Official Title: Clinical Validation for SpO_2 Function of Masimo INVSENSOR00069

Date of Protocol: August 23, 2023

NCT Number: NCT06120777

Clinical Investigation Title: Clinical Validation for SpO_2 Function of Masimo INVSENSOR00069

Clinical Investigation Number, Version: [redacted]

Study Device(s): Masimo INVSENSOR00069 – FDA-cleared

Sponsor: Masimo Corporation
52 Discovery
Irvine, California 92618 USA

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1. INVESTIGATOR PAGE

Principal Investigator: [redacted]
Sub-Investigator:

Investigation Site(s): Masimo Clinical Laboratory
Address: 52 Discovery
Irvine, CA 92618

IRB: Salus IRB Board #5 – IRB00013544
Address: 2111 W. Braker Lane
Suite 100
Austin, TX 78758

Agreement between Investigator and Sponsor Regarding Responsibilities for Good Clinical Practice

Sponsor and investigator agree to comply with International Conference of Harmonization (ICH) E6 Good Clinical Practice guidance. International Conference of Harmonization (ICH) E6 Good Clinical Practice guidance is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

It specifies general requirements intended to:

- Protect the rights, safety and well-being of human subjects,
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- Assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

The Principal Investigator of the clinical investigation shall:

- Obtain and maintain IRB approval of the study.
- Ensure all subjects are consented prior to enrollment, per FDA Code of Federal Regulations titled 21 CFR 50, unless the investigation is granted a waiver of consent by the IRB of record.
- 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 non-FDA cleared devices 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 (REC) 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:	Clinical validation for SpO_2 function of Masimo INVSENSOR00069
Study objective(s):	To validate the SpO_2 function of the Masimo INVSENSOR00069.
Study device(s):	Masimo devices: • Masimo INVSENSOR00069 – FDA-cleared Comparators: • Laboratory CO-oximeters/blood analyzers
Number of subjects:	Minimum of 18 subjects
Inclusion criteria:	**Influenced by study design:** • 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 ≤ 90 bpm. • Systolic blood pressure ≤ 140 mmHg and ≥ 90 mmHg and diastolic blood pressure ≤ 90 mmHg and ≥ 50 mmHg. If systolic blood pressure is lower than 100 mmHg and/or diastolic blood pressure is lower than 60 mmHg, subject passes an orthostatic blood pressure test. • CO value ≤ 3.0% FCOHb. • Subject is comfortable to read and communicate in English*. * This is to ensure the subject can provide informed consent (as study materials are currently available in English only) and can comply with study procedures.
Exclusion criteria:	**Influenced by device warning labels:** • Subjects with a skin condition affecting the digits, where the sensor is applied, which would interfere with the path of light (e.g., psoriasis, vitiligo, eczema, angioma, scar tissue, burn, fungal infection, substantial skin breakdown, etc.). • Subjects with nail polish or acrylic nails on the digits where sensor needs to be applied, who opt not to remove them. • Subject has hemoglobinopathies or synthesis disorders (e.g., thalassemia, sickle cell disease). • Subject has a peripheral vascular or vasospastic disease (e.g., Raynaud's disease). **Influenced by study design/environment:** • Subjects who do not pass the health assessment for safe participation in the study procedures. • Difficulty inserting an intravenous line in the subject's hand or arm and/or an arterial line in the radial artery of the subject's wrist.

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):	Assess the accuracy of INVSENSOR00069's peripheral oxygen saturation (SpO_2) against contemporaneous measurement from arterial blood gas (ABG) analysis.

3. DESCRIPTION OF THE STUDY DEVICE

The Masimo INVSENSOR00069 is an FDA-cleared handheld device with pulse oximetry and infrared thermometer functions, which provides SpO_2, PR, RRp®, pleth variability index (PVi®), and non-contact temperature measurements.

4. JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN PLAN

This study is designed to validate the performance of Masimo INVSENSOR00069 under a desaturation protocol, to support regulatory submission.

5. BENEFITS AND RISKS OF THE STUDY DEVICES, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

5.1. Anticipated Clinical Benefits

There will be no direct benefit to the enrolled subjects. This is a validation study on generally healthy volunteers to support regulatory submission.

5.2. Anticipated Adverse Events

The following adverse events are anticipated:

5.2.1. Risks Associated with the Study Devices

The noninvasive sensors/devices used in this study are similar in technology and design to some commercially available pulse oximeters and other non-invasive sensors/devices and hence have the same minimal risks.
Risks associated with sensors/devices include but are not limited to damage to the subject's fingers, or other locations where sensors are placed, including temporary skin irritation or discomfort associated with exposure to the sensor, temporary mechanical irritation or discomfort, sensor burn with a potential for permanent skin damage (scar/discoloration), and injury from tripping over or entanglement in sensor cables.
If there are any cuts or abrasions near the fingernail, certain types of sensors may not be placed on the particular finger to avoid any discomfort for the subject.

5.2.2. Risks Associated with Participation in the Clinical Investigation

- Risks Associated with Skin Preparation
  Risks associated with skin preparation include but are not limited to cuts, abrasions, rash, itching skin, flushing or redness of the skin, unusually warm skin, skin inflammation, and skin irritation.
  If there are any cuts 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 Skin Refrigerant (e.g., Pain Ease, Ethyl Chloride)

  Risks associated with skin refrigerant include but are not limited to changes in skin color (e.g., flushing or redness of the skin), delayed wound healing, rash, itching, and swelling.

- Risks Associated with Adhesives

  Risks associated with adhesives include but are not limited to skin irritation, redness of the skin, skin inflammation, itchiness, swelling, tingling sensation, rash, changes in skin color, and headache.

  Subjects who are allergic to adhesives will be excluded from participation in this study.

- Risks Associated with Shaving

  Risks associated with shaving include but are not limited to 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 inflamed hair follicles.

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

- Risks Associated with Lidocaine Injection

  Risks associated with lidocaine injection include discomfort, pinching sensation, warm/burning sensation, 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 tremors.

  Although not common, it is also possible to have an allergic reaction to injectable lidocaine. 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 any discomfort including hives, difficulty breathing, and swelling of the face, lips, tongue, or throat, or seizures.

- Risks Associated with Venous Blood Draw

  Risks associated with venous blood draw include discomfort, pain, bruising or hematomas, infection, tendon or tissue damage, damage to the blood vessel and surrounding nerves, inadvertent arterial puncture, and loss of feeling in the hand or arm.

  Additional risks include but are not limited to vasovagal syncope (fainting), lightheadedness, feeling flush/warm, feeling pain, feeling nauseated, throwing up, seizures, sudden drop/increase in blood pressure, sudden drop/increase in heart rate, blood loss, tingling sensation of face or extremities, sweating, and/or mouth dryness.

- Risks Associated with Venous Cannulation

  Risks associated with venous cannulation 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.

  Additional risks include but are not limited to vasovagal syncope (fainting), infiltrated IV, blood clot, lightheadedness, feeling flush/warm, feeling nauseated, throwing up, seizures, sudden drop/increase in blood

pressure, sudden drop/increase in heart rate, tingling sensation of face or extremities, sweating, mouth dryness, and injury from tripping over or entanglement in lines.

- Risks Associated with Arterial Cannulation

  Risks associated with arterial cannulation include discomfort, pain, bleeding, decreased blood supply, swelling, infection, bruising, hematoma, and damage to the blood vessel and surrounding nerves, tendons, or tissue.

  Additional risks include but are not limited to pain, vasovagal syncope (fainting), lightheadedness, feeling flush/warm, embolization (blood clot), feeling nauseated, throwing up, seizures, sudden drop/increase in blood pressure, sudden drop/increase in heart rate, irregular heart rate (e.g., premature atrial contraction (PAC), premature ventricular contraction (PVC), ECG abnormalities), tingling sensation of face or extremities, sweating, mouth dryness, arterial occlusion, arterial laceration, loss of feeling in the hand and/or arm, loss of the hand and/or arm due to rare complications of arterial cannulation, and injury from tripping over or entanglement in lines.

- Risks Associated with a Mask, Nasal Cannula, or Mouthpiece

  Risks associated with a mask, nasal cannula, or mouthpiece include but are not limited to irritation, redness, congestion, pressure, indentations on the skin, feelings of claustrophobia or anxiousness, and injury from tripping over or entanglement in lines or tubing.

- Risks Associated with Low Oxygen Concentration (Desaturation)

  Risks associated with low oxygen concentration include lightheadedness, dizziness, shortness of breath, drowsiness, or headache. If these symptoms occur, 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 would 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.

  Additional risks include but are not limited to vasovagal syncope (fainting), chest discomfort (e.g. chest tightness, chest pain), feeling flush/warm, feeling of anxiety, feeling nauseated, throwing up, seizures, sudden drop/increase in blood pressure, sudden drop/increase in heart rate, irregular heart rate (e.g., premature atrial contraction (PAC), premature ventricular contraction (PVC), ECG abnormalities), tingling sensation of face or extremities, sweating, mouth dryness, feeling claustrophobic or anxiousness from wearing a mask/mouthpiece.

- Risks Associated with Oxygen Administration

  Risks associated with oxygen administration include but are not limited to dryness, cough, congestion, throat or chest irritation, mucosal irritation, or nose bleeds.

  Risks associated with high flow/pressure oxygen administration of 2 one atmosphere absolute (ATA) include but are not limited to moderate carinal irritation on deep inspiration after 3-6 hours of exposure, extreme carinal irritation with uncontrolled coughing after 10 hours, and chest pain and dyspnea after more than 10 hours. Subjects will not be exposed to high flow/pressure oxygen for more than 1 hour.

- Risks Associated with Carbon Dioxide Administration

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

  Additional risks include but are not limited to dryness, cough, congestion, throat or chest irritation, mucosal irritation, nose bleeds, tingling, prickling sensations ("pins and needles" feeling), restlessness, sudden drop/increase in blood pressure, sudden drop/increase in heart rate, irregular heart rate (e.g., premature atrial contraction (PAC), premature ventricular contraction (PVC), ECG abnormalities), sweating.

[redacted]

- Risks Associated with Accidental Exposure to Bloodborne Pathogens

  While care is taken to ensure that blood samples are handled safely, and though unlikely, there is a possibility that study personnel could become exposed to bloodborne pathogens through accidental or occupational exposure to blood samples from subjects who carry bloodborne pathogens, such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), or Human Immunodeficiency Virus (HIV). In such circumstances, study participants could also be at risk and past study participants will be contacted regarding additional testing to be done at an outside facility (e.g., outside laboratory, urgent care clinic, etc.). Subjects will only be compensated for the cost of exposure determination testing and their time/travel accommodation to the testing facility.

5.2.2.1. Risks from Inflicted Knowledge

In the case that a subject becomes aware of a condition (arrhythmia, etc.) during the study, our study staff will recommend that they contact their primary care physician, and we will document this recommendation.

5.3. Rationale for Benefit-Risk Ratio

To minimize risks specified above, study staff will use subjects' answers to a health questionnaire to determine study eligibility and safe participate in the study. Subjects will be encouraged to let study staff know if they have any concerns. If subjects experience risks (including but not limited to the risks specified above), study staff will determine if the subject can safely continue participation in the study. ‡ While most of the anticipated risks specified in these sections are anticipated to be temporary, all adverse events will be recorded and followed up as appropriate (see Section 15).

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

‡ Note: Though extremely unlikely, complications from the study may result in death. The study would most likely be stopped by the subject or study staff long before this would occur.

6. OBJECTIVES OF THE CLINICAL INVESTIGATION

The objective of this study is to validate the SpO_2 function of the Masimo INVSENSOR00069. The study endpoint is as follows:

Assess the accuracy of INVSENSOR00069's peripheral oxygen saturation (SpO_2) against contemporaneous measurement from arterial blood gas (ABG) analysis.

7. DESIGN OF THE CLINICAL INVESTIGATION

7.1. General

This is a prospective validation study of Masimo INVSENSOR00069 in a diverse (sex, race, skin pigmentation) population, under a desaturation protocol (across a range of 70-100%) and no motion conditions (see *Appendix II*). Subjects will be pre-screened for skin pigmentation using various skin typing tools as detailed below. Peripheral oxygen saturation obtained via SpO_2 sensor values will be compared to simultaneous oxygen saturation via arterial blood gas analysis (SaO_2).

7.2. Investigation Site(s)

This is a single center study to be completed at Masimo Clinical Laboratory located at 52 Discovery, Irvine, CA, 92618.

Masimo Clinical Laboratory facility is a Phase 1 clinical study research center 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, arterial line pressure transducer, pulse oximeters, standard hematology analyzers, medical-grade oxygen tank, mask, and nasal canula, and has emergency crash carts available. Hospitals and urgent care facilities are within three miles of the Masimo Clinical Laboratory, in case of an emergency.

7.3. Definition of Completion of the Clinical Investigation

The study will be considered complete when quality data from approximately 18 subjects have been collected and evaluated.

7.4. Safety Equipment (FDA-Cleared)

- Blood pressure monitoring system
- A-line pressure transducer
- Electrocardiogram (ECG)
- Masimo Patient Monitoring Platform (Root® or comparable)
- Masimo Pulse Oximeters (Radical-7®, Rad-97, or comparable)
- Pulse Oximeter Sensors and Cables (Masimo SET, Masimo rainbow, or comparable)
- Medical-grade oxygen tank, mask, and nasal cannula
- Crash cart

7.5. Study Device(s)

Masimo devices:

- Masimo INVSENSOR00069 – FDA-cleared

Comparators:

- Laboratory CO-oximeters/blood analyzers

Research Equipment:

- Data collection research equipment [redacted]

7.6. Subjects

7.6.1. Inclusion Criteria

Refer to section 2.

7.6.2. Exclusion Criteria

Refer to section 2.

7.6.3. Number of Subjects

Minimum of 18 subjects.

7.6.4. Subject Classifications

Subjects will be classified according to the criteria below:

- **Screened** – Subjects who are assessed for study eligibility.
- **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 opts not to participate.
  - Subject was discontinued from study at the discretion of the clinical team.
- **Completed** – Subjects with a completed.

7.6.4.1. Withdrawal of Subjects

In addition to conditions noted above, subjects may be withdrawn under the following circumstances:
To ensure the subject's safety, the subject may be withdrawn from the study and not used as a participant in future studies of the same nature if the investigator(s) or the clinical team notice a concerning physiological trend. Examples include but are not limited to the following:

- Blood pressure fluctuations outside the normal range.
- Heart rate fluctuations outside of the normal range.
- Intolerance of desaturation protocol.
- Inability to remain still for the majority of a no motion study.

7.6.4.2. Replacement of Subjects

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

7.6.4.3. Recontacting Subjects

If the subject fails to properly document fields in their individual consent and/or other study related documents for any study, Masimo reserves the right to recontact the subject and ask them to return to Masimo Clinical Laboratory to properly complete the consent form or the subject bill of rights. The subject will be compensated for travel. The subject will be recontacted via phone or email and asked to return as soon as possible.

7.6.5. Study Duration

Expected duration of study enrollment is 1 to 3 months. Subject participation in the study will be approximately 180 minutes.

7.7. Procedures

7.7.1. Subject Recruitment and Pre-screening

7.7.1.1. Advertisement and Recruitment

Healthy volunteers will be recruited for desaturation studies at Masimo Clinical Laboratory through advertisements [redacted]

7.7.1.2. Pre-screening

Pre-screening for subject eligibility may be completed by clinical research staff via phone, virtually, or in person once a potential subject contacts Masimo to learn more about the study. Information from the pre-screening will be stored in a firewall protected Masimo internal network with user level access control enforced. Additionally, the database is encrypted, and password protected. The information may be used to contact subjects for other studies they may be eligible to participate in, and/or to track discrepancies in a subject's responses for the sake of study qualification.

7.7.2. Informed Consent, Health Assessment and Eligibility Determination

Following the identification of a potential eligible subject, the subject will be asked to provide a valid government photo ID to verify the subject's identity.

Monetary compensation to subjects will be reported to the Internal Revenue Services (IRS), as required by the law. As such, U.S. citizens and permanent residents may be asked to provide their social security number (SSN) and card and to complete a W-9 form to report earnings to IRS. Foreign persons (or nonresident aliens) may be asked to provide their taxpayer identification number (TIN) and card or equivalent and to complete a W-8BEN form to report earnings to IRS. Copies of these identification documents and forms may be stored electronically. The confidentiality and retention of these documents will be to the extent required by law.

7.7.2.1. Informed Consent

Subjects will be informed about the purpose of the study and given an overview of the study procedures. Study staff will explain the potential risks and benefits and discuss the subject's rights and privacy information. Subjects will be provided with ample time to review the consent form and ask questions. Study-related activities can only commence

once the subject's questions have been answered and the consent documents have been signed and dated. A copy of the signed consent document will be retained (either the physical copy or an electronic copy).

Additionally, subjects will be asked if they consent to photography, videography (which may include sound) recordings and/or an observational group. Recordings will be obtained only if subjects provide consent.

7.7.2.2. Health Assessment and Eligibility Determination

After informed consent, a clinician will conduct a health assessment to determine eligibility for study enrollment and safe participation in the study. Subjects must meet all inclusion criteria and none of the exclusion criteria to participate in the study. All subjects screened will be documented on the *Screening and Enrollment Log*. Subjects who do not meet the eligibility criteria will be considered screen failures and the reason for the status of screen failure will be documented on the *Screening and Enrollment Log*.

Information on subject demographics (including but not limited to sex, race and ethnicity, age, height, weight, and BMI), skin pigmentation, finger dimensions, and a medical history may be collected.

[redacted]

- Pregnancy Screening: Female subjects will be required to take a pregnancy test. Subjects will be notified of their pregnancy result and the result will be noted. Subjects will be excluded from the study if the result is positive.
- Vital Signs Screening: Vital signs such as blood pressure, heart rate, and pulse oximetry measurements such as SpO_2, SpCO, and SpHb may be checked and recorded for subject safety monitoring.

An orthostatic blood pressure will be required **ONLY** in subjects who meet the following criteria:

- Initial systolic blood pressure < 100 mmHg and ≥ 90 mmHg, and/or

[redacted]

- Initial diastolic blood pressure < 60 mmHg and ≥ 50 mmHg.

Table 2 below details the systolic and diastolic measurements that require performing an orthostatic blood pressure measurement. **If the criteria are not me 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 mmHg to meet inclusion criteria for the study.

Transient increases in blood pressure and heart rate can be expected during line placement, needle sticks, blood draw, 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.

- Venous and Arterial Access Screening:

An intravenous line needs to be placed in the subject's hand or arm, and an arterial line in the radial artery of the subject's wrist. The purpose of the intravenous line is to: (1) obtain venous blood samples for analysis (e.g., to verify subject meets inclusion criteria) and (2) intravenous fluid administration as needed. The purpose of arterial line is to: (1) obtain arterial blood samples for SpO_2-SaO_2 paired measurements and (2) blood pressure monitoring.

Prior to intravenous line placement, the intended site will be observed by the clinical staff to ensure there is no bruising (e.g., from any previous intravenous line placements); if there is bruising another location for line placement will be attempted.

Subjects will be given the option to have local anesthetics (such as lidocaine, ethyl chloride spray, and Pain Ease skin refrigerant spray) used at line placement sites to make line placement more comfortable.

Noninvasive ultrasound devices may be used to assist in line placement [redacted]

The subject will be excluded from the study if the clinical team is unable to insert an intravenous line in the subject's hand or arm and/or unable to insert an arterial line in the radial artery of the subject's wrist.

- Blood Parameters Screening:

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.

7.7.3. Study Procedures

7.7.3.1. General Preparation

Once the subject's eligibility has been determined, the subject is enrolled in the study. Subject may be offered a snack (e.g., granola bar) and/or beverage (e.g., water, juice), which they can refuse. Subject may have a blanket placed on them and/or hot water bottles placed under their hands (per request of subject or staff).

Subject may be asked to clean (with skin preparation materials such as an alcohol pad) or shave the area of application of study-related devices to allow a more secured placement of sensor and/or mask to skin. Adhesives may also be used to secure sensors, masks, arterial and/or venous lines, or other study equipment.

During data collection, the subject will be seated and/or lying in supine position and will be instructed to refrain from excessive movement during the study [redacted] Standard noninvasive monitors will be placed on the subject when preparing for the study procedures and used for subject monitoring during study procedures. A minimum of one FDA-cleared pulse oximeter sensor will be placed on the subject for the subjects' safety. Other monitors may include FDA-cleared ECG and blood pressure cuff(s). Blood pressure may be obtained from arm cuffs, leg cuffs, finger cuffs, or equivalent devices. Blood pressure may be taken/recorded manually or automatically depending on the device used. For data collection purposes blood pressure measurements may be obtained in various ways. [redacted]

Oxygen tank pressure will be checked and may be noted before the gas delivery procedures begin for subject safety purposes. For subject's safety, various vital sign parameters (including but not limited to end-tidal and/or partial pressure of carbon dioxide and respiration rate) will be monitored throughout the gas delivery procedures; these may be noted at the beginning and end of the procedures. Other vital sign parameters (including but not limited to blood pressure and/or temperature) may be monitored and recorded throughout the study for subject safety or data collection purposes [redacted]

Blood samples will be labeled with a numerical sample ID. Unlike diagnostic lab samples, these labels do not have personal identifying information such as name or birthdate. After testing, blood samples will be discarded in the appropriate biohazard waste bins.

7.7.3.2. Sensor Placement and Sensor Data Collection

Masimo INVSENSOR00069 will be placed on at least one finger. Raw device data from the study devices/sensors may be collected and stored using data collection software. Outputs from other devices may also be recorded (e.g., SpO_2, PVi, Pi, pulse rate, temperature, blood pressure, ECG and capnography).

7.7.3.3. Blood Sampling Procedures

A qualified person will complete blood draws. These blood draws may occur at various points during the length of the study and may include qualifying blood samples, baseline blood samples before study procedures begin, and blood

samples after study procedures are complete to ensure the subject's wellbeing.

A set of blood samples of approximately 2 mL each will be drawn at selected time intervals throughout the study for laboratory analysis. The blood sample will be collected in vacutainer tubes or syringes for analysis by standard laboratory methods which may include co-oximetry and analysis by other point of care devices.

The total amount of blood drawn during study participation will not exceed 400 mL (which is less than the standard amount in a blood donation).

[redacted]

7.7.3.5. Desaturation Procedures

Upon indication that the subject is comfortable, a gas mixture will be administered through the mask/mouthpiece. The gas mixture may include varying proportions of oxygen, carbon dioxide, and nitrogen. The proportion of oxygen in this mixture will be decreased in a controlled manner to lower the subject's blood oxygen saturation. The lowest targeted value will be 70% oxygen saturation. Readings near 70% will be immediately verified by a pulse oximeter or by blood gas analyzer to ensure that levels are within the targeted oxygen saturation range and to minimize time that the subject may drop below the targeted range.

[redacted]

Study personnel will record their observations. [redacted] The study will end with a FiO_2 greater than or equal to room air (21%) to help the subject re-saturate after the procedure.

[redacted]

7.7.3.6. Ending Procedures

At the conclusion of the procedures, the sensors/devices, intravenous and arterial lines and monitoring equipment will be removed from the subject. A set of predischarge vitals, such as heart rate and blood pressure, may be obtained and recorded on the case report form to ensure subject's wellbeing. Study staff may take final blood draws of approximately 2 mL, 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.).

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 may be 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 will be encouraged to remain in the study area until they feel fit to leave and may be asked to wait in the clinical lab or lobby waiting area for approximately 20 minutes.

The subject will be allowed to leave after medical personnel determine it is safe to do so. 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. The total overall study time is approximately 180 minutes. If the total procedure time exceeds 180 minutes, subjects will be compensated for the extra time.

7.8. Monitoring Plan

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

8. STATISTICAL DESIGN AND ANALYSIS

This is a validation study for the SpO_2 function of the Masimo INVSENSOR00069. The study targets one objective, to assess the accuracy of INVSENSOR00069's peripheral oxygen saturation (SpO_2) against contemporaneous measurement from arterial blood gas (ABG) analysis. A total of 18 subjects are needed to meet study objectives.

8.1. Sample size

To allow for assessment of SpO_2 function of INVSENSOR00069 across the two biological sexes of male and female and three skin pigmentation groups of light, medium, and dark, a total of six demographic subgroups will be studied.

8.1.1. Assumptions

- Independent observations (SpO_2-SaO_2) and the six subgroups are also independent of one another.
- Effect size of 1%, based on pulse oximetry reading resolution.
- 5% significance level and 80% power.

8.1.2. Sample size

[redacted] This study will target a minimum of 18 subjects but may be modified based on actual numbers required to maintain adequate power for the study. Depending

[redacted]

on dropout rates, additional subjects may be enrolled to obtain sufficient representative data for factors such as sex, skin pigmentation, oxygen saturation, and other factors as required.

The final A_{RMS} analysis will utilize statistical methods to ensure performance statistics are calculated with comparable density over the range 70-100% SaO_2 and account for multiple samples per subject. Statistical analysis for each subgroup will be performed to show differences in biases among different subgroups.

8.2. Data Analysis

8.2.1. Accuracy Calculations

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

$$Bias = \frac{1}{n}\sum_{i=1}^{n}(SpO_{2i} - SaO_{2i})$$

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

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

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

8.2.2. Acceptance Criteria

- SpO_2: $A_{RMS} \leq 2\%$ over the range 70-100%, under no motion.

8.2.3. Exclusion Criteria

The following data exclusion criteria will be applied before statistical analysis.

Data will be excluded in the event:

- Either reference or test device does not provide data.
- Incomplete study or early termination, where the desaturation protocol could not be completed.
- Reference device malfunctions and/or provides inconsistent saturation values.
- Discontinuities and abrupt dropouts due to instruments recalibration or device failure.
- Low signal quality, e.g., due to noise or interference. Specifically, the INOP Indicators with <SpO_2 Labels> : Chk Sensor, Extd, Update, Interference, Low Perf, and Poor Signal will be used for data exclusion.
- Subject's oxygen saturation is unstable. This is determined using multiple (up to 5) consecutive blood draws, to be stable within 1% to 2% SaO_2 of neighboring draws (as obtained from a reference device) to include the measurement pair.
- Exclusion of subjects that do not have desaturation points in the lowest saturation bin (70-80%).
- Exclusion of data to statistically equalize samples per subject, and across the 70-100% saturation bins.

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

9. DATA MANAGEMENT

9.1. 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.

9.2. 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.

9.3. 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, demographic information, device readings, occurrence of any adverse events and protocol deviation, and device deficiencies, if any. 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.

9.4. 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.

9.5. Record Retention

Study data will be retained for the necessary period of time as required by regulations. Study records shall be retained for a minimum of two years after study closure.

10. 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 PI 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.

11. 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 five working days of the IRB notification of withdrawal of approval.

12. DEVICE ACCOUNTABILITY

12.1. Receipt of Study Device

Upon receipt of the study device supplies, an inventory must be performed and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that

the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

12.2. Use of Study Device

Use of device will be documented in a CRF module for each subject. Any unused devices must be returned to the sponsor at the end of the study or before product expiration date.

12.3. Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices shipped, devices used, and devices remaining. This reconciliation will be logged on the device accountability log. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed onsite 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.

13. 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 IRB or Research Ethics Committee approval, federal and local regulatory requirements, 21 CFR 812, ISO-14155, ICH GCP guidance.

The protocol, ICFs, recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

14. INFORMED CONSENT PROCESS

See subsection on Informed Consent under *Study Procedures*.

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

15.1. Definitions

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

- adverse event: untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated (ISO 14155)
- adverse device effect: adverse event related to the use of an investigational medical device
- serious adverse event: adverse event that led to any of the following:
    - a) death

- b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function including chronic diseases, or
  - 3) in-subject 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 of 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 labeling.

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

15.2. List of Anticipated Adverse Events

15.2.1. Anticipated Device-Related Adverse Events

The investigational device used in this study is similar to commercially available wearables and is considered to have minimal risk.

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

15.2.2. List of Non-Reportable Adverse Events

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

15.3. Adverse Event Reporting

- All adverse events, both anticipated and unanticipated, must be recorded in the within the CRF and in the *Adverse Event Report Form.*
- All adverse events must be promptly reported to the sponsor.
- All unanticipated adverse device effects will be also reported to both the sponsor and the IRB.
- Both serious adverse events and unanticipated adverse device effects must be reported to the sponsor within 48 hours. All other adverse events should be reported to the sponsor within five 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, subject hospitalization, severe or permanent disability or were life threatening, their relationship to the study device, and resolution.

15.4. 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.

16. VULNERABLE POPULATION

16.1. Definition

Vulnerable population are research subjects, such as children, prisoners, pregnant women, handicapped, or mentally disable persons, or economically or educationally disadvantaged persons, who are likely to be vulnerable to coercion and undue influence. This study is not targeting these populations.

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

16.2. Protection of Vulnerable Subjects

- Not applicable as study follows standard of care procedures.

16.3. Responsible Parties

- The IRB will review research with vulnerable populations and evaluate consent, level of risk, coercion, and the reason for choosing this particular subject population. The 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 are handled in a compliant and timely manner.

17. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

17.1. 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 the sponsor moves to suspend or terminate the study site, the sponsor will provide notification in writing to the PI and IRB as necessary. The study site is eligible for reinstatement upon correction of any findings and any open action items prior to the suspension, and provides a written guarantee that the same non-compliance will not reoccur in the future. Site can only resume subject enrollment upon receiving written notification of reinstatement from the sponsor.

If for any GCP and Regulatory non-compliance reasons the study site is prematurely terminated by the sponsor, then the study site is not eligible for reinstatement under the same *Clinical Investigational Plan/Study Protocol*.

17.2. Termination of Clinical Investigation/Study due to UADE

The clinical investigation may be terminated if the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the subjects. Termination shall occur no later than five 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.

18. 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.

19. BIBLIOGRAPHY

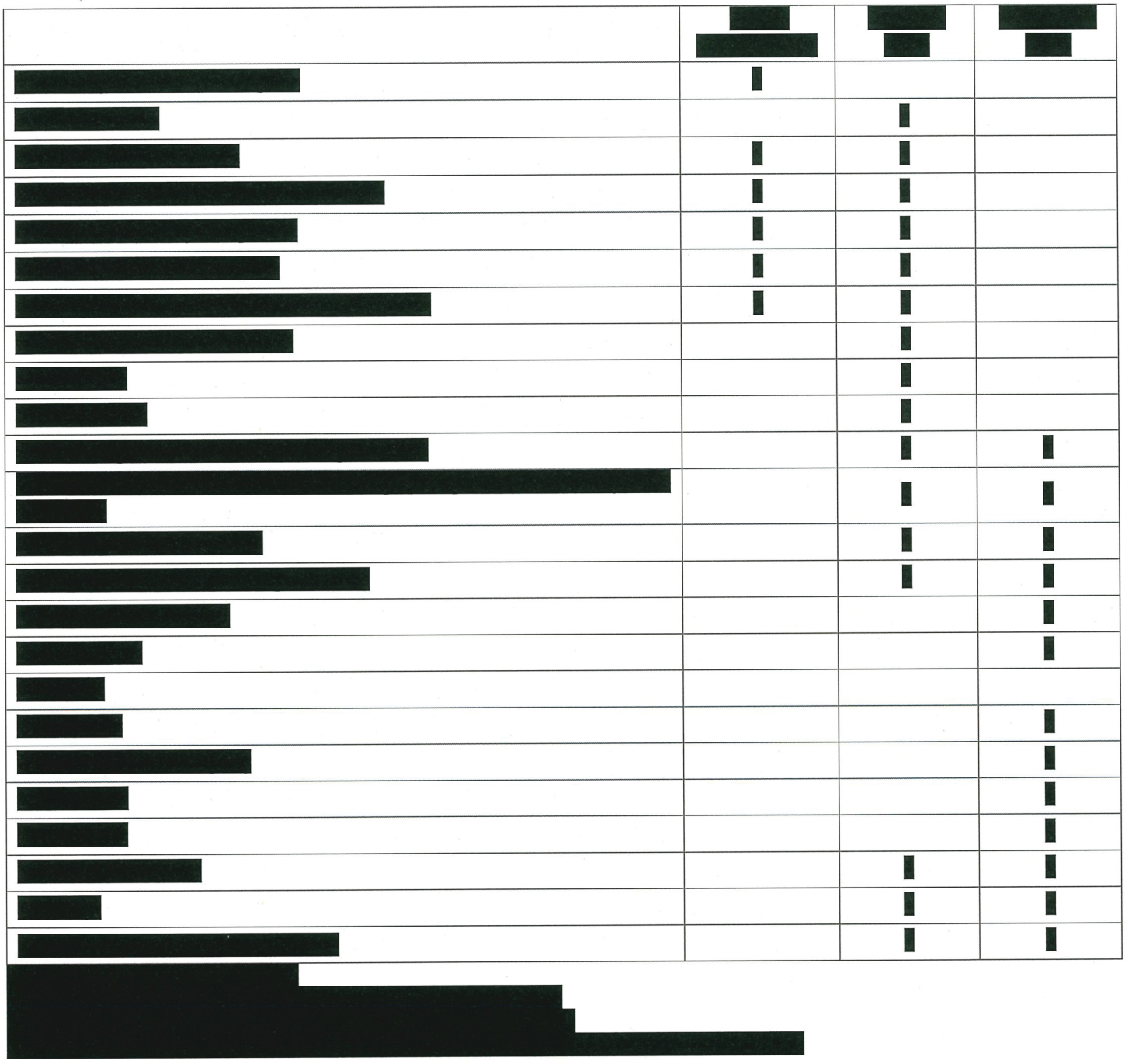
[redacted]

20. REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made
[redacted]	[redacted]	[redacted]

21. APPENDICES

21.1. Appendix II: Schedule of Events for Desaturation Study



21.2. Appendix III: Skin Pigmentation Screening Tools

[redacted]