Official Title: Validation of Noninvasive Blood Pressure Device

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Validation of Noninvasive Blood Pressure Device

Sponsor: Masimo
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Irvine, CA 92618

Principal Investigator(s): [redacted]

Study Devices: Masimo noninvasive blood pressure device

Sponsor Protocol Number: TORR0004

IRB: Aspire IRB
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1 INTRODUCTION

This document is a protocol for a clinical research study sponsored by Masimo Corporation. The study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki. In participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of IRB/IEC approval, 21 CFR 50, 21 CFR 56, 21 CFR 812, ISO-14155, and International Conference on Harmonization Good Clinical Practice guidelines ICH GCP.

1.1 Background and Rationale

Masimo Corporation is the developer of noninvasive technologies for the measurement and monitoring of physiological variables, such as arterial oxygen saturation (SpO2), total hemoglobin concentration (SpHb), carboxyhemoglobin concentration (SpCO), methemoglobin concentration (SpMet), acoustic respiration rate monitoring (RAM), End tidal CO2 (EtCO2), and other physiological parameters.

Assessment of blood pressure is vital in clinical practice. In hospitalized patients, blood pressure measurements are obtained as frequently as every day or prior to and during medical procedures. In outpatient clinic settings, blood pressure measurements are taken as part of routine physical examination, and also in the follow-up of known patients with high blood pressure for appropriate management. High blood pressure is one of the most chronic conditions that affects a large population in the United States, and a lack of adequate detection and management of high blood pressure may lead to coronary heart disease, stroke, heart failure etc. (Ventura and Lavie, 2018). Hypotension is associated with increased risk of falls, dementia, cardiovascular disease, syncope and mortality if left untreated (P&T 2019). Since both hypertension and hypotension can impair the function of vital organs such as the heart, brain, or kidneys, arterial blood pressure monitoring, is a mainstay of hemodynamic monitoring and is an important indicator of a person's state of health (Meidert & Saugel, 2018).The gold standard for measurement of arterial pressure is through direct arterial measurement using a catheter (Sahu & Bhaskaran, 2010). This technique is commonly performed during high-risk surgeries and in intensive care medicine; however, this technique is neither practical nor appropriate for non-hospitalized patients or asymptomatic individuals (Meidert & Saugel, 2018).

For these reasons, blood pressure is commonly measured noninvasively. The standard noninvasive method for blood pressure measurement is the auscultatory technique using an arm cuff, stethoscope, and a manometer. Blood pressure measurement is performed by placing the stethoscope over the brachial artery and then inflating the arm rubber cuff to a level higher than the systolic pressure. The cuff is then gradually deflated and blood pressure is noted when Korotokoff sounds are heard. Korotkoff sounds are the audible turbulent sounds of the blood in the brachial artery when blood flow is constricted. Traditionally, the systolic blood pressure is taken to be the pressure at which the Korotkoff sound is first heard and the diastolic blood pressure is the pressure at which the Korotkoff sound is just barely audible or when it becomes silent.

An alternative method to the auscultatory method is the oscillometric method. The term NIBP, for Non-Invasive Blood Pressure, is often used to describe oscillometric monitoring equipment (Sandham, n.d.). The equipment is functionally similar to that of the auscultatory method, but with an electronic pressure sensor fitted in to detect blood flow, instead of using the stethoscope and the clinician's ear (Sandham, n.d.). These devices automatically inflate the cuff pressures above systolic pressure and then deflate at a controlled rate. A proprietary algorithm is

then used to calculate the systolic and diastolic pressure. Masimo is currently developing a device for the noninvasive measurement of blood pressure that can be used by clinicians to assess patient physical status.

1.2 Investigational Devices

Masimo automated non-invasive blood pressure (NIBP) device

[redacted]

The device is not FDA-cleared and is considered investigational. The investigational device will undergo risk analysis and safety testing in accordance with applicable safety standards, including electrical safety, current leakage, mechanical safety and biocompatibility testing for patient contacting materials, prior to use in the study.

Laptop with data collection software

[redacted]

1.3 Risk/Benefits

Benefits: There is no direct benefit to the individual for participation in this research study. Future benefits might include a development of a noninvasive blood pressure device that can accurately estimate a person's blood pressure.

Risks: There is a potential for the blood pressure cuff to become over-pressurized during automated blood pressure measurement. The excess pressure on the skin tissue could potentially lead to skin injury, i.e. necrosis. To mitigate this risk, the system is designed with [redacted] The measurement will be monitored by a healthcare professional during the course of the study who will be trained and instructed to remove the cuff if the subject experiences any discomfort.

There is a risk of electric shock if defibrillation is performed while the subject is wearing the device. To minimize this risk, the device should be removed if the subject will undergo defibrillation.

2 STUDY OBJECTIVES

The objective of this study is to evaluate the clinical performance of a digital noninvasive blood pressure measurement device. The noninvasive blood pressure measurements will be compared to reference auscultatory measurements. The difference will be expressed in terms of mean and standard deviation.

3 STUDY DESIGN

This is a prospective, nonrandomized multi-center study, which is based on the ISO standard 81060-2:2018 for the investigation of noninvasive sphygmomanometers.

The study will be conducted at two sites where noninvasive blood pressure measurements will be [redacted]

The study will be conducted [redacted] to meet the blood pressure distribution requirements and the limb size distribution requirements in the ISO 81060-2:2018.

[redacted] Site 1 [redacted] will enroll [redacted] patients from among the physician's patients. Site 2 [redacted] volunteers.

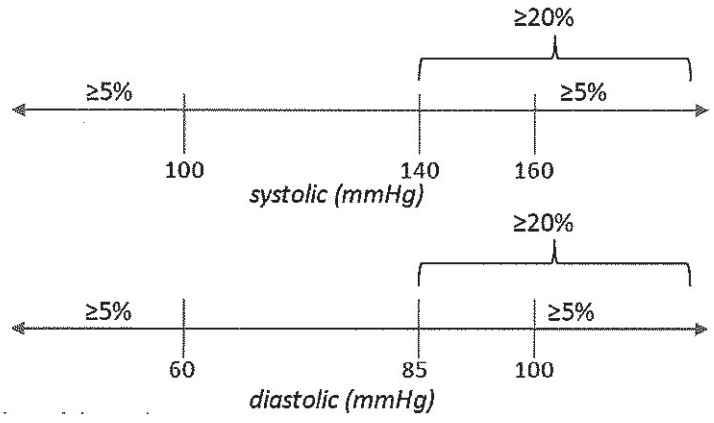

Figure 4: Blood pressure distribution (ISO 81060-2:2018)

Stage 2 will begin after the minimum subjects have been enrolled in the study to meet the blood pressure distribution requirements. Stage 2 will satisfy the cuff distribution requirements of ISO 81060-2:2018. Each cuff size will be tested as per requirements of ISO 81060-2:2018.

Cuff size	Upper half of range of cuff size	Lower half of range of cuff size
Small, Medium, Large	40% of subjects	40% of subjects

Figure 5: Cuff size distribution (ISO 81060-2:2018

Blood pressure measurements will be obtained using the Masimo NIBP device and also obtained using the auscultatory method as a reference. Each value from the Masimo device will be paired with two measurements from two observers using the reference auscultatory technique, for a total of 4 successful paired measurements per subject. A pair is considered valid if both observers' SBP and DBP readings are within 4 mmHg and the prototype successfully measures.

[redacted]

4 CLINICAL TEST SITES

Site 1

[redacted]

Site 2

[redacted]

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Number of Subjects

A minimum of 85 subjects with diversified demographics (i.e. age, gender, ethnicity, comorbidities etc.) will be enrolled.

5.2 Inclusion Criteria

- Age 18 years and older
- Site 1; Stage 1 only: Subjects with a history of hypertension (≥ 140/85 mmHg) or hypotension (≤ 100/60 mmHg) within the last 3 months. Stage 2 only: No criterion for blood pressure
- Site 2; Stage 1 and 2: Subjects with systolic blood pressure < 140/90 mmHg.
- Ability to provide informed consent

5.3 Exclusion Criteria

- Febrile subjects
- Subjects displaying respiratory symptoms, or with suspected respiratory illness
- Subjects whose skin is not intact, e.g. wounded, in or at the vicinity of the cuff placement site
- Subjects with removed axillary lymph nodes or mastectomies
- Subjects with peripheral artery disease
- Pregnant women (patient reported)
- Subjects deemed not suitable for the study at the discretion of the investigator

5.4 Study Timelines

Study participation is expected to last approximately 1 – 2 hours including the informed consent and screening procedures.

5.5 Subject Recruitment and Screening

Subjects will be recruited from the physician's practice and from a database of past volunteers. Potential subjects may be contacted by the site staff by phone using an IRB-approved phone script. Once a potential subject agrees to participate in the study, or see's the recruitment material (i.e. advertisement) and contacts the site, an appointment will be scheduled for the subject.

Subjects will be screened to determine eligibility for study enrollment. 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.

5.6 Withdrawal of Subjects

5.6.1 Informed consent documents and discussions will explicitly include emphasis that neither subject enrollment nor subject withdrawal from the study will result in any alterations to the standard clinical care. Participants may elect to withdraw at any time without any consequences or loss of benefits to which they are entitled. The subject may be withdrawn from the study prior to expected completion for reasons such as safety concerns, failure to protocol requirements, subject consent withdrawal, etc.

5.6.2 Any data collection until the time of subject's withdrawal may be included in the final data analysis, unless requested otherwise by the subject. Information of the subject's withdrawal should be documented in the case report forms (CRFs) and include clear documentation of the reason for withdrawal to the Sponsor.

6 STUDY DEVICES

FDA-cleared Devices:

Blood pressure cuff (for auscultatory measurement only)

Aneroid Sphygmomanometer

Dual Stethoscope

Investigational Devices:

Masimo blood pressure cuff

Masimo NIBP device

Data Collection Equipment:

Laptop computer with data acquisition software

6.1 Device Accountability

6.1.1 Receipt of Study Device

Upon receipt of the of the study device supplies, an inventory must be performed and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices 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.

6.1.2 Use of Study Device

Use of device will be documented on case report forms for each subject. Any unused devices must be returned to the Sponsor at the end of the study or before product expiration date.

6.1.3 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 on site will only be upon written instruction from the sponsor and will be documented in the study files.

6.1.4 Device Deficiencies

Device deficiencies are defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Record all device deficiencies on the case report form and report to the Sponsor.

7 OVERALL STUDY PROCEDURES

7.1 Informed Consent and Screening Procedure

7.1.1 Full written informed consent will be obtained for all subjects prior to enrollment in the study.

7.1.2 During the COVID19 pandemic, subjects will be asked to wear a face mask when they arrive at the research site.

7.1.3 In Stage 1, a screening blood pressure measurement will be taken for all consented subjects during the day of data collection. Subjects must meet the blood pressure requirements in order to be enrolled in the study. Subjects with screening blood pressure outside the Stage 1 values will be removed from the study as screen failures.

Screening Blood Pressure Values		
	Systolic	Diastolic
Hypertensive	> 140 mmHg	> 85mmHg
Hypotensive	< 100 mmHg	< 60 mmHg

7.1.4 In Stage 2, screening procedures for subjects will include a measurement of subjects' upper arm circumference. Subjects will be categorized into bins for the Masimo blood pressure cuff used, according to the table below. The Masimo blood pressure cuff sizes are: Small (20-26 cm), Medium (25-34 cm) and Large (32-43 cm).

	Small		Medium		Large	
Upper Arm Circumference	20-23 cm	23-26 cm	25-29.5 cm	29.5-34 cm	32-37.5 cm	37.5-43 cm

- Subjects may be removed from the study as screen failures if their arm circumference falls into a bin that has had sufficient enrollment.

7.2 Study Procedure

[redacted]

7.2.1 Ensure the subject is in a relaxed and comfortable position, either seated or lying down, with the arm at heart level and legs uncrossed. Subject should be in the same position for at least 5 minutes prior to blood pressure measurement. During that time, subject demographics and health history may be completed in the CRF.

7.2.2 [redacted].

7.2.3 Measure arm circumference and place the appropriate size cuff preferably on the left arm of the subject. The middle of the cuff should be at same level as the heart, see Figure 8. Do not place cuff on an extremity selected for IV infusions or any other intravascular access, e.g. dialysis.

[redacted]

7.2.4 Perform an auscultatory measurement. See section 7.3 for details on the auscultatory measurement procedure (reading R_0 in Figure 7).

7.2.5 Wait at least 60 seconds to allow venous blood flow to normalize.

7.2.6 [redacted].

7.2.7 Perform [redacted] blood pressure measurement procedure (T_0 in Figure 7).

7.2.8 Wait at least 60 seconds to allow venous blood flow to normalize.

7.2.9 Remove the Masimo cuff and automated blood pressure device and replace with the reference auscultatory cuff and stethoscope.

7.2.10 Perform an auscultatory measurement (R_1 in Figure 7).

7.2.11 Repeat 7.2.5-7.2.10 until at least four valid automated and auscultatory measurement pairs have been performed or eight measurement pairs have been attempted.

- A measurement pair is considered valid if the observer difference criteria in 7.3.4 is satisfied and the automated blood pressure device performs a successful measurement.
- Counting begins with measurement pair T_0-R_1 (e.g. T_0-R_1, T_1-R_2, T_2-R_3 … maximum up to T_7-R_8. See Figure 7).

7.2.12 If less than four paired measurements are obtained after eight paired attempts, subject participation in the study will end.

7.2.13 Be sure to check cuff site health and integrity between measurements.

7.2.14 Disinfect auscultatory blood pressure cuff and allow to air dry, per manufacturer's cleaning directions, after use with each patient.

7.2.15 No treatment decisions will be made based on blood pressure results from study devices.

7.3 Auscultatory Blood Pressure Measurement Procedure

7.3.1 Place the bell of the stethoscope on the brachial artery. Remind subject to refrain from speech and excessive movement during measurement. Two qualified observers, who may be research staff, will listen to the Korotkoff sounds using the ear pieces of the stethoscope. See Figure 9.

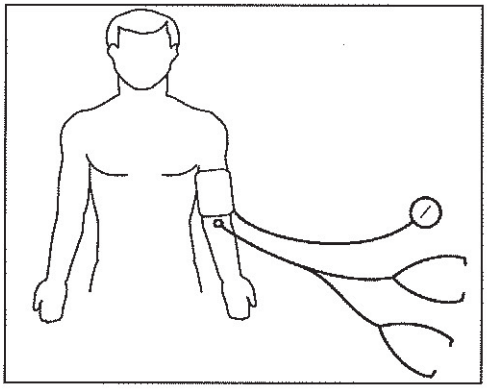

Figure 9. Auscultatory blood pressure measurement using a stethoscope.

7.3.2 Connect inflation pump to the cuff and inflate to 20-30 mmHg above the systolic pressure, the point at which radial pulse is no longer audible.

7.3.3 Deflate cuff slowly at a rate of approximately 2-3 mmHg/sec. Each observer will listen to Korotkoff sounds and record the systolic and diastolic values independently on a data collection sheet; observers will be blinded to each other's reading and will be provided with their own data collection sheet or will be recording the measurements on independent electronic forms. Observers should avoid parallax errors when reading the pressure gauge by orienting their line of sight directly above the gauge.

7.3.4 A research coordinator will obtain the blood pressure results from each observer's data collection sheet, and will record the values into the paper case report form (CRF). The coordinator will compute the results from the readings and confirm if the paired measurement is valid. A valid measurement is when the observers' blood pressure values are within 4mmHg (|Observer1 Systolic – Observer2 Systolic| ≤ 4mmHg, and |Observer1 Diastolic – Observer2 Diastolic| ≤ 4mmHg). If an electronic CRF is being used, difference between the Observer1 and Observer2 readings will be performed by the system.

7.4 Automated Blood Pressure Measurement Procedure

[redacted]

7.4.2 [redacted].

7.4.3 [redacted].

[redacted]

8 SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS

The sample size requirements and statistical analysis are completely defined by the international standard for non-invasive sphygmomanometers, ISO 81060-2:2018, 3rd Edition. A minimum of 85 subjects are required, and the predicted blood pressure values must pass the two accuracy criterions defined in the standard. Population distributions are clearly defined and will be followed for blood pressure ranges, gender, and arm circumference across each cuff size.

9 SAFETY AND ADVERSE EVENTS

9.1 Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, and unanticipated adverse device effect are provided below (ISO 14155:2011, 21 CFR 812.3(s)).

- Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
- Adverse Device Effect (ADE): an adverse device effect is any untoward or unintended response to a medical device which may result from insufficiencies in the instructions for use or deployment of the device, or from use error.
- Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.
- Serious Adverse Device Effect (SADE): a serious adverse device effect is an adverse device effect that results in death, inpatient hospitalization, severe or permanent disability or is life threatening.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life threatening problem or death cause by or associated with, a device, if the effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan, or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects. Refer to the Device Risk Analysis and Risk Assessment section in the investigator's brochure for details on anticipated adverse device effects.

9.2 Anticipated Adverse Events:

- Subject may feel slight discomfort temporarily during blood pressure cuff inflation.
- Bruising may be possible in some subjects.
- Subject may develop possible ischemia, purpura, and/or neuropathy at the site of the cuff or at the extremity. Cuff site will be inspected by research staff throughout measurements for any signs of adverse events. Subject participation will be stopped if adverse events are observed.

9.3 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 5 business days.
- All Serious Adverse Events will be also reported to the IRB per IRB reporting requirements. These reports may include, but will not be limited to: date of onset; brief description of the events; their treatment; whether they resulted in death, inpatient hospitalization, severe or permanent disability or were life threatening; their relationship to the study device; and resolution.

9.4 Deviations from the study protocol

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

9.5 Withdrawal of IRB approval

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

10 DATA MANAGEMENT

10.1 Data Management and Confidentiality

All documents associated with this protocol will be kept in the locked office of the PI or on password protected computers. All data will be de-identified before any statistical analysis. Only de-identified data will be shared with Masimo for research purposes stated in this protocol. Data collected by data capture software and data entered in case report form will be shared with Masimo via a secure, password protected server that only study staff and Masimo study team members will have access to. Data will be retained for a minimum to 2 years following completion of the final analysis.

10.2 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.

10.3 Case Report Forms

The Sponsor shall provide a paper Case Report Form (CRF) template to the site. The site shall capture study data in the CRFs for each subject enrolled. The CRFs will be completed and signed by principal investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis. CRF entries and corrections will only be performed by study site staff, authorized by the investigator. Entries and corrections to the CRF will be made following Good Documentation Practices.

The CRF will include the following information, including but not limited to: inclusion / exclusion criteria, whether patient consent obtained before start of study, demographic information, device readings, and if occurrence of any adverse event, protocol deviation, and device deficiencies, etc. The CRF will be signed by the PI and forwarded to Masimo.

CRF entries will be checked by study monitor and any errors or inconsistencies will be queried to the site on an ongoing basis. Query resolution will be assessed and confirmed by study monitor during site visit.

10.4 Data Transfer and Storage

The information will be stored in a password protected electronic database at the study site. Device data along with an electronic copy of the CRF will periodically be securely uploaded to sponsor via secure portal. Only authorized sponsor personnel will have access to the transferred data, and will move it to a secure and backed-up drive at Masimo. Device data and electronic copy of CRFs will be checked for completeness. If there are inconsistent or missing data points, a data query log will be generated and submitted to the site for correction. If the investigator is to correct the CRF, the PI shall follow GDP practices to strike through old entry, add in new entry, and initial and date it, and resend the updated corrected CRF copy to Masimo. Once all queries have been resolved, Masimo engineers are notified that data is ready for analysis. To ensure data integrity, Masimo engineers will only have read access to data, therefore are unable to unintentionally tamper with the original data files. Raw and processed physiological data will be analyzed by Masimo Engineering team.

10.5 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.

11 MONITORING PLAN

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

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

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment.
- At least one monitoring visit during initial enrollment, and/or at least one visit 4-6 weeks after data collection is complete.
- A final close out visit after the last patient had finished the study.
- NOTE DURING COVID-19 PANDEMIC: on-site monitoring visits will be highly unlikely. Monitoring activities may be modified or postponed until such a time that restrictions prohibiting travel and hospital access are lifted.

11.3 The monitor will contact and visit the investigator and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other GCP-related documents (IRB approvals, IRB correspondences, and ICFs) provided that subject confidentiality is maintained in agreement with HIPAA regulations.

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

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

11.6 After each visit, the monitor will provide a monitoring follow-up letter to the investigator within 4 weeks of visit completion. The monitoring follow-up letter will detail findings and open action items observed during the visit. It is the responsibility of the Principal Investigator and Study Coordinator(s) to respond to the findings of the monitoring follow-up letter, and complete any open action items as soon as possible but no later than 60 days of receiving the monitoring report. Any open action items not completed within the time allowed may be sufficient grounds for study site suspension or termination; it will be up to the sponsor to determine whether any incomplete action items are sufficient grounds for suspension or termination. See Section 13 for details on suspension and termination.

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

12 VULNERABLE POPULATIONS

12.1 Definition

12.1.1 Vulnerable population are research participants, 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 may enroll economically or educationally disadvantaged subjects.

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

12.2 Protection of vulnerable subjects

- Reasonable compensation will be provided for economically disadvantaged subjects to eliminate possibility of undue influence due to financial incentive.
- Educationally disadvantaged subjects will be provided ample time to ask questions and comprehend information.
- 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.

12.3 Responsible Parties

- The EC/IRB will review research with vulnerable populations and evaluate consent, level of risk, coercion, and the reason for choosing this particular subject population. The EC/IRB will be responsible for determining what practices will include continuing review for compliance while monitoring these studies.
- The Investigator holds the ultimate responsibility for protecting the rights, safety, and welfare of research subjects by ensuring that all regulations and proper documentation of consent is handled in a compliant and timely manner.

13 ADMINISTRATIVE ASPECTS

13.1 Confidentiality

All data collected will be kept confidential and de-identified. It can only be accessed by researchers and will be used for research purposes only.

13.2 Protocol Amendments

Any changes made to the clinical investigational plan/study protocol will be documented by way of an amendment. Before submitting protocol amendment to the IRB, the protocol amendment must be agreed upon and signed by both the principal investigator and the sponsor. The protocol amendment will be submitted to the IRB for approval. At a minimum, a redline version and a clean version of the new protocol amendment will be kept on file by the PI and the sponsor. Protocol amendments will need to be version controlled. Both PI and sponsor will retain the IRB approval letter as confirmation that the protocol amendment was approved.

13.3 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 determine that the study site's compliance to be inadequate at any point during the study, and sponsor move to suspend or terminate the study site, the sponsor will provide notification in writing to the principal investigator and IRB as necessary. The study site is eligible for reinstatement upon correction of any findings and any open action items prior to the suspension, and provides a written guarantee that the same non-compliance will not reoccur in the future. Site can only resume patient 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.

13.4 Termination of Clinical Investigation/Study due to UADE

The clinical investigation may be terminated if sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the subjects. Termination shall occur not later than 5 working days after the sponsor makes this determination, and not later than 15 working days after the sponsor first received notice of the effect.

The sponsor may resume the terminated clinical investigation with prior IRB approval if the device is non-significant risk.

14 AGREEMENT BETWEEN INVESTIGATOR AND SPONSOR REGARDING RESPONSIBILITIES FOR GOOD CLINICAL PRACTICE

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

It specifies general requirements intended to:

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

The Principal Investigator of the clinical investigation shall:

- Obtain and maintain IRB approval of the study.
- Ensure all subjects are consented prior to enrollment, per FDA Code of Federal Regulations titled 21 CFR 50.
- Ensure only appropriately trained personnel will be involved in clinical investigation.
- Maintain study records mentioned in the CIP.
- 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 determining whether the study is safe to continue.
- Allow the sponsor to conduct periodic monitoring of study activities to ensure GCP compliance.
- Not promote device prior to clearance by FDA for commercial distribution, except for academic purposes and scientific presentations.

The Sponsor shall insure existence and record of all necessary compliance documents, and will conduct monitoring visits to ensure appropriate conduct of the study.

15 REVISION HISTORY:

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

16 REFERENCES

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