Official Title: Validation of the performance of the electrocardiogram (ECG) function of the INVSENSOR00057

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Clinical Investigation Title:	Validation of the performance of the electrocardiogram (ECG) function of the INVSENSOR00057
Clinical Investigation Number, Version:	[redacted]
Other Study Identifier:	[redacted]
Study Device(s):	Masimo INVSENSOR00057 – Investigational
Sponsor:	Masimo Corporation 52 Discovery Irvine, California 92618 USA

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1. INVESTIGATOR PAGE

Principal Investigator:

Investigation Site(s): Multicenter study at the following sites:

Address:

IRB: WCG IRB

Address: 1019 39th Avenue SE, Suite 120
Puyallup, Washington 98374

Agreement between Investigator and Sponsor Regarding Responsibilities for Good Clinical Practice

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

It specifies general requirements intended to:

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

The Principal Investigator of the clinical investigation shall:

- Obtain and maintain IRB approval of the study.
- Ensure all subjects are consented prior to enrollment, per FDA Code of Federal Regulations titled 21 CFR 50, unless the investigation is granted a waiver of consent by the IRB of record.
- Ensure only appropriately trained personnel will be involved in clinical investigation.
- Maintain study records mentioned in the Clinical Investigation Plan.
- Maintain logs for study team delegation, site visit/monitoring, equipment disposition, study team training, subject recruitment and enrollment.
- Evaluate all adverse events and adverse device effects and determine whether the study is safe to continue.
- Allow the sponsor to conduct periodic monitoring of study activities to ensure GCP compliance.
- Not promote non-FDA cleared devices prior to clearance by FDA for commercial distribution, except for academic purposes and scientific presentations.

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

The principal investigator's signature on this page constitutes the investigator's affirmation that he or she is qualified to conduct the clinical investigation, agreement to adhere to all stipulations of this clinical investigation plan, the conditions of the Institutional Review Board (IRB) or Research Ethics Committee (REC) approval, federal and local regulatory requirements, 21 CFR 812, ISO 14155, and International Conference on Harmonization Good Clinical Practice (ICH GCP) guidance.

Principal Investigator:	**Title:** [redacted]	**Signature:**	**Date:**
Sponsor Representative: [redacted]	**Title:** [redacted]	**Signature:**	**Date:**

2. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical investigation title:	Validation of the performance of the electrocardiogram (ECG) function of the INVSENSOR00057
Study objective(s):	The objective of this study is to validate the performance of the electrocardiogram (ECG) function of the Masimo INVSENSOR00057 against contemporaneous measurements from reference 12-lead ECG gold standard.
Study device(s):	Masimo devices: • Masimo INVSENSOR00057 – Investigational Comparators: • FDA-approved 12-lead electrocardiogram (ECG) electrodes and monitors Research Equipment: • Data collection research equipment (e.g., laptops, automated data collection software, data collection application, or comparable)
Number of subjects:	[redacted]

Inclusion criteria:	• Subject is 22 years of age or older.
	• Subject is comfortable to read and communicate in English*.
	• Subject belongs to one of the two groups:
	  ○ Subjects without prior arrhythmia diagnosis presenting in normal sinus rhythm (Group 1)
	  ○ Subjects with history of paroxysmal or persistent atrial fibrillation presenting in atrial fibrillation (Group 2).
	*This is to ensure the subject can provide informed consent (as Masimo INVSENSOR00057 ECG study materials are currently available in English only) and can comply with study procedures.

Exclusion criteria:	• Subjects who are physically unable to wear a wristwatch. • Subjects whose skin is not intact (e.g., has open wounds, has inflamed tattoos or piercings, has visible healing wounds) in or at the vicinity of the device placement site. • Subjects with an implantable defibrillator or cardiac pacing device. • Subjects with a skin condition which would preclude proper ECG electrode placement. • Subjects with known allergic reactions to adhesive tapes or ECG gel. • Subjects previously diagnosed with lethal cardiac arrhythmia, determined by the investigator. • Subjects not suitable for the investigation at the discretion of the investigator or the clinical team.

Groups and Randomization:	Two groups of normal sinus rhythm and atrial fibrillation, where subjects are assigned to each group based on the clinical interpretation of the reference 12-lead ECG results. To ensure equal representation of two groups, a targeted enrollment approach will be taken at enrollment sites, where subjects with no known arrythmia (normal sinus rhythm) will be recruited at Masimo Clinical Laboratory and subjects with known diagnosis of atrial fibrillation will be recruited at external sites. • NSR - Subjects with no arrhythmia (normal sinus rhythm) based on the clinical interpretation of the reference 12-lead ECG results. • AFib - Subjects with known diagnosis of atrial fibrillation based on the clinical interpretation of the reference 12-lead ECG results.
Duration of the clinical investigation:	The study is anticipated to require ~ 3 months to complete. Subject participation in the study will be approximately 30 minutes.
Study endpoint(s):	Primary: Evaluate the diagnostic performance of ECG rhythm classification and waveform characteristics. • Sensitivity and specificity of the automatic classification of atrial fibrillation (AFib) and normal sinus rhythm (NSR) by the single-lead ECG module of INVSENSOR00057 against clinical interpretation of a reference 12-lead ECG. • [redacted]

3. DESCRIPTION OF THE STUDY DEVICE

As a leader in hospital pulse oximetry, Masimo brings over 30 years of innovation and breakthrough advances in noninvasive blood parameter monitoring to miniaturize its monitoring technology and integrate it into a wristwatch. Masimo INVSENSOR00057 [redacted] offers accurate, continuous health data and actionable health insights in a personal, lifestyle-friendly wristwatch. Masimo INVSENSOR00057 provides a variety of physiological data for consumers wanting to make better informed health and lifestyle decisions, improve their fitness, or track their health data. These parameters include hydration index (Hi), oxygen saturation level (SpO_2), pulse rate (PR), pulse rate variability (PRV), respiration rate (RRp®), pleth variability index (PVi), perfusion index (Pi). Additionally, Masimo INVSENSOR00057 is equipped with an ECG module, which captures the electrical signals of the heartbeat and informs user of potential atrial fibrillation (AFib) and their heart rate (HR). This validation study pertains to the ECG module of the Masimo INVSENSOR00057.

As shown in Figure 1, the Masimo INVSENSOR00057 ECG

Figure 2).

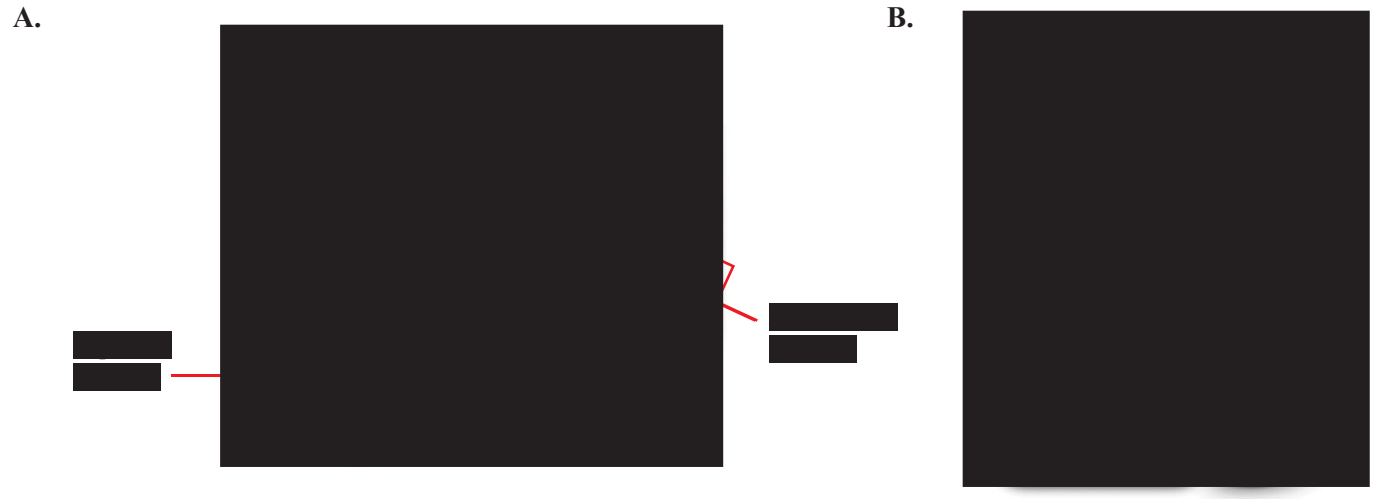

Figure 1. Overview of Masimo INVSENSOR00057. **A.** Front and Back view of Masimo INVSENSOR00057 **B.** Masimo INVSENSOR00057 can be paired with devices to provide users with important health data.

With each ECG spot check, Masimo INVSENSOR00057 provides the average heart rate, rhythm classification, and a description of the classification as detailed below.

INVSENSOR00057 Rhythm Classification:

- Normal Sinus Rhythm
  A Normal Sinus Rhythm ECG classification will indicate that ECG shows signs of a normal regular heartbeat with heart rates of 50 to 100 bpm. The ECG output of normal sinus rhythm only applies to the duration of the spot-check measurement and does not fully exclude cardiac arrhythmias. Subjects who are not feeling well should follow up with their healthcare provider.
- Atrial Fibrillation
  An atrial fibrillation ECG classification will indicate that ECG shows signs of irregular heartbeat. Atrial fibrillation is the most common pathologic cardiac arrhythmia. Masimo INVSENSOR00057 can detect signs of atrial fibrillation between heart rates of 50 to 150 bpm. Atrial fibrillation can often be accompanied by a rapid heart rate. Subjects who have not been previously diagnosed with atrial fibrillation and consistently receive this result or subjects who are not feeling well should consult with their healthcare provider. The resulting output does not guarantee the presence or absence of atrial fibrillation or other arrhythmias.
- Inconclusive
  An Inconclusive ECG classification indicates that the ECG recording could not be classified, which may be due to a number of reasons such as other arrhythmias, pacing, or heart conditions that Masimo INVSENSOR00057

is not designed to detect. It is recommended to repeat the measurement in a few minutes for subjects who get this result. An inconclusive classification does not indicate the presence or absence of any arrhythmias (including AFib) or other heart conditions. Subjects who consistently receive this result should follow up with their healthcare provider, particularly if they are feeling unwell.

- Noise
  This classification of the ECG means the ECG waveform quality and performance were compromised and the device cannot report any measurements from the ECG.

INVSENSOR00057 Heart Rate Classification:

- Low Heart Rate
  A low heart rate ECG classification will indicate a heart rate lower than 50 bpm, which can be commonly due to benign causes such as certain medication effects, or a normal finding during rest in particular among well-conditioned athletes or other cardiovascularly-fit individuals. However, subjects who are not feeling well should follow up with their healthcare provider as sometimes very low heart rates can indicate an underlying cardiovascular condition.
- High Heart Rate
  A high heart rate ECG classification will indicate heart rates greater than 100 bpm, which can be due to exercise, stress, the presence of cardiac arrhythmia, or consumption of alcohol, stimulants or caffeinated drinks. Subjects who are not feeling well should follow up with their healthcare provider.

4. JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN PLAN

Approximately 60 million individuals worldwide suffer from atrial fibrillation, which is the most common type of cardiac arrhythmia.[1] Patients with atrial fibrillation have approximately a 4-fold increased risk of mortality compared to the general population.[3] In addition to increased risk of death, atrial fibrillation also increases the risk of heart failure and stroke. The imminent risks of stroke can be mitigated with prompt administration of anticoagulants, which relies on timely diagnosis of atrial fibrillation.[4, 5]

Certain populations are more vulnerable to atrial fibrillation than others; studies have indicated that risk factors for increased risk include older age, sedentary lifestyle, obesity, diabetes mellitus, thyroid disease, obstructive sleep apnea, hypertension, myocardial infarction, heart failure, smoking, and alcohol. [2, 6] Detecting atrial fibrillation in its early stages can significantly reduce the high disability and mortality rate. A study reviewing the prevalence of atrial fibrillation in 2009 estimated that 700,000 cases were undetected, comprising 13.1% of all cases; half of these projected cases of undiagnosed atrial fibrillation were at increased susceptibility to stroke.[7]

The standard for diagnosis of atrial fibrillation is use of an electrocardiogram (ECG); advancement of this technology, especially via wearable technology, for early detection can improve the prognosis for patients and enable them to seek medical care before the arrhythmia progresses into more adverse complications. Prior studies have demonstrated usability and performance of wrist-wearable ECG spot check devices in the detection of atrial fibrillation.[8] This study is designed to validate the performance of Masimo INVSENSOR00057 ECG module in detecting atrial fibrillation in adults with persistent or paroxysmal atrial fibrillation who are in atrial fibrillation.

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

5.1. Anticipated Clinical Benefits

There will be no direct benefit to the enrolled subjects. This is a validation study to support regulatory submission for a new wrist-wearable ECG technology, which may enable users to identify potential life-threatening conditions more appropriately.

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. There is a risk of temporary discomfort to subjects at placement locations, including temporary skin irritation. If the device is worn too tight around the wrist, there is potential for a pressure injury. 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.

5.2.2. Risks Associated with Participation in the Clinical Investigation

5.2.3. Risks Associated with Placement of FDA-cleared 12-lead ECG Electrodes

Subjects may be asked to use an alcohol pad or fingertip abrasive pad on application sites of the FDA-cleared 12-lead ECG electrodes to allow the electrodes to adhere to the skin. Risks associated with skin preparation include cuts and/or abrasions, rash, itching skin, flushing or redness of the skin, unusually warm skin, skin inflammation, and/or skin irritation. Each of these discomforts are temporary and should fade over time.

Subjects may also be asked to shave the site of application of the FDA-cleared 12-lead ECG electrodes application to allow the sensors to adhere to the skin. Risks associated with shaving include cuts and/or abrasions, bleeding, infection, razor burn, rash, itching skin, flushing or redness of the skin, unusually warm skin, skin inflammation, skin irritation, ingrown hairs, and/or inflamed hair follicles. While some of these symptoms may last up to several days after shaving, discomforts are temporary and should fade over time. Subjects have the option to decline shaving the electrode application sites in the informed consent. Moreover, subjects can stop these measures at any time if they feel uncomfortable.

5.2.4. Risks from Inflicted Knowledge

The risk of inflicted knowledge will be reduced by assuring the subjects that device readings are for research use only. In the case that a subject becomes aware of a condition (arrhythmia, etc.) during the study, study staff will recommend that they contact their primary care physician, and will document this recommendation.

5.2.5. Risks Associated with Study Data

The other main risk associated with the study is a potential breach of confidentiality which will be minimized by limiting the collection of protected health information (PHI) and through secure data storage practices.

6. OBJECTIVES OF THE CLINICAL INVESTIGATION

The objective of this study is to validate the performance of the ECG function of the Masimo INVSENSOR00057 against contemporaneous measurements from reference 12-lead ECG gold standard. Study endpoints are as follows:

Primary: Evaluate the performance of ECG rhythm classification and waveform characteristics.

- Sensitivity and specificity of the automatic classification of atrial fibrillation (AFib) and normal sinus rhythm (NSR) by the single-lead ECG module of INVSENSOR00057 against clinical interpretation of reference 12-lead ECG.

[redacted]

7. DESIGN OF THE CLINICAL INVESTIGATION

7.1. General

This is a prospective validation study of Masimo INVSENSOR00057 ECG function (see *Appendix I* for a study workflow) in a mix of subjects with and without a diagnosis of AFib. Enrolled subjects will receive [redacted] on Masimo INVSENSOR00057. [redacted]. Clinician interpretation of reference 12-lead ECG classification will be used in classifying subjects to rhythm cohorts and establish the basis for analysis of subject data with respect to study endpoints.

7.2. Investigation Site(s)

[redacted]

[redacted]			

[redacted]

7.3. Definition of Completion of the Clinical Investigation

The study will be considered complete when quality data from [redacted] subjects have been collected and evaluated.

7.4. Study Device(s)

Masimo devices:

- Masimo INVSENSOR00057 – Investigational

Comparators:

- FDA-approved 12-lead electrocardiogram (ECG) electrodes and monitors

Research Equipment:

Data collection research equipment [redacted]

7.5. Subjects

7.5.1. Inclusion Criteria

- Subject is 22 years of age or older.
- Subject is comfortable to read and communicate in English*.
- Subject belongs to one of the two groups:
    - Subjects without prior arrhythmia diagnosis presenting in normal sinus rhythm (Group 1)
    - Subjections with history of paroxysmal or persistent atrial fibrillation presenting in atrial fibrillation (Group 2).

*This is to ensure the subject can provide informed consent (as Masimo INVSENSOR00057 ECG study materials are currently available in English only) and can comply with study procedures.

7.5.2. Exclusion Criteria

- Subjects who are physically unable to wear a wristwatch.
- Subjects whose skin is not intact (e.g., has open wounds, has inflamed tattoos or piercings, has visible healing wounds) in or at the vicinity of the device placement site.
- Subjects with an implantable defibrillator or cardiac pacing device.
- Subjects with a skin condition which would preclude proper ECG electrode placement.
- Subjects with known allergic reactions to adhesive tapes or ECG gel.
- Subjects previously diagnosed with lethal cardiac arrhythmia, determined by the investigator.
- Subjects not suitable for the investigation at the discretion of the investigator or the clinical team.

7.5.3. Number of Subjects

[redacted]

7.5.4. Subject Classifications

Subjects will be classified according to the criteria below:

- **Screened** – Subjects who are assessed for study eligibility.
- **Enrolled** – Subjects who have met all the inclusion criteria, do not meet any exclusion criteria, and have been assigned a subject identification number.
- **Screen Failure** – Subjects who do not meet all the eligibility criteria. (Reason for the subject's ineligibility will be documented on a *Screening and Enrollment Log*).
- **Withdrawn** – Subjects who do not complete the study due to reasons listed below:
  - Subject voluntarily opts not to participate.
  - Subject was discontinued from study at the discretion of the clinical team.
- **Completed** – Subjects with a completed simultaneous ECG measurement using Masimo INVSENSOR00057 and interpretable 12-lead reference ECG.

7.5.5. Study Duration

The study is anticipated to require ~ 3 months to complete. Subject participation in the study will be approximately 30 minutes.

7.6. Study Procedures

7.6.1. Subject Recruitment and Pre-screening

Subjects with no known arrythmia (normal sinus rhythm) will be recruited at [redacted] and subjects with known diagnosis of atrial fibrillation will be recruited at external sites from medical clinics or cardiology offices. Subjects in the AFib cohort may have paroxysmal, persistent, or permanent forms of AFib, and will be determined by the referring cardiologist to be in atrial fibrillation at the time of routine office visit.

7.6.2. Informed Consent and Screening

Following the identification of a potential eligible subject as defined by the inclusion and exclusion criteria, the subject 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. The research team will emphasize that participation is voluntary and declining participation in the study will not result in any penalty or loss of benefits that the subject is otherwise entitled.

Once the subject's questions have been answered and the consent documents are signed and dated, the Principal Investigator or delegate will also sign the informed consent documents, approving the subject to be enrolled in the study. The investigator shall retain the original copy of the signed informed consent documents in each subject's records and provide a copy to the subject. No study related activities shall be conducted until the consent form is signed.

Subjects will be screened to determine eligibility for study enrollment. 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, medical history including comorbidities and concurrent medications will be collected (see *Appendix II*).

7.6.3. Study Procedures

7.6.3.1. ECG Measurements

The Masimo INVSENSOR00057 placed on the wrist according to the *Investigator Brochure (IB)*. Site staff will check proper application of wrist strap. Next, the reference 12-lead ECG electrodes will be placed. INVSENSOR00057 will be paired via Bluetooth connection [redacted]

The subjects will be provided with assistance with INVSENSOR00057placement according to the user manual [redacted] Once the subject is familiarized with the device, study measurement commences.

[redacted]

The on-site trained research personnel will confirm the ECG recordings are of diagnostic quality prior to removing the electrodes. At the conclusion of the procedure, the 12-lead ECG electrodes and INVSENSOR00057 will be removed.

7.6.3.2. Data Analysis

The digital pdf ECG data will be downloaded and provided to Masimo. Three independent board-certified cardiologists will be tasked with rhythm classification and [redacted]

7.7. Monitoring Plan

Oversight for this clinical trial is provided by the sponsor, investigators, and IRB.

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

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

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment,
- At least one monitoring visit during initial enrollment, and/or every 2-3 months thereafter.
- A final close out visit after the last subject had finished the study.

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

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

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

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

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

8. STATISTICAL DESIGN AND ANALYSIS

The study objective is to evaluate the performance of the INVSENSOR00057 rhythm classification and waveform characteristics relative to a 12-lead ECG. The INVSENSOR00057 evaluates a 30 second duration, single lead, ECG waveform measurement. One of four possible outcomes for each measurement per Table 8a.

Outcome	Description
AFib	Waveform is classified as atrial fibrillation
NSR	Waveform is classified as Normal Sinus Rhythm
Inconclusive	INVSENSOR00057 cannot determine the rhythm classification
Noise	INVSENSOR00057 has determined that the waveform is too noisy and does not represent a physiological signal

Data from subjects where reference 12-lead ECG did not provide readable ECG waveforms (as assessed by medical personnel) will be excluded from the primary analysis.

8.1. Classification Accuracy Calculations

8.1.1. Data Analysis

Classification accuracy will be measured on all measurements where both the INVSENSOR00057 and the 12-lead reference ECG provided a classification of either AFib or NSR. (This incidence rate of Inconclusive and Noise outcomes on the INVSENSOR00057 will be evaluated separately.) Sensitivity is the probability that the diagnostic test is positive for the disease, given that the subject actually has AFib, while specificity is the probability that the diagnostic test is negative, given that the subject does not have AFib (or conversely, has NSR).

8.1.2. Sample Size Justification

Sample size was determined to meet simultaneous requirements for both sensitivity and specificity analysis. The PASS 2019[1] software package was used to calculate the appropriate sample size using the "Confidence Intervals for One-Sample Sensitivity and Specificity" module. [redacted]

[1] PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

[redacted]

8.3. Methodology for evaluating the accuracy of heart rate measurements

8.3.1. Data Analysis

Statistical analysis will be used to estimate the agreement between INVSENSOR00057 heart rate output and the reference 12-lead ECG. Bias, precision, and accuracy (ARMS) will be calculated per equations 8-10 below.

$$(8) \qquad Bias\ (mean\ difference) = \frac{1}{N}\sum_{i=1}^{N} TestHR_i - RefHR_i$$

$$(9) \qquad Precision = \sqrt{\frac{\sum_{i=1}^{N}((TestHR_i - RefHR_i) - Bias)^2}{N}}$$

$$(10) \qquad Arms\ (accuracy) = \sqrt{\frac{\sum_{i=1}^{N}(TestHR_i - RefHR_i)^2}{N}},\ Arms = \sqrt{Bias^2 + Precision^2}$$

where N is the total number of measurements and i is a single measurement

8.3.1.1. Data Exclusion Criteria

Points where the reference 12-lead ECG does not provide any HR measurements will be excluded. Rate of data exclusion for reference and test ECG will be reported.

8.3.2. Sample size

It is not possible to control the subject heart rate during this study, so it is not possible to validate the entire range of heart rate [redacted] Further, the heart rate of Afib patients is ill defined, so a comparison in this cohort is not possible.
Therefore, the data collected in this study for the NSR cohort only will be used as a convenience sample of the INVSENSOR00057 heart rate output.

8.3.3. Acceptance Criteria

$A_{RMSE} \leq 5$ bpm over the clinical range found in the normal sinus rhythm cohort.

The INVSENSOR00057 full range of [redacted] is validated separately using ECG simulators.

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 CRFs are to be completed on an ongoing (weekly) basis. CRF entries and corrections will only be performed by study site staff, authorized by the investigator. For paper CRFs, entries and corrections to the CRF will be made following good documentation practices (GDP).

The CRF may include the following information, including but not limited to: inclusion/exclusion criteria, demographic information, co-morbidities, device readings, occurrence of any adverse events and protocol deviation, and device deficiencies, if any. The CRFs will be signed by the PI or delegate to attest that the data are complete and accurate.

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

9.4. Data Transfer and Storage

Original paper CRFs will be stored in a secure location at the site. Copy of the original paper CRFs may be scanned and sent to sponsor. If using electronic CRFs, the site staff will be assigned unique usernames and passwords for data security. Final copies of the electronic CRFs in EDC are stored on a secure server.

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

CRFs will be checked for completeness and if there are inconsistent or missing data points, queries will be generated. If delegated study staff are to correct the paper CRF, they shall follow GDP practices to strike through old entry, add in new entry, initial and date it, and provide the corrected information to sponsor. Corrections made to electronic CRFs will be tracked by audit trail and require PI or delegate sign-off.

9.5. Record Retention

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

10. AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

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

11. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Deviations from the protocol must receive both sponsor and the investigator's IRB/ethics committee approval before they are initiated, with the exception that under emergency circumstances, deviations from the *Clinical Investigation Plan* to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor or the IRB/ethics committee.

Any protocol deviations initiated without sponsor and the investigator's IRB/ethics committee approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be documented and reported to the sponsor and to the investigator's IRB/ethics committee as soon as a possible, but no later than 5 working days after the occurrence of the protocol deviation. In addition to documenting deviations on the CRF, the *Protocol Deviation Form* may also be used. If protocol deviations continue to occur frequently at a study site, a corrective and preventive action (CAPA) may be opened by the sponsor.

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

12. DEVICE ACCOUNTABILITY

12.1. Receipt of Study Device

Upon receipt of the study device supplies, an inventory must be performed and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

12.2. Use of Study Device

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

12.3. Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices shipped, devices used, and devices remaining. This reconciliation will be logged on the device accountability log. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed onsite will only be upon written instruction from the sponsor and will be documented in the study files. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the sponsor in a timely manner.

13. STATEMENTS OF COMPLIANCE

This document is a clinical investigational plan for a human research study sponsored by Masimo Corporation. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. By participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of the IRB or Research Ethics Committee approval, federal and local regulatory requirements, 21 CFR 812, ISO-14155, ICH GCP guidance.

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

14. INFORMED CONSENT PROCESS

See subsection on Informed Consent under *Study Procedures*.

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

15.1. Definitions

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

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

- 1) a life-threatening illness or injury, or
- 2) a permanent impairment of a body structure or a body function including chronic diseases, or
- 3) in-subject or prolonged hospitalization, or
- 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

- c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the *Clinical Investigation Plan*, without serious deterioration in health, is not considered a serious adverse event.

- serious health threat: signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

  Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

- serious adverse device effect: adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

- unanticipated serious adverse device effect: serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

  Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

- device deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance

  Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

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

15.2. List of Anticipated Adverse Events

15.2.1. Anticipated Device-Related Adverse Events

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

Refer to section 5.2. for the description of anticipated events.

15.2.2. List of Non-Reportable Adverse Events

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

15.3. Adverse Event Reporting

- All adverse events, both anticipated and unanticipated, must be recorded in the CRF and in the *Adverse Event Report Form*.
- All adverse events must be promptly reported to the sponsor.
- All unanticipated adverse device effects will be also reported to both the sponsor and the IRB.
- Both serious adverse events and unanticipated adverse device effects must be reported to the sponsor within 48 hours. All other adverse events should be reported to the sponsor within five business days.
- All serious adverse events will be also reported to the IRB per IRB reporting requirements. These reports may include, but will not be limited to: date of onset, brief description of the events, their treatment, whether they resulted in death, subject hospitalization, severe or permanent disability or were life threatening, their relationship to the study device, and resolution.

15.4. Device Deficiencies Reporting

All Masimo device-related deficiencies should be reported to the sponsor and must be recorded in the CRF in a timely manner. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the sponsor in a timely manner.

16. VULNERABLE POPULATION

16.1. Definition

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

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

16.2. Protection of Vulnerable Subjects

- Not applicable as study follows standard of care procedures.

16.3. Responsible Parties

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

17. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

17.1. Suspension or Termination of Study Site

The sponsor can suspend or prematurely terminate the PI's and study site's participation in the study, particularly if sponsor finds serious non-compliance by the PI or site, and if such non-compliance was not resolved in a timely manner. The sponsor will document the decision to suspend or terminate the investigation in writing. A suspended study site cannot enroll new subjects.

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

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

17.2. Termination of Clinical Investigation/Study due to UADE

The clinical investigation may be terminated if the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the subjects. Termination shall occur no later than five working days after the sponsor makes this determination, and not later than 15 working days after the sponsor first received notice of the effect.

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

18. PUBLICATION POLICY

In compliance with 42 CFR Part 11, a study that meets the definition of an Applicable Clinical Trial (ACT) and that is initiated after September 27, 2007 must be registered on ClinicalTrials.gov. Results of this clinical investigation will be made publicly available on the ClinicalTrials.gov website.

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20. REVISION HISTORY

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21. APPENDICES

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21.2. Appendix II: Schedule of Events

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