Official Title: Validation Study of Mean Arterial Pressure (MAP) Parameter of Masimo INVSENSOR00073

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Clinical Investigation Title:	Validation Study of Mean Arterial Pressure (MAP) Parameter of Masimo INVSENSOR00073
Clinical Investigation Number, Version:	CIP-1091 [redacted]
Other Study Identifier:	N/A
Study Device(s):	Masimo INVSENSOR00073
Sponsor:	Masimo Corporation 52 Discovery Irvine, California 92618 USA

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1. INVESTIGATOR PAGE

Principal Investigator: [redacted]
Sub-Investigator(s): [redacted]

Investigation Site(s): Clinical Laboratory at Masimo Corporation
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 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 (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:	Validation Study of Mean Arterial Pressure (MAP) Parameter of Masimo INVSENSOR00073
Study objective(s):	The objective of this study is to validate the Mean Arterial Pressure (MAP) parameter of Masimo INVSENSOR00073 against the gold standard blood pressure measurements from the arterial line.
Study device under test:	Masimo INVSENSOR00073
Number of participants:	Approximately 20.
Inclusion criteria:	**Influenced by study design:** • Subject is 18 to 40 years of age. • Subject weighs a minimum of 110 lbs. • Baseline heart rate ≥ 45 bpm and ≤ 90 bpm. • Baseline blood pressure: Systolic blood pressure ≤ 135 mmHg and ≥ 100 mmHg. Diastolic blood pressure ≤ 95 mmHg and ≥ 55 mmHg. Valid systolic blood pressure (SBP) auscultatory measurements for lateral difference is ≤ 15 mmHg. Valid diastolic blood pressure (DBP) auscultatory measurements for lateral difference is ≤ 10 mmHg. • Hemoglobin value ≥ 11 g/dL. • 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:** • Subject is pregnant or breastfeeding. • Subject is experiencing dysrhythmia or arrhythmia. **Influenced by study design/environment:** • Subject is concurrently participating in another research study. • Subjects not suitable for the investigation at the discretion of the clinical team including but not limited to the items below. o Subjects who do not pass the health assessment for safe participation in the study procedures. o Inability to insert or difficulty with 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.
Groups:	A targeted enrollment approach will be used to ensure ISO 81060-2-2018[1] requirements (specified under section 7.5.3) pertaining to sex, cuff size, and blood pressures distributions are met.

Duration of the clinical investigation:	The expected duration of study enrollment is 1 to 3 months. Subject participation in the study will be approximately 180 minutes.
Study endpoint(s):	Accuracy and precision of mean arterial pressure (MAP) measured by Masimo INVSENSOR00073, in adult or adolescent patients, in comparison to radial arterial line.

3. DESCRIPTION OF THE INVESTIGATIONAL DEVICE

[redacted] is a continuous, scalable, patient-worn, vital signs monitor [redacted], which provides the versatility of a bedside monitor in a wearable device.

[redacted] monitors a wide range of physiological parameters. Designed to scale up or down with patient acuity, [redacted] combines the reliability and accuracy of a bedside monitor with the comfort and freedom of a wearable device, allowing for ambulation and movement during continuous monitoring. Suitable for use across the continuum of care, [redacted] offers advanced flexibility and is easily scalable to accommodate surges in patient volume and each patient's level of acuity.

The focus of this study is on the validation of the mean arterial pressure (MAP) parameter of Masimo INVSENSOR00073. Masimo INVSENSOR00073 provides systolic, diastolic, and mean arterial blood pressure readings through an oscillometric method. An oscillometric method of blood pressure measurement is a noninvasive method that monitors the amplitude of cuff pressure changes during cuff deflation to determine arterial blood pressure. Masimo INVSENSOR00073 consists of a reusable module and a disposable cuff, which plug into the [redacted] device, or a laptop for data collection purposes.

For blood pressure measurements, the cuff is wrapped around the non-dominant arm, making sure that the cuff's Artery Marker is aligned over the brachial artery. To locate the brachial artery, one should place the pads of his/her index and middle fingers halfway between the shoulder and elbow, in the middle of the inner arm, between the biceps and triceps muscles. The cuff should fit comfortably around the patient's arm for maximum oscillometric signal quality. The lower edge of the cuff should be located 2 cm above the antecubital fossa (interior bend of the elbow).

4. JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN PLAN

While arterial lines are the gold standard for blood pressure measurement, they are typically limited to high patient acuity situations due to their invasive nature and associated medical complications including hematoma, arterial thrombosis, and infection[2, 3]. Oscillometric non-invasive blood pressure measurement is the preferred choice in the majority of low and moderate patient acuity situations.

This is a clinical validation study of the mean arterial pressure parameter of Masimo INVSENSOR00073 against blood pressure measurements from invasive radial arterial line based on guidelines set forth in *ISO 81060-2, Non-invasive sphygmomanometers- Part 2: Clinical investigation of intermittent automated measurement type*.

Per *ISO 81060-2,* performance of Masimo INVSENSOR00073 needs to be investigated across a pre-specified distribution of blood pressures (detailed in section 8 below). Accordingly, in this study participants will undergo a blood pressure variation procedure using pharmaceuticals. Participants will be healthy volunteers, who will complete a clinical screening prior to being enrolled in the study to ensure subject eligibility as well as to reduce the occurrence of any potential harm that may arise because of study participation. Participants will be administered continuous infusions containing vasoactive medications and may participate in induced controlled hypertension (increased blood pressure) and/or induced controlled hypotension studies (decreased blood pressure). Consistent with other studies of blood

pressure[4-8], increasing and lowering of blood pressure will be achieved using [redacted] and [redacted] respectively[4-8].

While a blood pressure variation procedure is not free of risks, risks have been mitigated. Potential hazards associated with use of [redacted] and [redacted] include overdose and overreaction to the drug. There is also a possibility of cyanide poisoning, though highly unlikely. Accordingly, subjects will start at [redacted] $\frac{\mu g/kg}{min}$ of [redacted] and [redacted]. An increase of dose will only occur if the subject is asymptomatic. Safety drugs as outlined in Table 2 (see section 7) will also be used should it be deemed necessary by the presiding clinician. The infusion will be stopped through safety clamp or stopcock immediately, should continuation with the procedure be deemed unsafe for the participant.

Similarly, an invasive A-line placement for blood pressure measurements is not free of risks; accordingly, to mitigate risks, participants are monitored by study staff (including an Advanced Cardiovascular Life Support (ACLS)-certified physician) for the duration of blood pressure variation procedure, provided with post care instructions discharge, and can reach Masimo in the case of any complications after discharge.

Once the blood pressure variation procedure has been completed, the subject will be monitored until their pressure is within 10 mmHg of their baseline and they have been asymptomatic for approximately 30 minutes.

Other requirements of *ISO 81060-2* pertain to sex and cuff size distributions (detailed in section 8 below). Accordingly, a targeted enrollment approach will be used to select participants across the spectrum needed for the validation study.

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

5.1. Anticipated Clinical Benefits

There will be no direct benefit to the enrolled subjects. Benefit would be to the society at large, through paving the path for development and availability of a tetherless blood pressure monitor, which would provide reliable and accurate monitoring with the comfort and freedom of a wearable device.

5.2. Anticipated Adverse Events

The following adverse events are anticipated:

5.2.1. Risks Associated with the Study Devices

The noninvasive devices used in this study are similar in technology and design to commercially available FDA-cleared devices and hence pose minimal risk to subjects. A *Clinical Investigation Risk Assessment* has been conducted and documented where relevant biological, chemical, electrical, and mechanical hazards associated with Masimo INVSENSOR00073 were identified and mitigated as used in this clinical investigation. Refer to the *Investigator Brochure (IB)* and/or *Operator's Manual* for full description of warnings and cautions and instructions.

There is a risk of temporary discomfort to subjects at the blood pressure cuff placement location, including temporary skin irritation, redness, and itching. In the absence of intact skin (e.g., cuts or abrasions) at or near the application site, the subject will be disqualified from the study to avoid potential discomfort.

Device warning labels are as follows:

- Frequently check the blood pressure monitoring site to ensure adequate circulation to prevent patient injury.

- Do not apply the cuff to a limb that is on the same side of a mastectomy.
- Do not use or stop blood pressure measurements if the patient appears to be affected by the pressurization of the cuff due to a physical condition (e.g., pregnant, pre-eclamptic).
- Avoid too frequent blood pressure measurements to prevent injury to the patient due to blood flow interference.
- Do not attach the cuff to a limb being used for IV infusions or any other intravascular access, therapy or an arterio-venous (A-V) shunt. The cuff inflation can temporarily block blood flow, potentially causing harm to the patient.
- Before applying the cuff on the patient, confirm the cuff size is appropriate.
- When a blood pressure measurement error code occurs, any blood pressure values reported should be disregarded.
- Do not apply the blood pressure cuff over a wound to avoid further injury.
- A compressed or kinked connection hose may cause continuous cuff pressure resulting in blood flow interference and potentially harmful injury to the patient.

5.2.2. Risks Associated with Participation in the Clinical Investigation

A *Clinical Investigation Risk Assessment* has been conducted and documented for risks associated with blood pressure variation using pharmaceuticals, invasive arterial blood gas measurement and other study related procedures.

In order to further minimize risks specified below, study staff will use subjects' answers to a health questionnaire to inform study eligibility and determine if subjects can safely 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.

- 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. Each of these discomforts and side effects are temporary and should improve over time.

  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 [redacted]

  Risks associated with [redacted] include but are not limited to mild upset stomach, trouble sleeping, dizziness, lightheadedness, flushing, tingling, headache, nausea, nervousness, shaking, fast heartbeat, and hypertension.

  Subjects will be monitored closely for onset of symptoms while inducing controlled hypertension using vasoactive medications. These typically resolve quickly when blood pressure returns to baseline once infusion has stopped. The safety drug to reverse the effects of [redacted] is [redacted] and it will be administered at the discretion of a trained clinician.

- Risks Associated with [redacted]

  Risks associated with [redacted] include but are not limited to chest pain or discomfort, fast or irregular heartbeat or pulse, flushing, tingling, lightheadedness, dizziness, fainting, slow heartbeat, bluish-colored lips, blurred vision, confusion, dark urine, fever, headache, sweating, hypotension, and cyanide poisoning.

  Subjects will be monitored closely for onset of symptoms while inducing controlled hypotension using vasoactive medications. These typically resolve quickly when blood pressure returns to baseline once infusion has stopped. Sodium thiosulfate and sodium nitrite will be present to counter potential cyanide poisoning from [redacted]. The safety drug to reverse the effects of [redacted] is [redacted] and it will be administered at the discretion of a trained clinician.

- Risks Associated with [redacted]

  [redacted] is included for situations calling for inotropic support in addition to the vasoconstrictor. [redacted] is used in this protocol as a safety drug for [redacted].

  Risks include but are not limited to tachycardia, hypertension, headache, anxiety, apprehension, palpitations, diaphoresis, nausea, vomiting, weakness, and tremors. These typically resolve quickly when blood pressure returns to baseline once infusion has stopped.

- 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.

- 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.

- Risks from Loss of Confidentiality

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

5.3. Rationale for Benefit-Risk Ratio

The benefit-risk ratio for the study of the Masimo INVSENSOR00073 was found to be acceptable. Provided a successful validation of the Masimo INVSENSOR00073, there is a potential benefit to help clinician workflows and patient care in providing an accurate blood pressure device to measure MAP in comfortable wearable form factor (see *Section 5.1*).

This benefit was weighed against the acceptable risks associated with Masimo INVSENSOR00073 and study procedures which were addressed through a risk management process consistent with *ISO 14971*. The results supported the benefit-risk ratio of the study is acceptable.

6. OBJECTIVES OF THE CLINICAL INVESTIGATION

The objective of this study is to validate the performance of Masimo INVSENSOR00073.

7. DESIGN OF THE CLINICAL INVESTIGATION

7.1. General

This is a single-center prospective validation of Masimo INVSENSOR00073. A study workflow is included as an appendix (see *Appendix I*).

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 [redacted] clinical study research center staffed by [redacted]. 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 the number of pre-defined subjects and quality data points are achieved (per information discussed below, under section 8.1).

7.4. Study Device(s)

Masimo devices:

- Masimo INVSENSOR00073

[redacted]

Comparators:

- Blood pressure measurements from invasive radial arterial line (A-line)

Research Equipment:

[redacted]

7.5. Subjects

7.5.1. Inclusion Criteria

Influenced by study design:

- Subject is 18 to 40 years of age.
- Subject weighs a minimum of 110 lbs.
- Baseline heart rate ≥ 45 bpm and ≤ 90 bpm.
- Baseline blood pressure:
  Systolic blood pressure ≤ 135 mmHg and ≥ 100 mmHg.
  Diastolic blood pressure ≤ 95 mmHg and ≥ 55 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.
  Valid systolic blood pressure (SBP) auscultatory measurements for lateral difference is ≤ 15 mmHg.
  Valid diastolic blood pressure (DBP) auscultatory measurements for lateral difference is ≤ 10 mmHg.
- Hemoglobin value ≥ 11 g/dL.
- 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.

7.5.2. Exclusion Criteria

Influenced by device warning labels:

- Subject is pregnant or breastfeeding.
- Subject is experiencing dysrhythmia or arrhythmia.

Influenced by study design/environment:

- Subject is concurrently participating in another research study.
- Subjects not suitable for the investigation at the discretion of the clinical team including but not limited to the items below.
  - Subjects who do not pass the heath assessment for safe participation in the study procedures.
  - Inability to insert or difficulty with 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.

7.5.3. Number of Subjects

Approximately 20 subjects to satisfy the requirements listed in section 8.1.

7.5.4. Subject Classifications

Subjects will be classified according to the criteria below:

[redacted] **Screened** [redacted]

[redacted] **Enrolled** [redacted]

[redacted]

[redacted] **Screen Failure** [redacted]

[redacted]

[redacted] **Withdrawn** [redacted]

[redacted]

[redacted]

[redacted] **Completed** – [redacted]

[redacted]

7.5.4.1. Withdrawal of Subjects

In addition to conditions noted above, subjects must 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:

- Intolerance of blood pressure variation protocol.
- Inability to remain still for the majority of a no motion study.

7.5.4.2. Replacement of Subjects

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

7.5.4.3. Recontacting Subjects

If the subject fails to provide proper documentation on their individual consent 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 may also fill out other study documents. These documents aid in collection of data, tracking of subject count, etc. If the subject fails to provide proper documentation on other documents, the subject will not need to return to the laboratory to complete those specific forms. However, Masimo reserves the right to recontact the subject and ask them to return to the clinical lab to properly complete these documents if seen as necessary by study staff.

The subject will be recontacted via phone or email and asked to return as soon as possible.

7.5.5. Study Duration

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

7.6. Procedures

7.6.1. Subject Recruitment and Pre-screening

7.6.1.1. Advertisement and Recruitment

Volunteers will be recruited for studies at Masimo Clinical Laboratory through [redacted]

7.6.1.2. Pre-screening

Pre-screening for subject eligibility may be completed by clinical research staff via [redacted]

7.6.2. 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.

All monetary compensation to subjects will be reported to the Internal Revenue Services (IRS). 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, as required by the law. 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.

7.6.2.1. 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) in each subject's records.

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

Subject may withdraw their consent at any point during the study.

7.6.2.2. Health Assessment and Eligibility Determination

After informed consent, subjects will be screened 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, skin pigmentation, age, height, and weight), arms circumference, and a medical history may be collected.

- 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.

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.

Assessment of lateral difference in blood pressure measurements between the left and right arms will be done with simultaneous blood pressure reading in both arms. Simultaneous blood pressure reading in both arms will be performed using FDA-cleared auscultatory measure three times, following best practices (e.g., positioning the middle of the cuff on the patient's upper arm at the level of the right atrium [the midpoint of the sternum]). Study will only proceed if the lateral difference is ≤ 15 mmHg for the systolic blood pressure (SBP), and ≤ 10 mmHg for the diastolic blood pressure (DBP). Otherwise, the subject will be withdrawn from participating in the study.

- 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 for: 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, as well as data capture. Information and images may be taken into consideration during data analysis. Examples of how these devices may be used include image capture, continuous noninvasive monitoring of blood velocity in a vessel, etc. When used, these noninvasive devices may be secured to the body for continuous measurements and imaging. For instance, an ultrasound probe may be placed on various areas of the body using a strap or other type of apparatus (e.g., headset) to hold the probe in place.

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(s) 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. No more than 20mL of blood will be taken.

7.6.3. Study Procedures

7.6.3.1. Participant Preparation

7.6.3.1.1. General Preparation for Blood Pressure Measurement

Study staff will check with the study participant to ensure that the subject has emptied his/her bladder. The subject will be asked to be seated in a relaxed position on a chair, with his/her feet uncrossed and on the floor, and back supported for approximately 5 minutes. Study staff will explain to the subject that it is imperative that the subject refrains from motion and talking during the measurement. The subject will be asked to remove article(s) of clothing covering the location of cuff placement.

7.6.3.1.1.1. Cuff Size Selection

Circumference of both arms will be measured at the cuff placement location, to ensure the correct cuff size is used, such that the bladder encircles 80% of the arm.[9] Masimo INVSENSOR00073 comes with three cuff sizes as follows:

Small adult (20-26 cm)
Adult (25-34 cm)
Large Adult (32-43 cm).

7.6.3.1.2. Safety Precautions

To ensure subject safety, subjects will be monitored with standard FDA-cleared noninvasive monitoring technologies such as pulse oximetry monitoring and continuous Electrocardiogram (ECG) monitoring during the blood pressure variation procedures. This is for monitoring by the medical staff and may not be recorded. Subjects may also be asked to shave the site of application of the ECG electrodes application to allow the sensors to adhere to the skin.

If the subject has any irregular heart rhythm (e.g., dysrhythmias or arrhythmias), the subject will be withdrawn from the study.

Additionally, an Advanced Cardiovascular Life Support (ACLS) certified physician will be at the clinical site during the study procedures, in the study space during the blood pressure variation procedures, and the study will be completed under their general supervision.

Any emergency drug deliveries given in the case a subject loses consciousness or has another emergency arise shall be recorded. The individual will be monitored, and this information will be recorded and submitted to the IRB, if necessary, as outlined in section 15.3, *Adverse Event Reporting*.

7.6.3.2. Cuff Placement and Measurement

Masimo INVSENSOR00073 cuff shall be placed on the opposite limb from the arterial line. Care should be taken to ensure that both the arterial line transducer and Masimo INVSENSOR00073 cuff are at the level of the participant's left ventricle of the heart. Data collection software(s) will be set up for data acquisition.

[redacted]

7.6.3.3. Blood Pressure Variations Procedure

During the blood pressure variations procedure, participants will be administered continuous infusions containing vasoactive medications. There will be two study types:

Induced controlled hypertension (increased blood pressure)

Induced controlled hypotension (decreased blood pressure)

Both study types will involve the use of a primary drug to elicit the desired blood pressure change.

[redacted]

Vasoactive Medication

[redacted] will be used as the primary drug to induce hypertension (increased blood pressure) and [redacted] will be used to induce hypotension (decreased blood pressure).

Safety drugs will be used to counteract the effects of the primary drugs when deemed necessary by the presiding clinician. Table 1 outlines the possible primary and safety drug choices based on the pressure variation study type. [redacted]

Table 1. Drugs allowed for pharmacological variations of blood pressure variation studies.

Type of Pressure Variation Study	Primary Drug	Safety Drug
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Blood Pressure Safety Limits

Medication-induced blood pressure variation studies have strict pressure variation limits to ensure the subject's blood pressure stays within a safe range. Tables 2 and 3 below outline the maximum allowable pressure variations for each study type. If the blood pressure limits are reached or exceeded, drug infusion will be stopped immediately, and the subject will be monitored as blood pressure returns to the baseline values. The study may be continued if the subject is comfortable, and clinicians deem it is safe to proceed.

Target blood pressure changes must be determined prior to starting the study for each subject. The selected variation must be the lesser of the percent and absolute changes indicated in Table 2, provided the selected variation does not violate the limits established in Table 3. Vasoactive medications are titrated based upon the arterial line-derived mean arterial pressure (MAP) reading. Blood pressures must remain within the limits defined in Table 3 for the duration of the procedure.

Table 2. Maximum allowed pressure variations for each study type. Target pressure variations are calculated based on mean arterial pressure (MAP)

Study Type	Percent Change From Baseline MAP	Absolute Change From Baseline MAP
Controlled Hypertension	[redacted]	[redacted]
Controlled Hypotension	[redacted]	[redacted]

Table 3. Minimum and Maximum blood pressure levels

Blood Pressure	Minimum (mmHg)	Maximum (mmHg)
Systolic Blood Pressure	[redacted]	[redacted]
Diastolic Blood Pressure	[redacted]	[redacted]

Mean Arterial Pressure (MAP)	[redacted]	[redacted]

Medication Preparation and Administration

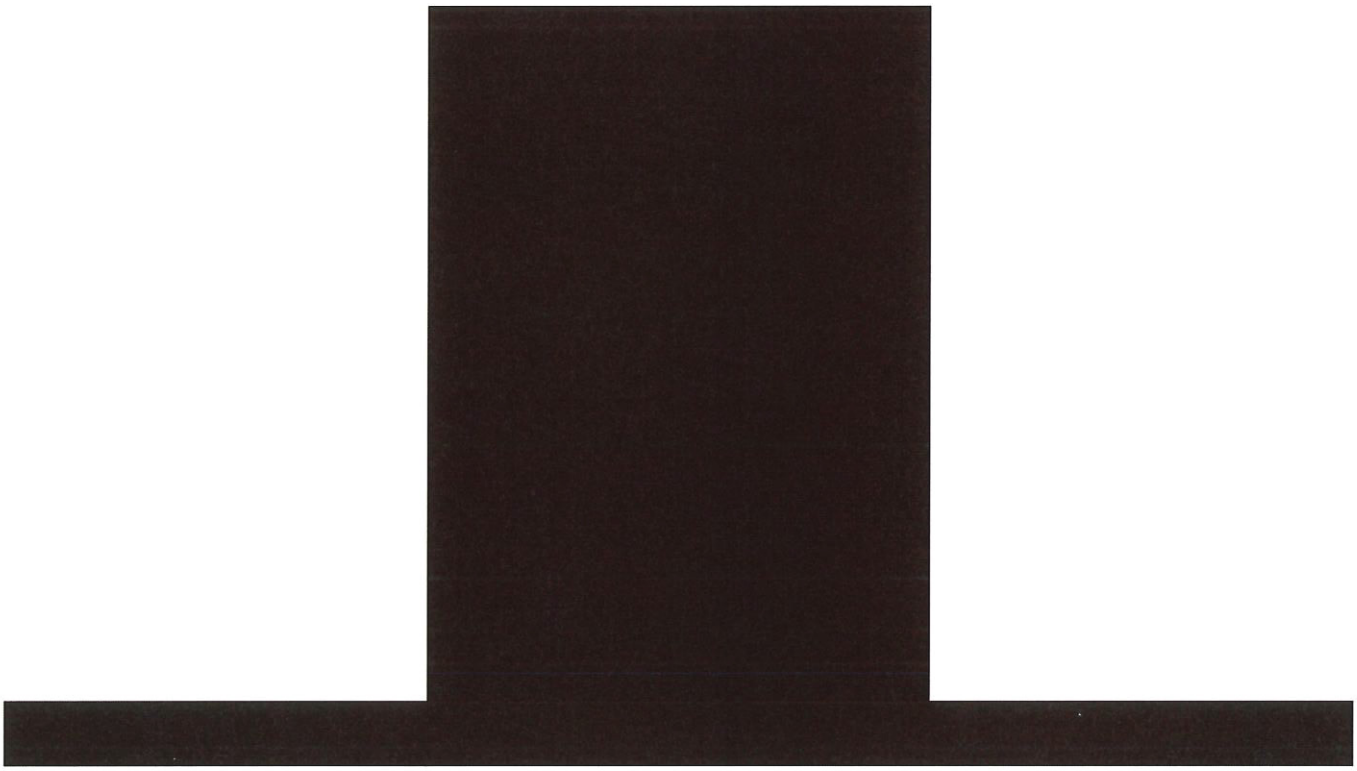
Primary and safety drugs will be prepared for each subject prior to beginning the blood pressure variation procedures. A trained clinician will prepare all infusions containing the primary drug. [redacted]

Only full and unused syringes will be used for each subject. Partially used syringes will be discarded after each subject completes the study.

Infusion rates for each titration step are calculated by the medication infusion pump based on the subject's weight [redacted] and the drug concentration. [redacted] Two independent clinicians must verify medication pump settings before changing the current setting.

If the subject participates in the induced hypertension procedure (increased blood pressure), the infusion with [redacted] will be given at a starting dose of [redacted] µg/kg/min. [redacted]

If the subject participates in the induced hypotension procedure (decreased blood pressure), the infusion with [redacted] will be given at a starting dose of [redacted] µg/kg/min. [redacted]



After gauging subject response to the initial infusion, the drug will be titrated to achieve the desired blood pressure variation. Dose increases may continue to titrate up to the targeted blood pressure change as long as the subject remains

asymptomatic and the dose does not exceed the maximum of [redacted] µg/kg/min. See Table 4 for the [redacted] and [redacted] dose schedules.

Table 4. Dose schedule for [redacted] and [redacted]

Drug	Starting Dose (µg/kg/min)	Step Size/Schedule (µg/kg/min)	Maximum Dose (µg/kg/min)	Dose Increase Wait Time
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Primary drug infusion stops when the target blood pressure change is maintained for the period of time [redacted] the subject develops symptoms, blood pressure limits are reached/exceeded, or the total drug infusion time per [redacted] After primary drug infusion ceases, the subject's blood pressure is allowed to passively return to baseline. Baseline is considered achieved when the subject's blood pressure is within 10 mmHg of their initial blood pressure levels.

The total drug infusion time (including all Rounds) must not exceed 180 minutes. If this limit is reached, the blood pressure variation procedures will be stopped.

Post-administration monitoring may exceed 60 minutes.

7.6.3.4. Safety Drug Administration Procedure

Safety Drugs will be prepared for administration prior to beginning the blood pressure variation procedures. Weight-appropriate doses will be chosen for each subject and verified by a clinician. If the presiding clinician deems it necessary to begin safety drug administration, the primary drug infusion will be stopped immediately and the clamp on the vasoactive drug line closed. The safety drug will be administered at the [redacted] Clinicians will monitor the subject's response to the safety drug, repeating the reversal as necessary and at the presiding clinician's discretion to facilitate the subject's return to baseline blood pressure.

7.6.3.5. Ending Procedures

At the conclusion of the procedure, the sensors/devices, IVs, and arterial lines will be removed. A set of pre-discharge vitals, such as heart rate and blood pressure, will be obtained and recorded on the case report form for subject safety purposes.

Subjects will not be allowed to leave until blood pressure has returned within 10 mmHg of baseline blood pressure values, they have been asymptomatic for a minimum of 5 minutes, and medical personnel determine it is safe to do so.

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 food and/or liquid prior to leaving the clinical lab area for their safety due to study procedures such as line placement and blood removal.

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

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

The total overall lab time will be approximately 180 minutes. If the total lab time exceeds 180 minutes, subjects will be compensated for the additional time. Subjects will be paid according to the compensation breakdown on the consent form.

7.6.3.6. Masimo INVSENSOR00073 Cleaning/Disinfection

Masimo INVSENSOR00073 will be thoroughly cleaned and disinfected before being applied to a new participant. Before cleaning, the device will be turned off and the batteries will be removed.
Cleaning instructions:

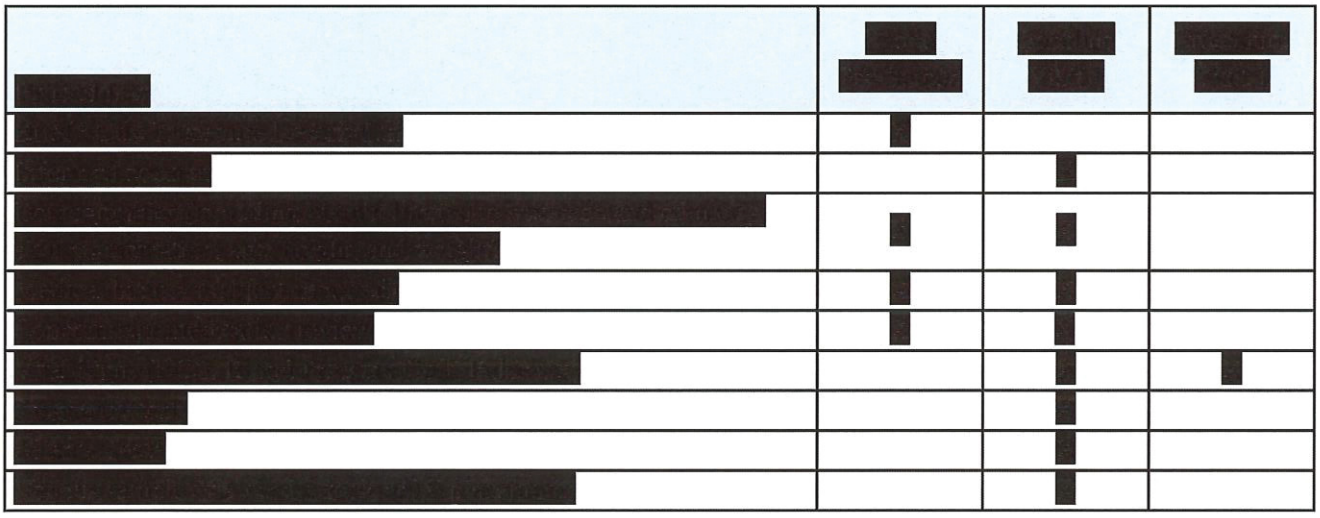
- Using a CaviWipes™ wipe the outer surfaces twice or until the surfaces are free of any visible residue.
- Repeat the above cleaning step using a fresh wipe.
- Allow the Masimo INVSENSOR00073 to dry thoroughly before using again.

Low level Disinfection instructions:

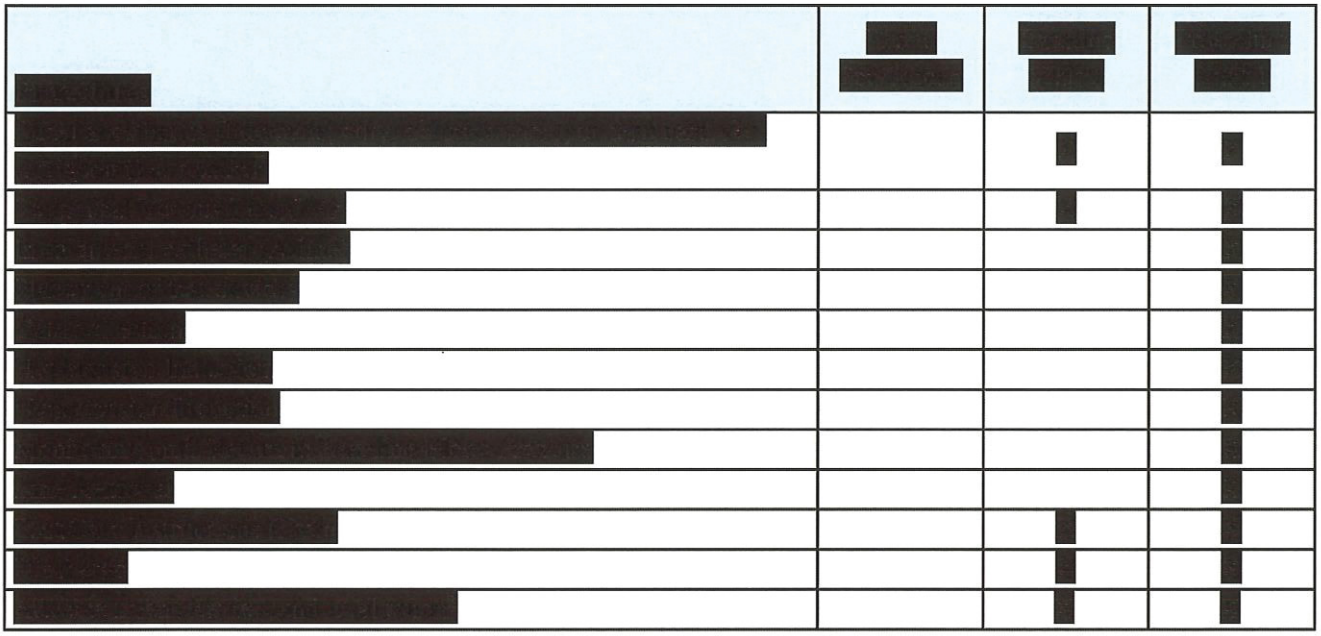
- Visibly wet the outer surfaces of the Masimo INVSENSOR00073 using a soft cloth dampened with a 10% (1:10) chlorine bleach to water solution.
- Allow the solution to sit for 10 minutes before wiping with a dry soft cloth.
- Allow the Masimo INVSENSOR00073 to dry thoroughly before using again.

Alternatively, the Masimo INVSENSOR00073 can be disinfected using CaviWipes™, following the same instructions except for a 5-minute exposure time.

7.6.4. Schedule of Events



[1] hCG (urine) pregnancy test (all persons with childbearing potential).



7.7. Monitoring Plane limb

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 Masimo INVSENSOR00073, which follows the *ISO 81060-2-2018 Non-invasive sphygmomanometers- Part 2: Clinical investigation of intermittent automated measurement type* requirements.

8.1. Sample size

According to ISO 81060-2:2018, a minimum of 150 valid data points from a minimum of 15 subjects are required; no more than 10 measurements per subject is permitted. Additionally, the following requirements pertaining to sex distribution, limb size distribution, and pre-specified blood pressure distribution shall be met:

- Minimum of 30% of participants are to be male and 30% female (i.e., minimum of 5 males and 5 females).
- At least 1/2n of participants tested with each cuff size, where n is the number of cuff sizes. Accordingly, at least three participants tested with each of the cuff sizes of small, medium, and large.
- Data shall meet blood pressure distribution requirements as follows:
    - At least 10% of shall have a reference systolic blood pressure (SBP) ≤ 100 mm Hg.
    - At least 10% of shall have a reference SBP ≥ 160 mm Hg.
    - At least 10% of shall have a reference diastolic blood pressure (DBP) ≤ 70 mm Hg.

[2] IV maybe placed during screening/baseline to obtain qualifying venous sample at discretion of medical staff. If the IV is placed during screening/baseline, medical staff will offer to use local anesthetics.

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

* At the discretion of the study staff

- At least 10% of shall have a reference DBP ≥ 85 mm Hg.

8.2. Data Analysis

The resonant frequency and damping coefficient of the reference invasive blood pressure monitoring equipment shall be characterized.

8.2.1. Accuracy Calculations

Mean error and standard deviation for the MAP measurements from the Masimo INVSENSOR00073 device under investigation in comparison with measurements from the reference invasive radial arterial line (A-line) will be calculated.

Since the opposite limb is used for reference site of intra-arterial blood pressure recording, the results shall be corrected for the lateral difference. The lateral difference will be calculated as the average difference between the reference readings or determinations made on each limb according to the formula (1) below:

$$(1)\ \text{Lateral Difference: } LD = \frac{1}{3} \times \left(\sum_{i=1}^{3} p_i - \sum_{j=1}^{3} p_j\right),$$

Where i is the index for the determination on the limb used for the sphygmomanometer-under-test determination, and j is the index for the reading on the limb used for the reference reading.

Lateral difference will be calculated for each subject prior to taking invasive measurements, using two identical automated sphygmomanometers. If the lateral difference of the reference systolic blood pressure is > 15 mmHg or the lateral difference of the reference diastolic blood pressure is>10 mm Hg, subject will not participate in the study.

For those who are eligible to participate in the invasive measurement, sphygmomanometer-under-test error, x, is calculated by taking the difference between the sphygmomanometer-under-test blood pressure and the reference blood pressure and by adding the lateral difference (LD) if the sphygmomanometer-under-test blood pressure was taken in the left arm, according to formula (2), or subtracting LD if the sphygmomanometer-under-test blood pressure was taken in the right arm, according to formula (3).

$$(2)\ \text{Sphygmomanometer-under-test error (worn on left arm), } x = p_{SUT\_L} - p_{REF\_R} + LD,$$
$$(3)\ \text{Sphygmomanometer-under-test error (worn on right arm), } x = p_{SUT\_R} - p_{REF_L} - LD,$$

Where p_{SUT_L} and p_{SUT_R} are sphygmomanometer-under-test blood pressures in the left (L) and right (R) arms, respectively; and similarly, p_{REF_L} and p_{REF_R} are refrence blood pressures in the left (L) and right (R) arms, respectively.

The reference MAP will be read from the values displayed on the reference invasive blood pressure monitoring equipment. Since the recording is not interrupted due to cuff inflation, the reference blood pressure ranges shall be determined from the recording of the invasive blood pressure for a duration of at least 30 seconds that includes the period of determination of INVESNSOR00073. Specifically, 30 seconds of reference recordings prior to the determination of INVESNSOR00073 will be used. Reference recordings and determination of Masimo INVSENSOR00073 will be synchronized based on the time stamp of the data acquisition device.

For the sphygmomanometer-under-test, the mean value of the errors $\bar{x}_n$ and experimental standard deviation s_n of the n individual paired determinations of the Masimo INVSENSOR00073 for all subjects shall be calculated according to the formulas (4) and (5) below:

(4) Mean Error: $\bar{x}_n = \frac{1}{n} \times \sum_{i=1}^{n} x_i$

(5) Standard Deviation: $s_n = \sqrt{\frac{1}{n-1} \times \sum_{i=1}^{n} (x_i - \bar{x}_n)^2}$,

where x_i is the error of the i[th] individual determination, n is the total number of determinations, and i is the index for the individual determination.

8.2.2. Acceptance Criteria

- Mean error of ≤ 5 mmHg with a standard deviation of ≤ 8 mmHg.
  Per *ISO 81060-2-2018 Non-invasive sphygmomanometers- Part 2: Clinical investigation of intermittent automated measurement type,* the mean value of the errors for systolic and diastolic blood pressures shall be within or equal to 5.0 mmHg with an experimental standard deviation no greater than 8.0 mmHg. The validation of Mean Arterial Pressure (MAP) for Masimo INVSENSOR00073 shall follow these requirements.

8.2.3. Data Exclusion Criteria

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

- Either reference or test device malfunctions and/or provides inconsistent values or not values.
- Discontinuities and abrupt dropouts due to device failure.
- Any invasive systolic blood pressure change greater than [redacted], or diastolic blood pressure changes greater than [redacted] during or before determination by the sphygmomanometer-under-test.

[redacted] Diastolic blood pressure outside of the Masimo INVSENSOR00073 specifications of [redacted]

- Systolic blood pressure outside of the Masimo INVSENSOR00073 specifications of [redacted]

8.2.4. Expected Dropouts and Study Participant Replacement

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. Accordingly, 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, whether subject consent was obtained before start of study, demographic information, device readings, and if occurrence of any adverse event, protocol deviation, and device deficiencies, etc. The CRFs will be signed by the PI or delegate to attest that the data are complete and accurate.

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

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 Process* 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 following would be considered as anticipated device-related adverse events: redness or itching at the site of sensor application, irritation or bruising at the site of sensor application, numbness or swelling at the site of sensor application, skin injury due to sensor placement on one finger for more than eight hours, injury due to tight sensor placement, choking due to small parts, and fire due to placement of device near flammable gases. For all other safety and performance warnings, subjects should refer to the study devices *Directions for Use* documents. Subjects should contact Study Staff as soon as possible if they experience a device-related adverse event while using the device at home.

15.2.2. List of Non-Reportable Adverse Events

Events related to expected post-surgical complications shall be recorded in the eCRF as data for clinical outcomes assessments but not reported as adverse events.

The following examples would be considered as non-reportable adverse events: all expected postoperative events such as but not limited to anemia, postoperative pain, itching outside of operative site location, bruising outside of operative site location, bleeding, swelling outside of operative site location, and drainage from the operative site.

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.

[redacted]

- 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

- Reasonable compensation (i.e., travel expenses) may be provided for economically disadvantaged subjects to eliminate the possibility of undue influence due to financial incentive.
- Educationally disadvantaged subjects will be provided ample time to ask questions and comprehend information.
- Medical care will be provided to these subjects after the clinical investigation has been completed if they are injured as a direct result of participating in this research study. The cost of treatment for any research related injury will be covered by Masimo.

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]
[redacted]	[redacted]	[redacted]

21. APPENDICES

[redacted]