for tattoos. Tattoos near the sensor site will be documented in the case report form. Subjects that have a tattoo(s) in the area of device placement may be disqualified; per PI and/or study staff discretion.

Physical examination: Including height, weight, calculated Body-Mass Index (BMI), and Allen's test. A directed physical examination with focus on cardiovascular and respiratory systems with airway examination and a focused neurological and musculoskeletal examination will be performed and assessed. Reported outcome as either WNL, NCS, or CS (within normal limits, not clinically significant or clinically significant). Comments added if NCS or CS to explain selection in Case Report Form (CRF).

Vitals: 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.

EKG: A 12-Lead EKG will be completed and reviewed by the Principal Investigator or delegate, if the subject has a clinically significant abnormal EKG the subject will be disqualified.

Pulmonary function test (PFT) assessment: PFT via Spirometry will be completed and reviewed by the Principal Investigator or delegate, if the subject has a clinically significant abnormal PFT the subject will be disqualified.

Venous Blood Samples: Blood samples will be taken (approximately 15 cc). One blood sample will be analyzed via co-oximeter for carboxyhemoglobin (COHb)/methemoglobin (MetHb) levels. The local laboratory will assess the hemoglobin electrophoresis sample to screen out any hemoglobinopathies, which may take up to 72 hours for analysis.

Urine samples: Urine drug screening to test for the presence of drugs such as amphetamines, barbiturates, benzodiazepines, marijuana, and opiates. and cotinine tests. Adult female subjects 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.

8.4. Data Collection Phase (Visit 2)

8.4.1. Desaturation General

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). This is assessed for subject monitoring only. Blood pressure may be obtained from arm cuffs, leg cuffs, finger cuffs, or equivalent devices.

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. 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. This line may be used for a qualifying blood draw to verify that the participant meets inclusion criteria.

Local anesthetics such as Lidocaine may be used in the event that an IV is placed to numb the site. Subjects will be given the option to have lidocaine be used during IV placement for the purpose of making catheter placement more comfortable.

The subject will be lying-in a supine position and should refrain from excessive movement during the study.

Masimo W1™ and Apple Watch Series 8 will be placed, per the manufacturer's instructions, on the subject's wrist(s) along with at least one FDA-cleared RD SET Adt which may be covered with an ambient light shield. 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.

[redacted]

During the study, study devices may be captured using digital photography. These photos will not be used to intentionally capture the subject's identifying features. These digital images may be used to verify proper sensor placement. They may be used in research, product development, product testing, training, and comparison study purposes. In studies with digital photography subjects will give consent for the photography prior to the start of any study-related activities. Consenting to photography does not determine a subject's ability to qualify for the study, subjects may decline photography and still qualify to participate.

Subjects will wear a mask during the desaturation procedure. The mask may be secured to the subject's face by Tegaderm adhesive dressing (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.

The gas mixture will 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 70% oxygen saturation. Note: At any point in the study, if the subject feels uncomfortable, the subject will be given oxygen.

There may be two types of desaturations, a subject can participate in: Condition A and/or Condition B-1, B-2, B-3 in the same visit.

8.4.1.1. Condition A: Slow Desaturation

The subject may participate in a slow desaturation procedure (Condition A[redacted]

In this desaturation (Condition A) the subject will have their palms facing down. The Apple Watch Series 8 will have manual spot checks taken approximately every minute after 1 minute of each desaturation level transition and noted in Masimo data collection software.

[redacted]

See **Figure 4** below for an example of the spot checks distributed approximately 1 minute throughout the slow desaturation procedure.

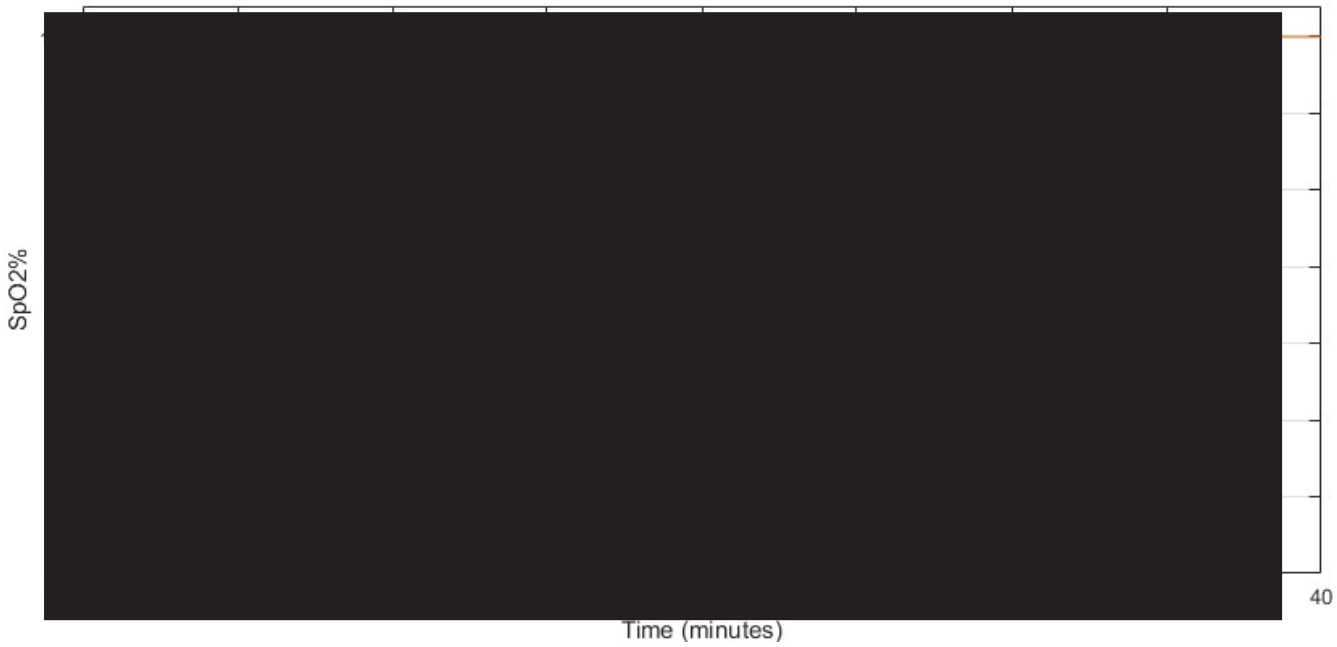

Figure 4 Example of a Desaturation sequence for Condition A Slow Desaturation

8.4.1.2. Condition B: Fast Desaturation

[redacted]

Figure 5 Example of each Desaturation sequence for Condition B Fast Desaturations

[redacted]

8.4.1.3. Ending Procedure

[redacted]

At the conclusion of the procedure, the sensor(s)/device(s) and IV(s) will be removed. The subject will be allowed to leave after medical personnel determine it is safe to do so.

All subjects will be encouraged to remain in the study area until they feel fit to leave.

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.

Subjects will be paid according to the compensation breakdown on the consent form.

8.5. Follow-Up Phase (Visit 3)

Each subject will receive a follow-up phone call from the Principal Investigator/delegate within 48-hours after completion of the data collection phase.

9. MONITORING PLAN

As the sponsor of this clinical investigation, Masimo Corporation is required by 21 CFR Part 812, of the Food and Drug Administration regulations to monitor and oversee the progress of the investigation. The monitor(s) assigned by Masimo Corporation to this task will be trained on departmental Standard Operating Procedures (SOPs) on conduct and monitoring of sponsored studies.

In accordance with good clinical practices guidelines, there will be at least three scheduled monitoring visits to ensure overall regulatory compliance of the study:

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment.
- At least one monitoring visit during initial enrollment, and/or every 2-4 weeks thereafter until completion of the study.

- A final close out visit after the last subject had finished the study.

The monitor will contact and visit the investigator and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other GCP-related documents (IRB approvals, IRB correspondences, and ICFs), provided that subject confidentiality is maintained in agreement with HIPAA regulations. The Investigator will provide the monitor access to all necessary records to ensure the integrity of the data (21 CFR 812).

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency, and accuracy of the data being entered on them.

During each visit, the monitor will also verify adherence to the inclusion/exclusion criteria, and documentation of SAEs/SADEs and protocol deviations/violations and check the CRF against source documentation.

After each visit, the monitor will provide a follow-up letter to the Investigator within four weeks of visit completion. The monitoring report will detail findings and open action items observed during the visit. It is the responsibility of the PI and study coordinator(s) to respond to the findings of the monitoring report and complete any open action items as soon as possible but no later than 60 days of receiving the follow-up letter. Any open action items not completed within the time allowed may be sufficient grounds for study site suspension or termination; it will be up to the sponsor to determine whether any incomplete action items are sufficient grounds for suspension or termination.

Depending on the quality of the data and/or changes to factors affecting subject safety, additional monitoring visits may be necessary at the sponsor's discretion.

10. STATISTICAL DESIGN AND ANALYSIS

10.1. Slow Desaturation

10.1.1. Sample Size

10.1.1.1. This study will include at least 10 Dark skin pigmentation subjects based on ISO-80601-2-61.

10.1.1.2. This study will include at least 10 Light skin pigmentation subjects based on ISO-80601-2-61.

10.1.2. Exclusion Criteria

10.1.2.1. Reference device malfunction and/or provides inconsistent SpO_2 value.

10.1.2.2. Data corruption by device failure or data communication problems.

10.1.2.3. Incomplete study or early termination, where the desaturation protocol could not be completed.

10.1.2.4. Discontinuities and abrupt dropouts due to instruments recalibration or device failure.

10.1.2.5. Low signal quality, e.g. due to noise or interference.

10.1.2.6. Subject's oxygen saturation is unstable. This is determined using multiple consecutive SpO_2 values from reference the device, to be stable within 2% SpO2 (as obtained from a reference device) to include the measurement pair.

10.1.3. Accuracy Calculations

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

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

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

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

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

10.1.4. No Read Rate for Spot Checks:

No Read Rate = (Nf / Nspotcheck) x 100 (%)

Where, Nf = Number of Spot Checks without Valid SpO_2

Nspotcheck = Number of All Spot Checks using Apple Watch

No Read Rate will be calculated for overall and for each no-motion and motion spot check subgroup.

10.2. Fast Desaturation

10.2.1. Sample Size

10.2.1.1. This study will include at least 10 Dark skin pigmentation subjects based on ISO-80601-2-61.

10.2.1.2. This study will include at least 10 Light skin pigmentation subjects based on ISO-80601-2-61.

10.2.2. Exclusion Criteria

10.2.2.1. Reference device malfunction and/or provides inconsistent SpO_2 value.

10.2.2.2. Data corruption by device failure or data communication problems.

10.2.2.3. Low signal quality, e.g. due to noise or interference.

10.2.2.4. Subject without valid fast desaturation event of 92% or lower reference SpO_2.

10.2.3. Detection Rate of Fast Desaturation Events:

Detection Rate = (Nt / Ndesat) x 100 (%)

Where, Nt = Number of Detected Event by Test Device

Ndesat = Number of All Valid Fast Desaturation Events by Reference SpO_2

Detection Rate will be calculated for overall and each desaturation sequence (Condition B-1~3)

10.2.4. No Read Rate for Spot Checks:

No Read Rate = (Nf / Nspotcheck) x 100 (%)

Where, Nf = Number of Spot Checks without Valid SpO_2

Nspotcheck = Number of All Spot Checks using Apple Watch

No Read Rate will be calculated for overall and each desaturation sequence (Condition B-1~3)

11. DATA MANAGEMENT

11.1. 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 the eCRF data capture software 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 two years following completion of the final analysis.

11.2. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, and copies or transcriptions certified after verification as being accurate and complete.

11.3. 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 PI 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. The eCRFs are to be completed on an ongoing (weekly) 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 (GDP).

The CRF may include the following information, including but not limited to: inclusion/exclusion criteria, whether subject consent was obtained before start of study, demographic information, device readings, and if occurrence of any adverse event, protocol deviation, and device deficiencies, etc. The CRFs will be signed by the PI or delegate to attest that the data are complete and accurate.

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

11.4. Data Transfer and Storage

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.

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

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, 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.

11.5. Record Retention

Study data will be retained for the necessary period of time as required by the institution's regulations. Study records shall be retained for a minimum of two years after study closure. The institution's own retention policies and regulations may apply in addition to the minimal requirement.

12. 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.

13. 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.

14. DEVICE ACCOUNTABILITY

14.1. 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.

14.2. 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.

14.3. 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.

15. 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.

16. INFORMED CONSENT PROCESS

See subsection on *Informed Consent Process* under *Study Procedures*

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

17.1. 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.

17.2. List of Anticipated Adverse Events

The noninvasive device used in this study is similar to commercially available pulse oximeters and hence has minimal 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 skin 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).

17.2.1. List of non-reportable adverse events

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

17.3. 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.

17.4. 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.

18. VULNERABLE POPULATION

18.1. 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.

18.2. Protection of Vulnerable Subjects

- Employees may participate in this study. 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.
- 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.

18.3. 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.

19. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

19.1. 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.

19.2. 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.

20. 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 this clinical investigation will be made publicly available on the ClinicalTrials.Gov website.

21. BIBLIOGRAPHY

ISO-80601-2-61:2017 Medical electrical equipment -- Particular requirements for the basic safety and essential performance of pulse oximeter equipment for medical use.

22. REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made
1.0	18MAY2023	Original version