CLINIMARK Clinical Investigation Plan
BORA Band SpO2 Validation Study
PR 2018-312

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STUDY PROCEDURE:

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CONFIDENTIALITY:

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Synopsis

Introduction

The clinical use of pulse oximeters has reduced the frequency and necessity of invasive arterial blood sampling and has helped to improve patient safety by providing continuous information to clinicians about patients' oxygenation status.

BiOSENCY is dedicated to developing and applying innovative electronic medical solutions that improve clinical workflow and enhance patient care. The BORA BAND™ wristband Pulse Oximeter is to be used in continuous applications for monitoring oxygen saturation.

Objectives of the Clinical Investigation Plan

The purpose of this clinical study is to validate the SpO_2 accuracy of the BiOSENCY BORA BAND™ wristband Pulse Oximeter during non-motion conditions over the range of 70-100% SaO_2 as compared to arterial blood samples assessed by CO-Oximetry. The end goal is to provide supporting documentation for the SpO_2 accuracy validation of BORA BAND™ wristband Pulse Oximeter.

It is required that the Accuracy Root Mean Square (A_{RMS}) performance of the BORA BAND™ wristband Pulse Oximeter will meet a specification of 3.5 or better in non-motion conditions for the range of 70 – 100% SpO_2 thereby demonstrating an acceptable SpO_2 accuracy performance specification.

Background

Pulse oximetry monitoring is considered a standard physiological measurement and is used by clinicians in everyday situations to estimate arterial oxygen saturation. In general, pulse oximeters use two-wavelength absorption spectrophotometry to measure oxygen saturation. The wavelengths are selected to provide the best separation of absorbencies of oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (RHb) states. The ratio of the two absorbencies is used to calculate the oxygen saturation (SpO_2) value. Because an arterial sample of blood is not required to make the measurement, the pulse oximeter can provide continuous non-invasive real time information. The clinical use of pulse oximeters has reduced the frequency and necessity of invasive arterial blood sampling and has helped to improve patient safety by providing continuous information to clinicians about patients' oxygenation status.

The BiOSENCY BORA BAND™ wristband Pulse Oximeter studied under this protocol will be investigational. All appropriate pre-clinical testing on the BiOSENCY BORA BAND™ wristband Pulse Oximeter system has been successfully performed and demonstrates safety and efficacy for use in human studies prior to Clinimark's receipt of the devices.

Summary Overview

The SpO_2 accuracy performance of BiOSENCY BORA BAND™ wristband Pulse Oximeter will be evaluated during non-motion conditions over the range of 70-100% SaO_2 and compared to arterial blood samples assessed by CO-Oximetry. A minimum of 10 healthy adult male and female subjects, ranging in age and pigmentation from light to dark, will be enrolled in the study to meet the study design requirements defined by ISO 80601-2-61:2017 and by the FDA's Guidance for Pulse Oximeters (March 4, 2013). The

subjects will have an arterial catheter placed in the radial artery to allow for simultaneous blood samples during stable plateaus of induced hypoxic levels. The investigational device will be placed on the wrist opposite for the test per the instructions for use. Simultaneous data collection will be set up for the system under test and control oximeter.

For the data analysis, the control oximeter will be used to assess the stability of each data point. Data that is found to be unstable will be removed prior to the comparative analysis. Data that is determined to be too low of perfusion will be removed. The CO-Oximeter data will be reviewed to make sure it does not contain any anomalous values such as elevated, low or inconsistent COHb, MetHb, or tHb data. Anomalous values will be removed from the analysis prior to pairing of the SpO_2 and SaO_2 data. The statistical analysis is performed on a minimum of 200 data points collected from at least 10 subjects for the range of 70% to 100% SaO_2 with allowance of ± 3% of the target range. Functional SaO_2 as measured by Reference CO-Oximetry will be used as the basis for comparison. The Accuracy Root Mean Square (A_{RMS}) calculation is used to determine the SpO_2 accuracy performance. Success will be achieved with an A_{RMS} of 3.5 or better showing equivalence to the Gold Standard Reference CO-Oximetry providing documentation to support SpO_2 accuracy claims for the investigational device.

The study population will include 10-15 healthy non-smoking (or has refrained from smoking for 2 days) competent adults, 18-50 years of age. The subject selection will be an equitable distribution of males and females of any race with varying skin tones including at least 2 darkly pigmented subjects or 15% of the subject pool, whichever is larger. The subjects must understand the study and consent to participate by signing the Informed Consent Form. The subjects must be healthy showing no evidence of medical problems as indicated by satisfactorily completing the health assessment form.

Inclusion Criteria

- 10-15 Adults with a minimum of 3 males and a minimum of 3 females, with the balance made up of either
- Subject must have the ability to understand and provide written informed consent
- Subject is 18 to 50 years of age
- Subject must be willing and able to comply with study procedures and duration
- Subject is a non-smoker or who has not smoked within 2 days prior to the study
- Wrist size should be between 15-23 cm (5.9 – 9 inches)

Exclusion Criteria

- Subject is considered as being morbidly obese (defined as BMI >39.5)
- Compromised circulation, injury, or physical malformation of fingers, wrist, hands, ears or forehead/skull or other sensor sites which would limit the ability to test sites needed for the study. (Note: Certain malformations may still allow subjects to participate if the condition is noted and would not affect the particular sites utilized.)
- Female subjects that are actively trying to get pregnant or are pregnant (confirmed by positive urine pregnancy test unless the subject is known to be not of child-bearing potential).
- Smoker Subjects who have refrained will be screened for COHb levels >3% as assessed with a Masimo Radical 7 (Rainbow)
- Subjects with known respiratory conditions such as: (self-reported)
    - uncontrolled / severe asthma,

- flu,
- pneumonia / bronchitis,
- shortness of breath / respiratory distress,
- unresolved respiratory or lung surgery with continued indications of health issues ,
- emphysema, COPD, lung disease

- Subjects with known heart or cardiovascular conditions such as: (self-reported, except for blood pressure and ECG review)
  - hypertension: systolic >140mmHg, Diastolic >90mmHg on 3 consecutive readings (reviewed during health screen).
  - have had cardiovascular surgery
  - Chest pain (angina)
  - heart rhythms other than a normal sinus rhythm or with respiratory sinus arrhythmia (reviewed during health screen)
  - previous heart attack
  - blocked artery
  - unexplained shortness of breath
  - congestive heart failure (CHF)
  - history of stroke
  - transient ischemic attack
  - carotid artery disease
  - myocardial ischemia
  - myocardial infarction
  - cardiomyopathy
- Self-reported health conditions as identified in the Health Assessment Form (self-reported)
  - diabetes,
  - uncontrolled thyroid disease,
  - kidney disease / chronic renal impairment,
  - history of seizures (except childhood febrile seizures),
  - epilepsy,
  - history of unexplained syncope,
  - recent history of frequent migraine headaches,
  - recent symptomatic head injury (within the last 2 months)
  - cancer / chemotherapy
- Subjects with known clotting disorders (self-reported)
  - history of bleeding disorders or personal history of prolonged bleeding from injury
  - history of blood clots
  - hemophilia
  - current use of blood thinner: prescription or daily use of aspirin
- Subjects with severe contact allergies to standard adhesives, latex or other materials found in pulse oximetry sensors, ECG electrodes, respiration monitor electrodes or other medical sensors (self-reported)
- Subjects with severe allergies to iodine (only applicable if iodine is used)
- Subjects with severe allergies to lidocaine (or similar pharmacological agents, e.g. Novocaine)
- Failure of the Perfusion Index Ulnar/Ulnar+Radial Ratio test (Ratio < 0.4)
- Unwillingness or inability to remove colored nail polish from test digits.

- Other known health condition, should be considered upon disclosure in health assessment form
- Wrist size should be between 15-23 cm (5.9 – 9 inches)

Data collection will occur over a 3-5 day period for this study population. Follow-up with each subject will be conducted within 5 days following participation in the study and will be conducted via telephone, text or email.

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Objectives of the Clinical Investigation Plan

The purpose of this clinical study is to validate the SpO_2 accuracy of the BiOSENCY BORA BAND™ wristband Pulse Oximeter during non-motion conditions over the range of 70-100% SaO_2 as compared to arterial blood samples assessed by CO-Oximetry. The end goal is to provide supporting documentation for the SpO_2 accuracy validation of the BiOSENCY BORA BAND™ pulse oximetry.

It is required that the Accuracy Root Mean Square (A_{RMS}) performance of the BiOSENCY BORA BAND™ pulse oximetry will meet a specification of 3.5 or better in non-motion conditions for the range of 70 – 100% SaO_2 thereby demonstrating an acceptable SpO_2 accuracy performance specification.

Identification and Description of the Investigational Device

An oximeter is a device used to transmit radiation at a known wavelength(s) through blood and to measure the blood oxygen saturation based on the amount of reflected or scattered radiation. Pulse oximetry monitoring is considered a standard physiological measurement and is used by clinicians in everyday situations to estimate arterial oxygen saturation. Because an arterial sample of blood is not required to make the measurement, the pulse oximeter can provide non-invasive real time information. The clinical use of pulse oximeters has reduced the frequency and necessity of invasive arterial blood sampling, and has helped to improve patient safety by providing continuous information to clinicians about patients' oxygenation status.

The BiOSENCY BORA Band is a wearable multi-parameter medical monitoring system, composed of a sensor head mounted on a wearable wristwatch-like module. Pulse oximetry data are produced by a reflective photoemitter/detector element which acquires data from the wrist.

The device under test will be connected over Bluetooth Low Energy to a mobile and/or PC application that will be in charge of collecting data over the air continuously during the hypoxia protocol. Collected data will include:

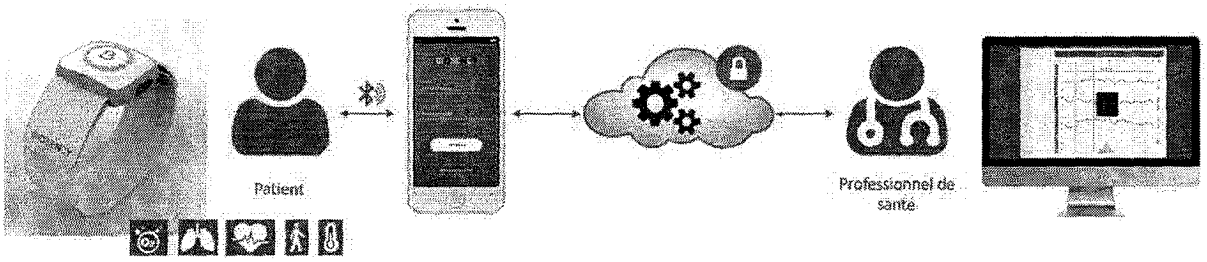
- Measured Heart Rate
- Measured Ratio of Ratios and/or SpO2 value
- Raw data coming from the sensor including PPG signal stored for offline process
  The accompanying acquisition software will be provided by BiOSENCY.

Intended Use:
The BORA BAND™ wristband Pulse Oximeter is indicated for the noninvasive spot checking of:

- functional oxygen saturation of arterial hemoglobin (%SpO2),
- pulse rate (PR),
- respiratory rate (RR),
- and a peripheral temperature differential (ΔT°C).

The BORA BAND™ wristband Pulse Oximeter is indicated for use with adult patients during both rest and motion conditions, and for patients who are well perfused. The intended use environment are home environment, outdoor environment and medical facilities. The BORA BAND™ is suitable in a hospital environment only in rehabilitation center or long-stay institution. The BORA BAND™ is not suitable for

emergency unit or intensive care unit (the BORA BAND™ does not provide alarms).
This study will focus on the pulse oximetry, SpO_2 parameter under non-motion conditions.



The BORA BAND™ wristband Pulse Oximeter is investigational and has not been cleared by the FDA.

Device model numbers, software version, serial numbers, date(s) of use, subject ID number(s) will be recorded on the Case Report Forms.

The manufacturer of the investigational device followed the good manufacturing practice regulation of 21 CFR 820 as appropriate.

The oximeter is under investigation for the continuous non-invasive monitoring of oxygen saturation (SpO_2) over a wide range of normal to hypoxic levels for subjects who are well perfused.

All appropriate pre-clinical testing on the BORA BAND™ wristband Pulse Oximeter has been successfully performed and demonstrates safety and efficacy for use in human studies prior to Clinimark's receipt of the devices. Such documentation resides in the Design History Files at BiOSENCY. Documentation will be provided regarding the safety of the investigational device for electrical current leakage, dielectric strength, surface temperatures and biocompatibility testing. The sensors are expected to come in contact with the subjects.

Instructions for installation, use, storage, and handling can be found the Device Operator's Manual. Device model number, software / firmware version, serial numbers, date(s) of use, subject ID number(s) will be recorded in the study documentation.

The Clinimark staff is familiar with the use of pulse oximeters and their application. Training by the sponsor will be provided as needed.

Data Acquisition System for the Investigational Device

The data from the investigational devices will be collected by the sponsor separate from the Clinimark automated data collection system.

Desaturation Gas Delivery System

The Clinimark proprietary Desaturation Fixture with Automated Data Collection is a single limb blow by system used to deliver medical grade oxygen and nitrogen gas mixtures to induce various hypoxic levels in subjects at a slow steady rate allowing an automatic marking and collection of the Control

or secondary transfer reference pulse oximeter and other pulse oximetry systems at 1 second intervals.

Description of Clinimark Desaturation Fixture with Automated Data Collection:

- Computer with desaturation gas control software and automated data collection system
- Sealink Mux box – 8 channel, communication cables
- Gas control fixture
- Medical grade oxygen and nitrogen cylinders

Control Oximetry System

The Control Pulse Oximeter, an FDA cleared device, is used to monitor the oxygen saturation levels real time throughout the study for subject safety and to target stable plateaus. This device is used to assess the stability of the data.

- GE Healthcare (Datex-Ohmeda) 3900 TruTrak+ / OxyTip+ Oxy-F-UN Sensor and Oxy-OL3 cable
- Covidien Nellcor N-600x with MaxFast Forehead and DS100A Finger sensor and DOC-10 cable additional stability monitor.
- Nonin 3150 pulse oximeter / sensor (optional)
- Masimo Mightysat (optional)

Safety Equipment

Multi-parameter monitor used during the study to observe a subject's vital signs including ECG tracing, heart rate, respiratory rate, end-tidal CO_2 with capnograph, secondary monitor for the oxygen concentration being delivered to the subject. This device will also serve as the pulse rate reference for additional pulse rate performance documentation.

- GE Healthcare S5 Compact Monitor, M-NESTPR module with ECG
- Portable oxygen tank, mask and ambu bag
- Blood pressure cuff and stethoscope

Breathing Apparatus for Subject

The breathing apparatus sits over the subject's nose and mouth and is held in place by a four-tailed head strap and connected to a gas mixer and O_2 analyzer as well as the patient monitor. The breathing apparatus consists of the following (or similar) components.

- air cushion breathing mask with hook ring
- gas sampling adapter
- tee connector
- CO_2 sampling line: connected to the patient monitor for respiratory rate, $ETCO_2$ and capnograph.

Arterial Syringes

Arterial Blood Sample Syringe with Dry Lithium Heparin for Gases and Electrolytes

- Portex 3ml Pro-Vent

Reference CO-Oximeters

A whole blood analyzer (CO-Oximeter) is used as the reference standard device for obtaining the functional SaO_2 value from arterial blood samples obtained during the study.

- Radiometer ABL 80 Flex OSM and associated supplies ID#: 302125, 306173, 307205, 313093, 313102 or equivalent (utilizing Radiometer and / or IL682 calibration)

Preliminary Investigations and Justifications of the Study

BiOSENCY is dedicated to developing and applying innovative electronic medical solutions that improve patient care in multiple clinical settings.

As part of the product development, BiOSENCY retained the services of Clinimark, LLC to conduct an oxygen saturation (SpO_2) accuracy study comparing the BiOSENCY BORA BAND™ wristband Pulse Oximeter to a Clinimark Transfer Standard reference system(s) previously correlated to arterial blood CO-Oximetry during non-motion conditions over the range of 70-100% SpO_2. " BORA Band SpO2 Calibration Verfication Study, Clinimark Study ID# PR 2018-316.

The study was conducted January 22-24, 2019. The data was analyzed by the sponsor and determined positive results were achieved for the development phase.

In review of the literature, the FDA Guidance Document for Pulse Oximeters and ISO 80601-2-61 clearly define the accepted guidelines for evaluation and documenting the SpO_2 accuracy in humans. See the Reference Documents section below.

Risks and Benefits of the Investigational Device and Clinical Investigation

Currently the FDA defines pulse oximeters as Class II devices which transmit radiation at a known wavelength(s) through blood and to measure the blood oxygen saturation based on the amount of reflected or scattered radiation and may be used alone or in conjunction with a fiberoptic oximeter catheter. Oximeters being used in this study work by transmittance and reflectance of radiation at known wavelength(s) through tissue to measure blood oxygen saturation based on the amount of reflected and scattered radiation. **The devices under test and this study procedure are considered Non-Significant Risk (NSR).**

The device and use of the device under test does not meet the definition of significant risk device under 21 CFR 812.3(m)

For the purpose of this study:

- It is not intended as an implant.
  - Pulse oximetry sensors are applied to the surface of the site (such as forehead, wrist and fingers) and is removed following data collection, less than 1 day.
  - Sensors may be warm to the touch but are not expected to overheat during normal operations
  - The control pulse oximetry system and BiOSENCY BORA BAND™ investigational device include clip on sensors, reusable sensors, wrist worn sensor with strap, and the forehead headband which may exert a small amount of pressure with mild discomfort
  - Adhesives may cause some skin irritations.
- It is not purported or represented to be for use in supporting or sustaining human life, nor does it present a potential for serious risk to the health, safety, or welfare of a subject.
  - Pulse oximeters are monitors and are not used to support or sustain human life.

- It is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
    - Pulse oximeters are Class II devices used to measure the blood oxygen saturation. They are not used to diagnose; cure mitigate or treat disease. These devices are typically labeled with a general indication for non-invasive measurement of blood oxygen saturation.
- The device as used in this investigation does not present a serious risk to the health, safety, or welfare of a subject.
    - See below for discussion of risk associated with the device and use of the device.

Invasive Laboratory Testing on Healthy Volunteers

The risk determination is based on the use of the device in an investigation in addition to the device itself. Generally, the FDA believes pulse oximeters as addressed in the FDA Guidance Document for Pulse Oximeters (March 4, 2013) are non-significant risk devices. Further, the recommendation is to conduct the study in accordance with Clause 201.12.1.101.2 and Annex EE.2 of ISO 80601-2-61:2017, where Annex EE.2 describes the procedure for invasive laboratory testing on healthy volunteers.

Controlled Desaturation Study

Desaturation of the subject involves the administration of oxygen/nitrogen mixtures that are less than that of normal air, i.e., less than 21% oxygen. The minimum percentage of oxygen to be delivered is 9% which results in blood oxygen saturation levels similar to those that are seen in healthy individuals who are at a 14,000 to 17,000 feet elevation. Potential symptoms include air hunger, dizziness, faster breathing, higher pulse rate followed by slowing of the heart rate, anxiety, changes in the heart rhythm, sweating, flushing or feelings of being hot and tingling in the hands or feet or loss of consciousness. Vision changes such as 'starring' or 'tunnel vision' can also occur. In the event of any of the above symptoms the subject can be returned to room air or given high levels of oxygen. All of these symptoms, if they occur, reverse within minutes of discontinuation of the testing. During the test, the subject is closely monitored and constant communication regarding the subjects comfort and sense of well-being is assessed. The ECG, pulse oximetry saturation, inspired and expired oxygen, and exhaled carbon dioxide are monitored. Since 1983 Clinimark has performed these types of tests in this and other laboratories where we conducted approximately 10,000 desaturation tests with no significant negative events.

The mask allows gas for maximum delivery. The mask is made of soft flexible plastic so as to minimize the discomfort level as much as is reasonably possible. Materials may cause some skin irritations.

Radial Arterial Line

Radial Arterial Line placement involves introduction of a standard arterial catheter or angiocath into the radial artery. Since the arterial catheter is placed into the artery using a needle, there will be mild to moderate discomfort. The total amount of blood drawn during the procedure is less than 150cc. The possible risks from the arterial catheter include: pain, hyperventilation, pressure, muscle/artery spasm, fracture of the catheter under the skin (which may require an additional procedure for catheter retrieval) with insertion; discomfort with saline flush (cool, burning, or tingling sensation distal to the arterial line site, especially in the finger tips), or pain, hematoma (bruising), clotting, and scar formation. All precautions to minimize discomfort will be taken, including a small injection of Lidocaine (a numbing medicine) under the skin at the insertion site. A vascular assessment will be conducted prior to

cannulation of the artery to verify the presence of adequate collateral blood flow to the hand. The risk of radial arterial catheterization is believed to be minimal.

Lidocaine

The risks associated with use of Lidocaine as a numbing medicine may include discomfort or pain (burning or stinging) with injection; allergic reaction to medication; transient numbness in finger(s).

Pulse Oximetry Sensor

Pulse Oximetry Sensor placement involves positioning pulse oximetry sensors on the volunteer subject in the same manner that is used on hospitalized patients. The sensors may be warm to the touch. Under normal operating conditions, (no fault conditions), the sensors are not expected to overheat. If the sensors are too warm, they will be removed immediately. Clip on and soft reusable sensors and wrist straps exert a minimal amount of pressure. They should not cause discomfort. Sensor retention headband for the forehead sensor exert a minimal amount of pressure and may cause a headache if on for extended periods of time. If the sensors are too uncomfortable, they will be removed immediately. Adhesive sensors or tape may cause some irritations to the skin in some subjects. Every effort will be made to minimize products with natural rubber or latex. Products containing natural rubber or latex will be identified. The risk in the use of pulse oximetry sensors is believed to be minimal.

ECG Electrodes

Materials (such as the adhesive and/or gel contact) used in the electrodes may cause some skin irritations in some subjects. Typical skin irritations present with redness of skin and in some cases of sensitivity is an allergic reaction. Because the adhesive is aggressive on the ECG pads, it may cause pulling of the skin or hair upon removal. Biocompatibility testing for surface contact electrodes is a requirement of the International Standards Organization (ISO) 10993 – Biological Evaluation of Medical Devices. The risk in the use of ECG electrodes is believed to be minimal.

Ultrasound

Ultrasound utilizes high frequency sound waves to produce images of internal body structures. There are no anticipated risks. The ultrasound will be used to detect bifurcations of the radial artery in screening and assist in placement of the arterial catheter before data collection. The placement of the arterial line will be performed under sterile conditions. Subjects will be excluded if they have a known allergy to the ultrasound gel.

Blood Pressure Cuff

The reported risks associated with NIBP include A) slight discomfort upon inflation of the cuff, B) possible bruising, C) petechial rash and D) discoloration of the skin beneath the cuff. In rare instances the reported risks associated with NIBP include A) peripheral nerve injuries B) skin tear, and C) compartment syndrome (swelling of muscles in the limb causing the reduction of the blood supply to the muscle).

More than 3,946 adults, children, and newborn babies have had their blood pressures taken repeatedly in 104 studies using similar equipment. In these previous studies, the complications of taking repeated blood pressures were temporary and involved either bruising/rash; for example, petechiae rash (less than 2.2%), skin redness/lines (0.8%), or tingling/discoloration in the extremity wearing the cuff while the cuff is inflated (0.1%).

It is possible that the test subject may experience an allergic reaction to the material in the cuff. However, cuffs used in this trial for screening utilize standard material that has undergone skin sensitivity testing.

Heating Pad / Hot Water Bottles

A heating pad or hot water bottles may be used on the arm to improve the circulation to the finger and wrist sites. Mild discomfort can be expected if it is too warm. To minimize the discomfort, the subject will be asked about comfort level. If the heating is too warm, it will be turned on the lowest level possible, removed or additional separation will be used between the heater and the site for comfort.

Perfusion Index Ulnar/Ulnar+Radial Ratio test

During the Perfusion Index Ulnar/Ulnar+Radial Ratio test for assessment of sufficient collateral circulation, the wrist is squeezed for less than 1 minute. This may cause minimal discomfort.

There are no anticipated risks or adverse device effects to be assessed. There are no contraindications for use in the proposed study / study population. There may be other risks to the subject associated with the device or procedure that are unforeseeable at this time.

Benefits

The benefits to the study are to the advancement of non-invasive medical monitoring of patients by improving accuracy and performance of pulse oximeters. There are no direct benefits to the subjects participating in this study other than being a paid volunteer. The only alternative to this study is to NOT participate.

Design of the Clinical Investigation

Method

This study is a comparative, single-center, non-randomized study with a minimum of 10 subjects. Each subject test is expected to take approximately 1.5 to 2 hours. The overall data collection process will occur over a 3-5 day period for this study population.

Subjects will be provided an IRB approved Informed Consent which covers the essential information in the protocol, ISO 14155 (as reference only) and applicable regulatory requirements for a non-significant risk medical device investigation. Subjects will be provided sufficient time to review the informed consent and have all questions answered regarding their participation before enrollment or conduct of study specific procedures. As applicable, subjects will be told about any new information that might change their decision to participate.

Subjects who have completed (signed and dated) the informed consent and health questionnaire form and meet inclusion criteria and none of the exclusion criteria will be enrolled in the study. If the Informed Consent Form (ICF) is amended/updated throughout the life-cycle of the study, a determination will be made as to whether the subjects who have completed the study need to re-consent by reviewing, signing and personally dating the updated ICF.

Qualified healthy volunteers will be enrolled into the study. Subjects will recline for the study. Reference sensor(s) will be placed on each subject to evaluate the SpO_2 accuracy and performance. Shield material may be used between any adjacent finger sensors to prevent optical crosstalk.

Simultaneous data collection will be set up for device under test and the control pulse oximeter. The data from the test device will be collected by the sponsor or trained Clinimark Study staff. Data will be collected for 1 second intervals data analysis. The SpO_2 accuracy of the test devices will be evaluated over the oxygen saturation range between 70-100%.

The investigational device will only be placed on the wrist. The control pulse oximeter may be alternated through fingers between subjects.

A photo or video may be recorded to document the study if acceptable with the subject. Photo or video may be used for internal purposes, such as training by the sponsor.

Endpoint / Comparator

The primary objective of this study is to validate SpO_2 accuracy performance of BiOSENCY BORA BAND™ wristband Pulse Oximeter by an Accuracy Root Mean Square (A_{rms}) value. Reference CO-Oximetry will be used as the basis for comparison for the investigational device SpO_2 readings. The study population will include 10 to 15 subjects. The data for analysis will have approximately 200 data points equally distributed across the range of 70-100% by decade. All data will be used for the analysis unless a rational is provided for its removal. Possible reasons for data removal include, but are not limited to, unstable control, dashed or zero values, poor perfusion at the site, inconsistent or invalid CO-Oximetry values. Data that is found to not be useable will be removed prior to the comparative analysis. For the statistical analysis, the Accuracy Root Mean Square (A_{RMS}) calculation is used to determine the SpO_2 accuracy performance providing documentation for the SpO_2 accuracy for the device under test during non-motion conditions.

There are no deviations expected from this investigation plan, should deviations be needed, discussions will be conducted with the sponsoring company and reported to the reviewing IRB per standard operating procedures.

Study Population

The study population will include 10 to 15 healthy non-smoking (or has refrained from smoking for 2 days) competent adults, ages 18 to 50 years. The subject selection will be an equitable distribution of males and females of any race with varying skin tones including at least 2 darkly pigmented subjects or 15% of the subject pool, whichever is larger.

The subjects must understand the study and consent to participate by signing the Informed Consent Form. The subject must be healthy showing no evidence of medical problems as indicated by satisfactorily completing the health assessment form and health screen.

Subject enrollment is based on meeting the inclusion criteria and none of the exclusion criteria, a satisfactory health screen, and the subject and data demographics needed for the study.

Inclusion Criteria

- 10-15 Adults with a minimum of 4 males and a minimum of 4 females, with the balance made up of either
- Subject must have the ability to understand and provide written informed consent
- Subject is 18 to 50 years of age
- Subject must be willing and able to comply with study procedures and duration
- Subject is a non-smoker or who has not smoked within 2 days prior to the study
- Wrist size should be between 15-23 cm (5.9 – 9 inches)

Exclusion Criteria

- Subject is considered as being morbidly obese (defined as BMI >39.5)
- Compromised circulation, injury, or physical malformation of fingers, toes, hands, ears or forehead/skull or other sensor sites which would limit the ability to test sites needed for the study. (Note: Certain malformations may still allow subjects to participate if the condition is noted and would not affect the particular sites utilized.)
- Female subjects that are actively trying to get pregnant or are pregnant (confirmed by positive urine pregnancy test unless the subject is known to be not of child-bearing potential).
- Smoker Subjects who have refrained will be screened for COHb levels >3% as assessed with a Masimo Radical 7 (Rainbow)
- Subjects with known respiratory conditions such as: (self-reported)
    - uncontrolled / severe asthma,
    - flu,
    - pneumonia / bronchitis,
    - shortness of breath / respiratory distress,
    - unresolved respiratory or lung surgery with continued indications of health issues ,
    - emphysema, COPD, lung disease
- Subjects with known heart or cardiovascular conditions such as: (self-reported, except for blood pressure and ECG review)
    - hypertension: systolic >140mmHg, Diastolic >90mmHg on 3 consecutive readings (reviewed during health screen).
    - have had cardiovascular surgery
    - Chest pain (angina)
    - heart rhythms other than a normal sinus rhythm or with respiratory sinus arrhythmia (reviewed during health screen)
    - previous heart attack
    - blocked artery
    - unexplained shortness of breath
    - congestive heart failure (CHF)
    - history of stroke
    - transient ischemic attack
    - carotid artery disease
    - myocardial ischemia
    - myocardial infarction
    - cardiomyopathy

- Self-reported health conditions as identified in the Health Assessment Form (self-reported)
    - diabetes,
    - uncontrolled thyroid disease,
    - kidney disease / chronic renal impairment,
    - history of seizures (except childhood febrile seizures),
    - epilepsy,
    - history of unexplained syncope,
    - recent history of frequent migraine headaches,
    - recent symptomatic head injury (within the last 2 months)
    - cancer / chemotherapy
- Subjects with known clotting disorders (self-reported)
    - history of bleeding disorders or personal history of prolonged bleeding from injury
    - history of blood clots
    - hemophilia
    - current use of blood thinner: prescription or daily use of aspirin
- Subjects with severe contact allergies to standard adhesives, latex or other materials found in pulse oximetry sensors, ECG electrodes, respiration monitor electrodes or other medical sensors (self-reported)
- Subjects with severe allergies to iodine (only applicable if iodine is used)
- Subjects with severe allergies lidocaine (or similar pharmacological agents, e.g. Novocaine)
- Failure of the Perfusion Index Ulnar/Ulnar+Radial Ratio test (Ratio < 0.4)
- Unwillingness or inability to remove colored nail polish from test digits.
- Other known health condition should be considered upon disclosure in health assessment form

Duration of Clinical Investigation

Each subject, and therefore use of the device, is expected to take 1.5-2 hours. Data collection will occur over a 3-5 day period for this study population.

Criteria for Study Termination

The study will be terminated if any of the following conditions occurs:

- Study is complete
- Unable to obtain vascular access
- Initial blood draw values of, COHb >3%, MetHb > 2%, and tHb <10g/dl (Note: COHb may be lowered through an exercise of hyperventilation and elevated levels of oxygen being administered to the subject.)
- Subject withdrew consent. The subject may stop the study for any reason without prejudice
- Withdrawal by Sub-Investigator / Investigator. The clinician or gas controller may terminate the study at his/her discretion
- Study Stopped due to Technical Problems
- Study may be stopped due to Protocol Deviation
- Study Terminated by Sponsor
- Study Stopped due to Adverse Event
- Development of any cardiac arrhythmia, except sinus arrhythmia <120 bpm
- Development of clinically significant ST or T segment changes in the ECG

- Sustained sinus tachycardia ≥120 bpm
- Onset of PVCs
- Sustained levels lower than the target SpO_2. The lowest target is 70% SpO_2. Due to unpredictable human physiology, the subject may drift below 67%. Should this occur, an attempt will be made to increase the oxygen saturation level by increasing the FiO_2 level to achieve an SpO_2 in the 67-73% range or a decision is made to increase the FiO_2 to a new SpO_2 range or terminate the study.

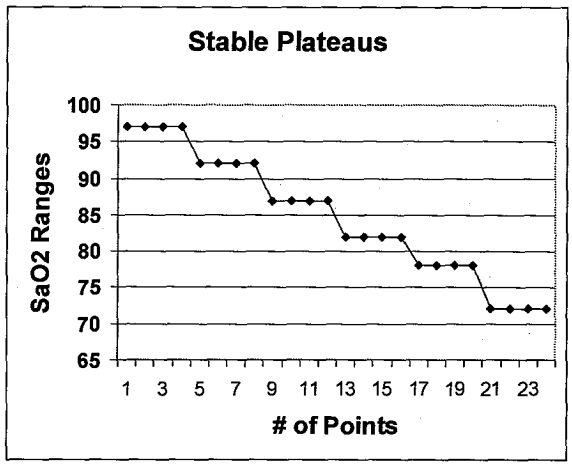
Any data collected to the point of a decision to terminate the study will be reviewed for inclusion to the analysis prior to generation of the final results. Data excluded from the analysis will be documented with justifications.

Procedure

1. Complete Equipment checkout list prior to starting study. Calibrate / check FiO_2 monitor(s).
2. Set the clocks to sync data collection between the Sponsor and Clinimark systems.
3. Explain the procedure to the subject. Have them read the Informed Consent Form, and review the information answering all questions. Once all questions have been answered, have the subject sign the form. Have the subject complete the Health Assessment Form and verbally question the subject about their health history. Each subject will be asked if they want a copy of the consent form prior to release.
4. Apply Finger sensor to thumb of hand where the arterial line will be placed. Record perfusion index (PI) value from 3900 TT+ Pulse Oximeter. Perform a modified Allen's test to ensure sufficient blood flow to the hands. Occlude both radial and ulnar arteries until there is no plethysmographic waveform and the PI is essentially zero. Release the ulnar artery holding the radial artery firm. Record the PI level. The ratio of the ulnar artery PI measurement to the starting PI level should be greater than or equal to 0.4 to qualify for the study. This is a safeguard to ensure there is a sufficient blood flow supply to the hand should the flow from the radial artery become altered.
5. Take subject's blood pressure and record values.
6. Apply ECG leads to the subject, review for normal sinus rhythm.
7. Based on the responses to the Health assessment form, record accepted or declined from the study. Continue if accepted into the study.
8. A qualified clinician will use local anesthesia and with the assistance of ultrasound, place the arterial catheter in the radial artery of the non-dominate (preferred) hand. The arterial line is then secured with tape to the subject's arm.
9. Setup and verify communication between the devices and data collection system.
10. Record device information for tracking. (manufacturer, model #, serial or lot, hardware / software control info).
11. Record subject information. Subject number and demographics information for subject description.
12. Have subjects recline.
13. Apply sensors to the subject. Shield any adjacent sensors to prevent optical cross-talk.
14. Adjust sensors as appropriate and record on test form.
15. A hot water bottle may be placed on each arm to improve the perfusion and facilitate the blood draws.
16. Allow readings to stabilize. Record baseline SpO_2 and Pulse rate on the test form.

17. Begin program to start gas flow. Verify that FiO_2 is at appropriate starting level (typically 18-21%) prior to connecting subject to breathing circuit.
18. Connect the subject to the breathing circuit and adjust the gas flow delivery for subject comfort.
19. Start data collection.
20. The program will be run in manual mode. Gas mixture changes will be set by the controller. The gas mixture will be delivered to induce hypoxia in a stair stepped manner. Data collection will be evenly distributed by decade over the oxygen saturation range.
21. The clinician monitors and records the following information periodically. SpO_2, pulse rate, $EtCO_2$, respiration rate, relevant information on the ECG rhythm, FiO_2. The clinician will monitor the arterial line and subject's well-being throughout the test confirming that the subject is doing "ok". Subject will be advised during the study that he/she may stop the test at any time.
22. While breathing room air mixtures, collect baseline arterial samples and measure on the CO-Oximeter. The method for sampling will be:
    - Mark data for start of stability period hold 30 seconds to 1 minute
    - Draw waste or leader blood sample prior to draw, mark data
    - Draw arterial blood sample marking data
    - Wait approximately 15 to 30 seconds, draw waste or leader blood sample prior to draw
    - Draw additional arterial blood sample marking data
    - Change to next gas level

    Note timing may vary based on the subject's stability.
23. Should the initial COHb reading be out of range (>3%) as measured by Reference CO-Oximetry, then a determination will be made as to the viability of blowing off the COHb levels through an exercise of hyperventilation and elevated levels of oxygen being administered to the subject. If this is the case, blood samples will be drawn to monitor the COHb level until it is acceptable or a determination is made to withdraw the subject.
24. Multiple plateaus will be achieved throughout the range from 100% to 70%.
25. The clinician monitors and records the following information periodically. SpO_2, pulse rate, $EtCO_2$, respiration rate, relevant information on the ECG rhythm, FiO_2. The clinician will monitor the subject's wellbeing throughout the test confirming that the subject is doing ok.
26. Subject will be advised during the study that he/she may stop the test at any time.
27. The gas controller monitors the gas delivery and data collection system to ensure proper functionality. Performance of the test devices may be noted on the form as well.
    - The test may be stopped at any time by the subject, the clinician, the gas controller. The test will also be stopped if the SpO_2 level goes below the minimum SpO_2 or the FiO_2 goes below 9%.
28. Arterial blood sampling will be repeated at each stable plateau. Method used will be same as described in step #22 above.



Goal is to collect 20 – 30 data points per subject with an equal distribution of data by decade across all subjects. The stable plateaus will allow for data to be collected in the following ranges 95-100, 90-95, 85-90, 80-85, 75-80, 67-75. In general, 4 to 8 discrete points will be collected at each of the levels such that the overall data of the population is evenly distributed by decade and the minimum number of points is met for the data analysis. A fewer number of data points are expected on some subjects that are unable to tolerate the duration of the lower hypoxic levels.

29. During the course of the study, the subject may be re-saturated to above 80% SpO_2 for a recovery period. The subject then may reattempt the lower SpO_2 levels.
30. Once the lowest level SpO_2 has been achieved and data collection has been completed, the subject will be given a gas mixture returning him/her to baseline levels.
31. The breathing circuit is disconnected and the subject is monitored for a few minutes to ensure he/she maintains normal baseline levels.
32. All equipment will be removed from the subject.
33. The arterial line will be removed and a pressure bandage will be applied to the subject for approximately 15 minutes or until bleeding has stopped.
34. The clinician will review any final questions with the subject and ask if there were any effects from the study. The subject will be given final instructions for care of the wrist which had the arterial line. The subject will be provided with phone numbers for questions pertaining to participation in this study or research-related injury or reaction post the study. The subject will be informed of the follow up procedure post the study.

Statistical Analysis

The purpose of this clinical study is to validate the SpO_2 accuracy of the BiOSENCY BORA BAND™ wristband Pulse Oximeter during non-motion conditions over the range of 70-100% SaO_2 as compared to arterial blood samples assessed by CO-Oximetry. Data analysis may occur in the following manner:

Data analysis will follow ISO80601-2-61:2017, Annex EE and the FDA Guidance Document for Pulse Oximeters (March 4, 2013). The reference guidance documents clearly define the study, number of subjects, data points needed for the analysis and handling of missing data or data that is removed from the analysis. This is achieved through a minimum of 200 paired observations of Test and Reference values equally distributed over the specified SpO_2 accuracy range (70-100%) of the device under test.

The data will be collected on a minimum of 10 healthy adult volunteer subjects who range in age, gender and skin tone with 2 of the subjects or 15% of the subject pool (whichever is larger) having deep skin pigmentation tones. An Accuracy Root Mean Square (A_{RMS}) calculation is used as a means to define the SpO_2 Accuracy. The controls of the study will be provided in the following manner. The control oximeter will provide the real time oxygen saturation level of the subject for determination of plateau levels and safety. Additionally, the oxygen saturation values (SpO_2) of a control oximeter will be used to assess the stability of the plateaus for data collection. There are no provisions for an interim analysis. For the validation, the SpO_2 accuracy of test pulse oximetry system is compared to the Gold Standard measurement of blood SaO_2 by a CO-Oximeter. Data analysis & demographics will be presented in the final report.

Control oximeter stability criteria

The control oximeter will provide the real time oxygen saturation level of the subject for determination of plateau levels and safety.

The data points are considered unstable and removed from the analysis:

- if the Control Oximeter SpO_2 value varies by >2% during the draw time
- if the combined minimum and maximum deviations of the Control Oximeter SpO_2 value are > 3% during the review period of 20-30 seconds prior to draw period through the draw as defined by ISO 80601-2.

CO-Oximeter Data

The CO-Oximeter data is reviewed for outliers or anomalous readings from which these plateaus are subject to removal. The functional oxygen saturation value will be used for the basis of comparison to SpO_2 value collected from the pulse oximeter. Draws with COHb values >3% or MetHb values >2% or tHb <10 g/dl will be excluded from the data. When multiple CO-Oximeters are used, data that presents outliers from the other CO-Oximeters will be removed from the average of the CO-Oximeters. Outliers are defined as a CO-Oximeter SO_2 values (functional oxygen saturation) that are >2% from the other CO-Oximeter's values. In the case where 2 CO-Oximeters are used, the data will be averaged unless the difference between the 2 CO-Oximeters is >2%. When the 2 CO-Oximeters deviate by >2%, the tHb, COHb, MetHb values will be reviewed for consistency to the other draws for this subject. If those values are found to be similar in readings for a given subject, then it is determined that the true reference value is unstable and the point will be removed from the analysis. If the finding is that one of the CO-Oximeter's has an SO_2 value offset due to tHb, COHb or COHb values that are not similar for a given subject, then the offending CO-Oximeter will be rerun and if the offset persists, the value will not be used and the other CO-Oximeter SO_2 value will be used as the reference for comparison.

Draws with CO-Oximeter data that are < 67% will be removed.

Test SpO_2 Data will be removed for the following reasons:

- The test SpO_2 values truncated at 100% or recorded >100% will be removed prior to the analysis.
- Zero values (drop outs in SpO_2 or pulse rate) will be excluded from the calculations for the test SpO_2.
- Perfusion level at the test site is determined to be too low for a valid reading.

A rationale will be provided for any data that is excluded from the data analysis.

The data will be plotted and analyzed through the following statistics, using the Reference CO-Oximetry SaO_2 value for the x value and the Test Devices SpO_2 value for the y value.

Ref = Reference CO-Oximetry SaO_2
DUT = Device Under test SpO_2

SpO_2 accuracy will be evaluated for root-mean-square (rms) difference between the DUT and the reference for the specified SpO_2 ranges (70-100%) and by SpO_2 decade (90-100%, 80<90%, 70-<80%). The number of data points will be included for each statistic.

$$Arms = \sqrt{\frac{\sum_{i=1}^{n}(DUT_i - \mathrm{Re}f_i)^2}{n}}$$

The average difference is calculated to show the bias of the device under test as compared to the reference. The bias is calculated for the specified SpO_2 ranges (70-100%) and by decade (90-100%, 80-<90%, 70-<80%).

$$Bias = \frac{\sum_{i=1}^{n}(DUT_i - \mathrm{Re}f_i)}{n}$$

A least squares line (slope and intercept) will be generated for the overall range.
The minimum and maximum deviations will be calculated from the reference.

Bland-Altman graphical plots, error ($SpO_2 - SaO_2$) versus average $SaO_2 + SpO_2$ will be generated with linear regression fit, mean, and upper 95% and lower 95% limits of agreement according to Section 3 of "Agreement Between Methods Of Measurement With Multiple Observations Per Individual" by Bland and Altman in 2007 Journal of Biopharmaceutical Statistics. Individual test subjects will be color coded in the Bland-Altman graphical plot.

Values for the population mean bias (μ0), between-subject variance (σμ2) and within-subject variance (σ2) will be calculated according to Section 3 of "Agreement Between Methods Of Measurement With Multiple Observations Per Individual" by Bland and Altman in 2007 Journal of Biopharmaceutical Statistics. Individual test subjects will be color coded in the Bland-Altman graphical plot.

Error plots (i.e., SaO_2 versus (SpO_2-SaO_2) for both individual test subjects and all subjects pooled) will be generated.

Additionally, a scatter plot will be generated.

Test device outliers with a value >5% difference from the Reference CO-Oximeter will be discussed in the Final report per the FDA Guidance document for Pulse Oximeters.

Pass / Fail Criteria

The statistical results of the data will be reviewed for the following pass/fail criteria:

- SpO_2 Accuracy for the range of 70-100%, ≤ 3.5 (A_{RMS}) is a Pass for reflectance technology.

Deviations from the Statistical Plan

Any deviations from this statistical plan will be described and justified in the final report.

Investigational Review Board (IRB)/Independent Ethics Committee (IEC)

Prior to the start of subject enrollment, the sponsor/investigator will be responsible for obtaining approval from the authorized IRB/IEC for the institution at which the proposed clinical investigation is to be conducted. Written approval from the IRB/IEC should specifically refer to the investigator, the protocol title and date, and subject informed consent date. Written IRB/IEC approval and any conditions of approval imposed by the IRB/IEC will be obtained by the sponsor/investigator.

Protocol amendments must also undergo IRB/IEC review and approval at each clinical site. The written approval from the IRB/IEC for the amendment should specifically refer to the investigator, the protocol version number and title, and any amendment numbers that are applicable.

Monitoring Arrangements

Clinimark personnel (Louisville, CO, USA) will provide all monitoring. The Monitor shall be responsible for maintaining a record of the findings, conclusions, and actions taken for the results of monitoring the study ensuring that:

The monitoring requirements for an NSR device study is identified in 21 CFR 812.2(b) *Abbreviated requirements.* For monitoring an NSR device investigation, the requirement is to comply with 21 CFR 812.46 with respect to monitoring investigations: (a) Securing Compliance, (b) Unanticipated adverse device effects, (c) Resumption of terminated studies

- Compliance to the signed agreement between the Investigator and sponsor
- The study follows the protocol and any amendments that apply
- Compliance to any conditions of the approval imposed by the IRB or FDA

Additionally:

- The conditions for the study continue to be acceptable
- Accurate, complete, and current records are maintained and required reports are written
- Any adverse effects are documented and reported to the Sponsor and IRB as appropriate
- Monitor activities may include for example: performing source data verification and requesting corrections to feedback forms where potential inconsistencies or missing values are identified.
- Findings of non-compliance or required modifications are reviewed with the investigator and the Sponsor, and is presented in a written report to both
- Providing a Monitoring Report at the end of the Clinical Investigation

Monitoring Plan

1. Informed Consent
    - Verify that the consent form was signed prior to any study procedures being conducted
    - Verify that the staff conducting the consent is listed for approval on the Delegation of Authority Log
    - Ensure that the consent process is documented.
2. Subject Eligibility
    - Verify that the subject meets the inclusion criteria and none of the exclusion criteria.
3. Baseline Data
    - Verify demographic information with the health assessment form
    - Check that informed consent time and date is prior to start of the procedure
4. Verify all CRFs are completed
5. Adverse Events
    - Verify that Adverse Events and Serious Adverse Events / UADEs are being documented and reported accordingly to the IRB and Sponsor in the required timeframe.
6. Protocol Deviations
    - Verify that Protocol Deviations are being documented and reported accordingly to the IRB and Sponsor in the required timeframe
7. Device Deficiencies
    - Verify that Device Deficiencies are being documented and reported accordingly to the IRB and Sponsor in the required timeframe
8. Electronic Data Review
    - Verify that the filename matches the filename entered on the CRF and that the appropriate number of Oximeter channels were recorded.
9. Ensure the Trial Master File is complete.

Data and Quality Management / Confidentiality

A checklist will be maintained identifying the contents of the Trial Master File / Project folder PFC# 2018-312

The subject's name and signature will be recorded on the Informed Consent, Health Assessment Form, Subject Follow-up, Clinician: Subject Flow Sheet form and a subject participation list. The data collection form will only use a subject number and initials for the day of the test along with subject demographics. A name will not be recorded on the case report form.

Records identifying the subject's name will be kept in a secured location with either a locked file or locked door. Access to these files will be on a limited basis. Potential reviewers of this information include: Clinimark representatives collecting the information and conducting the study, Medical Director for Clinimark, the U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, Governmental agencies in other countries, Salus Independent Review Board and representatives of the Sponsor. This group may use the information to conduct independent audits and reviews to verify compliance of the regulatory requirements for these studies but not copy the information.

Data files stored electronically will be associated with a subject based off of subject #, date and by filename recorded on the data collection forms. The original device electronic data files will be preserved in its original form. Data analysis will be performed as a separate electronic file.

Data files, data collection records with subject demographics and subject number may be additionally copied, (after de-identification, if applicable) reviewed and supplied to the commercial sponsor for the study or Contractors associated with Clinimark for data analysis purposes.

All study records will be stored for at least 2 years post the release of the product or project cancellation. The investigator will notify sponsor prior to destruction of study records. Other storage arrangements may be executed per contractual agreement between the sponsor and the investigator.

Records - Study Documentation / Case Report Forms

Study Procedure: BORA Band SpO2 Validation Study
PR 2018-312

Subject Documents

Provided as separate documents to this protocol:

- Informed Consent form (IRB approved)
- Health Assessment Form (Clinimark Control # F2000-001-001 current revision) (IRB Reviewed)
- Arterial Puncture Wrist Care Instructions (IRB Reviewed)

Study Conduct Documents:

- CRF2018-312 – Case Report Forms
- Clinimark Control # F2000-001-005 – Clinician: Subject Flow Sheet form
- CO-Ox data collection forms
- Electronic Files – electronic data collected from the pulse oximetry systems

Data Collection Forms / Case Report Forms

To ensure the quality and integrity of the data, it is the responsibility of the Investigator(s) or designee to complete the Case Report Forms (CRFs) for each subject who is enrolled to participate in this study. In some cases the data collection forms will also be the source document for some information that is not directly collected in the Health Assessment Form. The following information will be recorded on the site's data collection forms (CRF):

- Study date, Subject ID#, Subject Initials, and Relevant Subject Demographics, Associated Electronic Filename(s)
- Evidence that informed consent was signed and dated prior to the subject participating in the study
- Information for Subject Inclusion or Exclusion to the study
- Equipment calibration and communication check out
- Device usage / sensor placement on the subject
- Baseline SpO_2 and pulse rate
- Annotations on data point markers, stability, and other observations used in the data analysis
- Protocol deviation reporting (only if needed)
- Adverse Events reporting (only if needed)

- Study termination
- Subject Follow up form

A black or blue pen will be used to record data on the data collection forms. Recorded information should be legible and completed. Erroneous entries should be crossed out, corrected with the change, initialed and dated by the individual making the correction. The Investigator(s) or designee will sign and date at indicated places on each page of the data collection form. The Protocol Deviations Reporting can be signed and dated by the designee only if there are no deviations, otherwise the Sub-Investigator or Investigator should review, sign and date. The Adverse Events Reporting should be signed and dated by the designee and a Sub-Investigator or Investigator. The Principal Investigator needs to review, sign and date all serious adverse events. The Investigator or designee will provide a final signature indicating that a thorough inspection of all subject data has been performed and will thereby certify the contents of the forms. The Investigator's Certification Statement will disclose the overall documentation, study oversight and certification of the study.

Trial Master File Documents

- Clinimark Control # B3000-000-003 - Adverse Events and Protocol Deviation Reporting System
- Clinimark Control # F2000-001-029 - Device Deficiency Form
- Clinimark Control # F2000-001-016 - Device Accountability Form
- Clinimark Control # F2000-001-015 - Delegation of Authority
- Clinimark Control # F2000-001-017 - Investigator Financial Interest Disclosure
- Clinimark Control # F2000-001-022 - Investigator's Certification Statement
- Clinimark Control # F2000-001-028 - Subject Enrollment Log
- Clinimark Control # F2000-001-027 - Site Personnel Training Log
- Clinimark Control # F2000-001-033 - Site Visit/ Monitoring Log
- Clinimark Control # F2000-001-034 - Data Clarification Form
- Clinimark Control # F2000-001-037 - Protocol Deviation Log
- Clinimark Control # F2000-001-038 - Adverse Events Log
- Clinimark Control # F2000-001-035 - Regulatory Binder Bullet Checklist
  Current revision of these documents apply.

Amendments to the Clinical Investigation Plan

BiOSENCY or site may need to make protocol changes during the study. Such amendments will be documented, reviewed and changes will be submitted to BiOSENCY for first approval, then to the IRB for approval. BiOSENCY and the site will make a decision regarding the continuation of subject enrollment during this period. The site may proceed with the amendment upon receipt of IRB approval.

Deviations from the Clinical Investigation Plan

Investigators are not allowed to deviate from the Clinical Investigation Plan (CIP) except under emergency circumstances. Deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB as soon as possible but within 5 working days of the occurrence of such deviation per the deviation reporting policy.

Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study must be reported to the Sponsor within 5 working days from awareness of occurrence and reported to the IRB per the deviation reporting policy. Deviations that do not affect the safety, efficacy, integrity, or conduct of the study will be documented in the case report forms, regulatory binder Protocol Deviation Log as appropriate.

Device Accountability

A Device Accountability Log will be maintained for the sponsor's equipment documenting date of receipt, description of device (including model#, lot#, serial number or unique code, and quantity) and date of return for used and unused product. Device usage will be recorded in the Case Report Form for each individual subject.

Packaging and Labeling

Research conducted for this study will utilize investigational devices and devices cleared through the 510k regulatory process. The Sponsor is responsible for packaging and labelling of the device for delivery to the study site. FDA cleared devices do not require special labelling. Investigational devices or its immediate package shall bear a label with the following information: name and place of the manufacturer, packager, or distributor, the quantity of contents, if appropriate, and the following statement:

"CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use."

The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. It is the investigator's responsibility to ensure the appropriate labelling is visible and remains intact throughout the life of the study. The Instructions for Use (IFUs) are provided as separate documents from this protocol.

Storage and Accountability

The site will store the investigational product. The storage area should be locked/secure with access limited only to approved study staff.

The site will record/track use of the investigational device by each participant. Documentation should verify that the device use was in accordance with the approved protocol. Equipment Document in the Case Report Form shall provide documentation of the devices used on the study participant(s).

Statement of Compliance

The study will be conducted in accordance with the Declaration of Helsinki, 21 CFR 50, and 21 CFR 812 for non-significant risk device study investigations. The study will not commence until the approval has been received from the IRB.

Reference Documents

- IRB Approved Informed Consent for Study Title: BORA Band SpO2 Validation Study PR 2018-312
- ISO 80601-2-61, second edition 2017-12, Corrected version 2018-02, applicable sections, Clause 50 and Annex EE.3 Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment

- FDA Guidance Document for Pulse Oximeters, March 4, 2013
- World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects
- ISO 14155, second edition 2011-02-01, Clinical investigation of medical devices for human subjects — Good clinical practice
- Clinimark Adverse Events Reporting Document B3000-000-003 (current revision)
- Salus IRB reporting forms

Informed Consent Process

- The Principal Investigator or his / her designee conducts the informed consent process
- Verify that the subject acknowledges ability to read English
- Instruct the subject to ask questions at any time during this process, especially about things they do not understand.
- Allow subject ample time to read the entire form and ask questions.
- Give a thorough description of the study and the subject's involvement – especially explain that they may withdraw from the study at any time.
- After the subject has read the form ask if they understand everything
- Ask if they would like to take part in the study and if so explain that they may sign and date the form.
- Once the subject has signed and dated the informed consent, the principal investigator or authorized designee will sign and date the form.
- Give a copy of the informed consent to the subject.
- No procedure may be performed before the informed consent is signed by the subject

If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

Safety

Investigators

All experimenters must review the protocol prior to test and sign that they read and understood the contents.

Subject

Equipment is checked out for proper functionality prior to being placed on the subject.
The Clinimark Desaturation Fixture does not require maintenance. At the start of each day of the study, the fixture is calibrated with calibration gas. A secondary monitor independent of the fixture is used to measure and document the FiO_2 delivered at 3 levels. The measurement is expected to be within ± 1 of the FiO_2 setting for the fixture.

There are three steps used to ensure safe gas mixture delivery. The fixture implores continuous monitoring of gas flow and mixtures. Should the measurements drop below a predetermined level either the primary O_2 and / or N_2 flow valves are adjusted or a secondary O_2 delivery system is switched on. Error messages and status messages are displayed. Second, the gas controller directly observes the monitoring status and gas delivery displays of the fixture. Third, a clinician directly

observes the subject and other monitors independent of the gas delivery fixture to ensure the subject's well-being during the test.

The subject will review and sign the informed consent following a discussion of the test procedure and when all questions regarding the study have been answered and prior to start of any study procedures. The subject will complete the health assessment questionnaire and disclose any pertinent issues that may affect his/her health during the test. The subject may withdraw from the study at any time. The subject may be withdrawn per the Procedure section below.

A clinician will be present to monitor the subject at all times. Safety monitoring includes, SpO_2, pulse rate, relevant information on ECG rhythm, FiO_2, $EtCO_2$, respiration rate, direct observation and communication with the subject.

Adverse Event Definitions

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

- **Adverse Device Effect (ADE):** Adverse event related to the use of an investigational medical device resulting from insufficiencies or inadequacies in the instructions for use, the deployment, installation, the operation, or any malfunction of the investigational medical device or from error use.
- **Adverse Event (AE):** Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device or investigational procedure
- **Anticipated Serious Adverse Device Effects (ASADE):** ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
- **Mild:** a mild adverse event is one in which the subject is aware of the event, but it is easily tolerated without intervention.
- **Moderate:** a moderate adverse event is one that causes sufficient discomfort to interfere with usual activities.
- **Serious Adverse Device Effect (SADE):** adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
- **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.
- **Severe:** a severe adverse event is one that results in the inability to perform usual activities.
- **Unanticipated Adverse Device Effect (UADE):** serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Management of Adverse Event Reporting

Should the subject experience an adverse or non-typical event, assessment of the situation is first initiated, and a determination will be made of appropriate actions. The Medical Director and Principle

Investigator will be contacted as appropriate. Adverse Events are reported through standard Clinimark Procedures, IRB requirements and per BiOSENCY's SOPs.

Records of Adverse events will be recorded in the Case Report Form
The following information will be obtained:

- Type of effect (ADE, AE, ASADE, SADE, SAE, UADE)
- Date of onset and resolution
- Intensity (mild, moderate, severe)
- Serious (yes/no)
- Relationship to device (unknown, not related, possibly related, probably related, definitely related)
- Anticipated (yes/no)
- Treatment given and / or action taken (procedure stopped, withdrawn from study, no action)

Reporting of Serious Adverse Events and / or UADE

All SAE's, SADE, ASADE and UADE will be reported in writing to the Principal Investigator, Medical Director, Sponsor and IRB as soon as possible and no later than 10 working days after the investigator first learns of the event.

If the event resulted in death of a subject, the event shall be reported to the Principal Investigator, Medical Director, Sponsor and IRB within 24 hours of knowledge of the event.

Sponsor Records and Reports

Records 21 CFR 812.140 (b) 4,5

The following records shall be consolidated in one location and available for FDA inspection and copying:

- The name and intended use of the device and the objectives of the investigation;
- A brief explanation of why the device is not a significant risk device:
- The name and address of each investigator:
- The name and address of each IRB that has reviewed the investigation:
- A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and
- Any other information required by FDA.
- Records concerning adverse device effects (whether anticipated or unanticipated) and complaints

Reporting 21 CFR 812.150 (b) 1,2,3,5,6,7,8,9,10:

The sponsor shall prepare and submit the following complete, accurate, and timely reports.

Unanticipated Adverse Device Effect

A sponsor shall immediately conduct an evaluation of an unanticipated adverse device effect. The results of such evaluation shall be reported to the FDA, IRB and participating investigators within 10 working days after the sponsor first receives notice of the effect.

Withdrawal of IRB approval
Withdrawal of IRB approval shall be reported to the FDA, IRB and the investigator within 5 working days after receipt of the withdrawal approval by the sponsor.

Withdrawal of FDA approval
Withdrawal of FDA approval of an investigation shall be reported by the sponsor to the IRB and the investigator within 5 working days after receipt of notice the withdrawal approval.

Progress Reports
The sponsor shall submit progress reports to the IRB at least yearly.

Recall and device
The sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

Final Report
The Clinimark shall submit a final report to the IRB with 6 months after termination or completion of the investigation.

Informed consent
The sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

Significant risk device determinations – (does not apply to NSR studies)
If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

Other
A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Investigators Records and Reporting

Records 21 CFR 812.140 (a)(3)(i)
The investigator maintains records of each subject's case history and exposure to the device and supporting data including signed and dated consent forms, health assessment form, and progress notes during the study. Records should show evidence that informed consent was signed and dated prior to the subject participating in the study.

Reports 21 CFR 812.150 (a) 1,2,5,7
The investigator shall prepare and submit the following complete, accurate, and timely reports:

Unanticipated adverse device effects
The investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Withdrawal of IRB approval
The investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

Informed consent
If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

Other
The investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Withdrawal, Early Termination or Suspension of the Investigation

Participation in the study is voluntary. Subjects may choose to withdraw from the study at any point. If a subject officially withdraws from the study, the laboratory staff will document the reason for withdrawal in the case report.

It is recognized that some subjects may not be able to tolerate the lowest hypoxia levels in a stable manner. These subjects will be moved to higher SaO_2 levels for final data collection if needed. This is not considered to be a withdrawal or discontinuation of the subject and therefore will not be reported as such. These subjects are considered to have completed the study procedure without incidence or any adverse events.

Participation in the study may also be stopped at any time by the principal investigator or by the Sub-investigators or sponsor.

- The subject's failure to cooperate fully (as determined by the investigator in his or her sole discretion) with the required conduct of this study.
- The subject's development of an illness as determined by the investigator in his or her sole discretion.
- A determination by a Clinimark representative (in his or her sole discretion), for whatever cause, that the study should be discontinued.
- A determination by the sponsor (in his or her sole discretion), for whatever cause, that the study should be discontinued

The collection of data for study subjects will cease in the following cases:

- Subject completes all study requirements
- Subject withdraws consent
- Investigator's decision that it is in subject's best interest to be discontinued from the study
- Subject death
- Adverse event other than death requiring withdrawal of the subject from the study
- Determination that the subject was ineligible for the study.

There will not be any follow-up procedures for withdrawn or discontinued subjects required, unless a follow-up is required at the Investigator's discretion.

Consideration for early termination or suspension of the investigation is tied to unanticipated equipment failure or a decision by the sponsor or the site. Both BiOSENCY and Clinimark reserve the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of, but not limited to, inadequate data collection, low subject enrollment, or non-compliance with the protocol or other research requirements.

Early termination results when the study is closed prior to the end of the study. A study suspension is a temporary postponement of the study activities related to enrollment. Both are possible for the study.

If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol.

If the study is terminated prematurely or suspended by the sponsor/investigator, the sponsor /investigator will promptly inform the regulatory authorities (if required) of the termination and the reason(s). IRB/IECs will also be promptly informed and provided with the reason(s) for termination or suspension by the sponsor/ investigator. The investigator will promptly inform the subjects and assure appropriate follow-up for the subject.

If the investigator (or IRB/IEC) terminates or suspends the investigation the investigator will promptly inform the institution (if required) and the IRB/IEC to provide a detailed written explanation of the termination or suspension. The investigator will promptly inform the subjects and assure appropriate therapy and follow-up for the subjects. The sponsor will inform the regulatory authorities (if required).

Withdrawal of IRB approval shall be reported to the sponsor by the investigator within 2 working days.

In case of early termination of the study, all study subjects should be followed until the resolution of any pending adverse event(s).

Publication Policy

The results of this investigation will not be submitted for publication.

Attachment A - Protocol Signature Page

Protocol No. PR 2018-312

As the Principal Investigator, I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in accordance with the Declaration of Helsinki, 21 CFR 50, and 21 CFR 812: or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual.

- Ensuring informed consent of each subject is obtained prior to the start of any study procedure
- Ensuring the investigation is conducted according to the Clinical Investigation Plan,
- Personally conducting or supervising the investigation,
- Protecting the rights, safety, and welfare of participants,
- Preparing and maintaining adequate, current, and complete case histories or records,
- Retaining records for two years following the date the marketing application is approved or withdrawn,
- Furnishing the required reports to the sponsor, including reports of adverse events and study completion,
- Providing timely reports to the IRB, including reports of changes in the research activity needed to avoid immediate hazards to participants, unanticipated problems involving risks to participants or others, including adverse events to the extent required by the IRB,
- Ensuring that changes are not implemented without prospective IRB approval, unless required to eliminate immediate hazard to participants,
- Complying with all FDA test article requirements,
- Adequately maintaining control of test articles, including appropriate tracking documentation for test articles to the extent that such control and documentation are not centrally administered,
- Supervising the use and disposition of the test article,
- Disclosing relevant financial information, and
- Ensuring that all associates, colleagues, and employees assisting in the conduct of the investigation(s) are informed about their obligations in meeting the above commitments.
- An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Signature of Investigator

04 FEB 2019

Date

Arthur Cabrera, MD

Investigator Name (print or type)

Principal Investigator

Investigator Title

Clinimark Laboratory

Name of Facility

Louisville, CO USA

Location of Facility (City, State, Country)