CLINIMARK Clinical Investigation Plan

Vital USA Respiratory Rate Validation in Adults
PR 2019-326

COMMERCIAL SPONSOR:
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Document Ownership: Document is in accordance with Code of Federal Regulations for Non-Significant Risk Investigations and ISO 14155 where applicable

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STUDY PROCEDURE:

Vital USA Respiratory Rate Validation in Adults
Clinimark Study ID# PR 2019-326

COMMERCIAL SPONSOR:

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CONFIDENTIALITY:

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Summary

Introduction

Vital USA is dedicated to developing and applying innovative electronic medical solutions that improve patient care in multiple clinical settings. Vital USA is a manufacturer of a multi-parameter patient monitor that is intended to be used in a variety of medical settings including hospitals, medical offices and patients' homes.

Objectives of the Clinical Investigation Plan

The purpose of this study is to conduct a Respiratory Rate accuracy validation comparing the Vital Detect to an FDA cleared End Tidal Carbon Dioxide monitor Reference Standard (GE Datex-Ohmeda).

Background

Respiration Rate and Pulse Rate are an important physiological measurement in the healthcare setting. End Tidal Carbon Dioxide ($EtCO_2$) is considered to be the highest level of safety and accuracy in Respiratory Rate monitoring by the American Society of Anesthesiology and the American Association of Respiratory Care.

The medical device studied under this protocol will be the non-invasive and investigational Vital USA, Vital Detect. The Vital Detect uses multiple sensors in a portable device to measure a wide array of patient parameters. Respiratory rate is determined using a combination of sensors of the Vital Detect.

Clinical testing of this device will occur only after bench testing and safety testing have been completed at Vital USA.

Protocol Overview

After IRB Approval, a minimum of 20 healthy volunteer test subjects, 18 or older will be entered into this study designed to validate the accuracy of the respiratory rate feature of the Vital Detect (Device Under Test). The subjects will be selected to represent a range of body types including small, average, muscular, and large with a range of BMIs.

Each subject will be connected to a FDA cleared $EtCO_2$ monitor (GE Datex-Ohmeda) and will be instrumented with a mouthpiece or open system mask that allows for measurement of $EtCO_2$ derived respiratory rate. A range of stable respiratory rates will be elicited from each volunteer test subject with the use of a paced breathing application on a mobile phone. The rates will be approximately 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 breaths per minute; with some natural variation from these exact numbers and tailored to the subject's capabilities as some subjects may not be able to breathe at the lower and higher respiration rates.

The respiratory rate will be measured simultaneously for the Reference and the Device Under Test.

For the data analysis, the $EtCO_2$ monitor will be used to assess the stability of the data. If the respiratory rate varies by more than three breaths per minute during the target respiration rates, then the data for that period will be considered unstable and removed from analysis.

To 'Pass' this test the Vital USA, Vital Detect must demonstrate a respiratory rate A_{RMS} of ≤3 when compared to the Reference $EtCO_2$ monitor over the range of 5 to 45 breaths per minute. An additional goal would be for the A_{RMS} to be ≤2 over this range.

Study Population

The study population will include 20 healthy competent adults, ages 18 years and older. The subject selection will be a mix of males and females with small to large physiques. 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 and passing the health screening. Eligible subjects need to meet all of the inclusion criteria and none of the exclusion criteria for participation.

Inclusion Criteria

- Subject must have the ability to understand and provide written informed consent
- Subject is adult over 18 years of age
- Subject must be willing and able to comply with study procedures and duration
- Subject is a non-smoker
- Male or female of any race

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

- 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.)
- Subjects with known respiratory conditions such as:
    - uncontrolled / severe asthma,
    - flu,
    - pneumonia / bronchitis,
    - shortness of breath / respiratory distress,
    - respiratory or lung surgery,
    - emphysema, COPD, lung disease
- Subjects with self-reported heart or cardiovascular conditions such as:
    - have had cardiovascular surgery
    - Chest pain (angina)
    - heart rhythms other than a normal sinus rhythm or with respiratory sinus arrhythmia
    - 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
    - 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 head injury within the last 2 months,
- Cancer / chemotherapy

- Other known health condition, should be considered upon disclosure in health assessment form

It is expected that the data collection will take approximately 4-7 days to complete. There is no additional follow-up required for the investigation.

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Objectives of the Clinical Investigation Plan

The purpose of this study is to collect data to validate the respiratory rate performance of the Vital Detect developed by Vital USA. The Vital USA Vital Detect respiratory rate will be evaluated during non-motion conditions over the range a range of 5-50 breaths per minute via Reference $EtCO_2$.

A FDA cleared, GE Healthcare S5 Multi-parameter monitoring system with End Tidal Carbon Dioxide ($EtCO_2$) will be used for the Respiratory Rate Reference. There are no risks or adverse device effects to be assessed. There are no contraindications for use in the proposed study / study population.

Identification and Description of the Investigational Device

The Vital Detect is a non-invasive device designed for spot-checking physiological parameters, such as Non-Invasive Blood Pressure (NIBP), Oxygen Saturation (SpO_2), Pulse Rate (PR), Body Temperature (TEMP) and Respiratory Rate (RR). This device is a finger-cuff technology which is applicable for use at-home use or in healthcare facilities in/on individuals 18 years of age and older. It may be used by the individual themselves, or an operator. The Vital Detect is not intended for continuous monitoring, or for use with high frequency surgical equipment. It is non transit-operable.

This study will focus on the respiratory rate, RR parameter. The Vital USA Vital Detect is composed of a sensor head mounted on a base connected to a phone or computer via Vital Detect App which is free to download. Respiratory Rate and Heart Rate. The Vital Detect analyzes the data collected during the NIBP and SpO_2 measurement cycles to determine the user's respiratory rate and heart rate. The pulse oximeter being used in this study collects data from the finger by transmittance of radiation at known wavelength(s) through tissue to measure respiration rate. The Vital Detect pulse oximetry system is investigational and has not been cleared by the FDA.

The intended purpose of the device under test is spot-checking, non-invasive monitoring / logging of respiratory rate on humans. For this evaluation, the device will be run in a continuous data collection mode.

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

Figure 1 – Vital Detect the Device Under Test

All appropriate testing to demonstrate safety for use in human studies was completed prior to Clinimark's receipt of the device. Such documentation will reside in the design history files of the Sponsor. Documentation will be provided regarding the safety of the investigational device for electrical current, dielectric strength, surface temperatures and biocompatibility testing. The manufacturer of the investigational devices followed the FCC licensing requirements for product builds.

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

Data Acquisition System for the Investigational Device

The data from the Device Under Test will be collected on an application installed on the iOS or Android mobile device separate from the reference equipment.

Safety Equipment

Multi-parameter monitor used during the study to observe a subject's vital signs include ECG tracing, heart rate, respiratory rate, and $EtCO_2$ with capnograph.

- GE Healthcare S5 Compact Monitor, M-NESTPR module with ECG, and/or Multi-parameter monitor
- Portable oxygen tank, mask and ambu bag
- GE Healthcare (Datex-Ohmeda) 3900 TruTrak+ / OxyTip+ Oxy-F-UN or Oxy-AF Sensor and Oxy-OL3 cable (SpO_2 monitoring)
- Blood pressure cuff and stethoscope

Preliminary Investigations and Justifications of the Study

This will be the first clinical study conducted at Clinimark as part of the development of the Vital USA, Vital Detect respiratory rate measurement capability.

Risks and Benefits of the Investigational Device and Clinical Investigation

Currently the FDA defines respiration rate devices as Class II devices. **The Device Under Test in this study is considered non-significant risk device.**

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.
    - Sensors are applied to the surface of the site and are removed following data collection typically less than 1 day.
    - Adhesive ECG electrodes for health screening and monitoring 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.
    - 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.
    - Monitors are Class II devices used to measure respiratory rate. 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 respiratory rate.
- 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.

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.

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. Biocompatibility testing for surface contact electrodes is a requirement of the International Organization of Standardization (ISO) 10993 – Biological Evaluation of Medical Devices. The risk in the use of ECG electrodes is believed to be minimal.

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 exert a minimal amount of pressure. They should not cause discomfort. 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.

Benefits

The benefits to the study are to the advancement of non-invasive medical monitoring of patients by improving accuracy and performance of the monitors. 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 in a minimum of 20 subjects. Each subject test is expected to take approximately 1 hour. The overall data collection process is expected to be completed in 4-7 days.

The purpose of this study is to conduct a Respiratory Rate accuracy validation comparing the Vital Detect to an FDA cleared End Tidal Carbon Dioxide monitor Reference Standard (GE Datex-Ohmeda).

The procedures will be explained to the volunteer test subject and an Informed Consent will be signed by the subject. A health form and health screening will be conducted prior to the start of the test. Subjects will be seated to apply the devices and take baseline data, as well as the remainder of the study.

For the respiratory measurement the Test Subject will be outfitted with a mouthpiece attached to a monitoring line allowing for measurement of the $EtCO_2$ derived respiratory rate. Nose plugs/clips will be used so the subject can only breath through the mouthpiece. The subject is able to take out the mouthpiece between data sets.

A GE Healthcare Datex-Ohmeda S/5 Multi-parameter Monitor will be utilized to monitor tidal volume, respiratory rate, $EtCO_2$, and ECG. A pulse oximeter will be placed on the subject and monitored for safety during the test.

A range of stable respiratory rates will be elicited from each volunteer test subject. The rates will be approximately 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 BPM; with some natural variation from these exact numbers and tailored to the subject's capabilities as some subjects may not be able to breathe at the lower and higher

respiration rates. The subject will follow a paced breathing app. Once stable breathing at specified rate is achieved, data will be collected for one and a half to three minutes. If the respiratory rate changes more than three bpm during the target respiration rates, then the data for that period will be considered unstable.

After starting with a stable respiration rate at the subject's natural rate (without the breathing app), the breathing pattern on the app will be set to begin near the natural respiration rate of the subject and continue to go down by five breath per minute intervals until reaching the respiration rate of 5 BPM. After that, data collection will continue by picking back up at the rate above the subject's natural respiration rate and continue upwards until reaching 50 BPM.

The respiratory rate will be collected simultaneously from the Reference and the Device Under Test. The data will be recorded separately and electronically. Additional study notes that describe conditions of the test as well as deviations, device issues, and any adverse events will be recorded in written documentation.

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 product development /training by the sponsor.

Equipment

The software collects the Reference and acceptance data at 1 second intervals and allows for marking events.

Description of Clinimark Gas Mixing Fixture with Automated Data Collection:

Computer with gas mixing/control software and automated data collection system
Sealink Mux box – 8 channel, communication cables
Gas control fixture (not used to deliver gas in this study but needed to run the software)

Safety Equipment

GE Healthcare Datex-Ohmeda S/5 Multi-parameter Monitor, M-NESTPR module with ECG, M-COVX module – Spirometry
GE Healthcare (Datex-Ohmeda) 3900 TruTrak+ / OxyTip+ Oxy-F-UN Sensor and Oxy-OL3 cable
Portable oxygen tank, mask and ambu bag
Blood pressure cuff and stethoscope

Supplies for Subject

Ventilation tubing and open system mask
Mouthpiece with $EtCO_2$ sample line

Reference – Respiration Rate Monitoring

GE Healthcare Datex-Ohmeda S/5 Multi-parameter Monitor, M-NESTPR module with ECG, M-COVX module – Spirometry (K021279) (Reference $EtCO_2$)

Investigational Device

Vital USA, Vital Detect

There are no deviations expected from this investigation plan. Should deviations be needed, discussions will be conducted with Vital USA and Principal Investigator and reported to the IRB per the reviewing IRB guidelines.

Study Population

The study population will include 20 healthy competent adults, ages 18 years and older. The subject selection will be a mix of males and females with small to large physiques. 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 and passing the health

screening. Eligible subjects needed to meet all of the inclusion criteria and none of the exclusion criteria for participation.

Inclusion Criteria

- Subject must have the ability to understand and provide written informed consent
- Subject is adult over 18 years of age
- Subject must be willing and able to comply with study procedures and duration
- Subject is a non-smoker
- Male or female of any race

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

- 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.)
- Subjects with known respiratory conditions such as:
    - uncontrolled / severe asthma,
    - flu,
    - pneumonia / bronchitis,
    - shortness of breath / respiratory distress,
    - respiratory or lung surgery,
    - emphysema, COPD, lung disease
- Subjects with self-reported heart or cardiovascular conditions such as:
    - have had cardiovascular surgery
    - Chest pain (angina)
    - heart rhythms other than a normal sinus rhythm or with respiratory sinus arrhythmia
    - 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
    - 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 head injury within the last 2 months,
    - Cancer / chemotherapy
- 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 approximately 1 hour. The study is expected to take 4-7 days to complete for this subject population.

Criteria for Study Termination

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

- The subject may stop the study for any reason without prejudice
- Development of any cardiac arrhythmia, except sinus arrhythmia <120 bpm
- Sustained sinus tachycardia ≥120 bpm
- Onset of PVCs

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 setup and checkout prior to starting study.
2. Set and / or synchronize the computer clocks for Vital USA and Clinimark data collection 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 and date the Informed Consent Form. Have the subject complete, sign and date the Health Assessment Form. Each subject will be given a copy of the consent form prior to release.
4. The clinician or PI will confirm appropriate signatures on the Informed Consent Form and verbally question the subject about their health history.
5. Apply ECG leads to the subject, review for normal sinus rhythm or sinus arrhythmia.
6. Record all baseline vital signs (SpO_2, Pulse Rate/Heart Rate, ECG rhythm, Respiratory Rate, Antecubital fossa check and alcohol smell check).
7. Based on the responses to the health assessment form and verbal health assessment, record accepted or declined from the study. Continue if accepted into the study.
8. Setup and verify communication between the devices and data collection systems.
9. Record device information for tracking (manufacturer, model #, serial/lot, hardware/software control info).
10. Record subject information. Subject number and demographics information for subject description.
11. Apply Device Under Test sensors to the subject. Adjust sensors as appropriate and record on test form.
12. Instruct the subject how to use the mouthpiece. Starting data collection, the subject is instructed to breathe at their natural rate (without the breathing app) for a baseline data set.
13. A range of stable respiratory rates will be elicited from each volunteer test subject using a paced breathing app. The rates will be approximately 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 breaths per minute; with some natural variation from these exact numbers and tailored to the subject's abilities. Once a stable breathing at specified rate is achieved data will be collected for one and a half to three minutes.
    a. The breathing pattern on the app will be set to begin near the normal Respiration Rate of the subject (baseline) and continue to go down by five BPM intervals until reaching the Respiration Rate of 5 BPM. After that, data collection continues at the rate above the subject's normal Respiration Rate and continue upwards until reaching 50 bpm or whatever level the subject can tolerate comfortably.
14. The respiratory rate will be simultaneously monitored and recorded electronically for the $EtCO_2$ (Reference) and the Device Under Test. Record any additional study notes that describe conditions of the test as well as deviations and device issues.
15. End the data collection and take all equipment off.

Statistical Analysis

Statistical Analysis will be performed by Clinimark.

The Reference Respiratory Rate based on $EtCO_2$ will be collected simultaneous to the Device Under Test Respiratory Rate at a given level for 1 to 3 minutes. The data will be paired based on syncing of the data collection system clocks. During the stable plateaus at each level, the data will be averaged in approximately 20 second intervals. The goal is to have 3 to 5 data points per level. If the respiratory rate varies by more than 3 bpm during data collection period of the target respiration rates, then the data for that period will be considered unstable and removed from analysis. The final pairing to be analyzed is the average of the 20 second periods of the Reference $EtCO_2$ with the average of the simultaneous 20 second period for the DUT. The Accuracy root-mean-square (Arms) will be the basis for evaluation and acceptance.

Endpoint / Comparator

The primary objective of this study is to compare the accuracy of the Device Under Test for the measurement of respiratory rate to the Reference, which is an End Tidal Carbon Dioxide Monitor ($EtCO_2$). Twenty second periods will be averaged to provide one respiratory rate value. Each stable respiratory rate plateau will result in three to five respiratory rate values which will be included in the A_{RMS} calculation.

The endpoint of interest is accuracy as measured by the Accuracy root-mean-square (Arms) difference between the Device Under Test (DUT) and the Reference $EtCO_2$ (Ref) for all stable respiratory periods where:

$$A_{rms} = \sqrt{\frac{\Sigma(DUT-Ref)^2}{n}}$$

Acceptance Criteria: Passing requires an Arms of $\leq$3 with a goal of achieving 2.

Sample Size Justification

The Pulse Oximetry FDA Guidance Document (March 4, 2013, Section 4.1.*1 In vivo testing for SpO2 accuracy under laboratory conditions*) calls for 10 or more healthy subjects with 200 data points evenly distributed over the full range. This information is used as a guideline for sample size justification in this study. This study will utilize a sample size of 20 subjects with 20-28 stable periods per subject, providing $\geq$200 data points over the specified breath per minute range.

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

Prior to the start of subject enrollment, the Primary 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 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

Vital USA or 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 Vital USA
- 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 Vital USA 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 Vital USA, 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 reported accordingly to the IRB and Vital USA in the required timeframe
6) Protocol Deviations
    - Verity that Protocol Deviations are being reported accordingly to the IRB and Vital USA in the required timeframe
7) Electronic Data Review
    - Verify that the filename matches the filename entered on the CRF and that the appropriate number of Oximeter channels were recorded
8) 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# 2019-326.

The subject's name and signatures will be recorded on the Informed Consent, Health Assessment Form, and a subject screening and enrollment logs. 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 subject #, date and by filename recorded on the data collection forms. The device's 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

Sponsor Respiratory Rate Validation in Adults
Clinimark Study ID# PR 2019-326

Subject Documents

Provided as separate documents to this protocol:

- Informed Consent form (IRB approved)
- Health Assessment Form (Clinimark Control # F2000-001-001 Rev 13 or current revision)

Study Conduct Documents:

- CRF2019-326 – Case Report Forms
- Electronic Files – electronic data collected from the Refence and Device Under Test

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

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 # F2000-001-042 - Adverse Event CRF
- Clinimark Control # F2000-001-043 - Protocol Deviation Form
- Clinimark Control # F2000-001-044 - Subject Screening Log
- Clinimark Control # F2000-001-052 - Device Deficiency Log
- Communications

Current revision of documents applies.

Amendments to the Clinical Investigation Plan

Vital USA or study site may need to make protocol changes during the study. Such amendments will be documented, reviewed and changes will be submitted to Vital USA for first approval, then to the IRB for approval. Vital USA and the study site will make a decision regarding the continuation of subject enrollment during this period. The study 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 and within 5 working days of the occurrence of such deviation.

Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study must be reported to Vital USA 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 and 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. Vital USA is responsible for packaging and labeling of the investigational 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, and the quantity of contents if appropriate, along with 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 labeling 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/secured 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: Vital USA Respiratory Rate Validation in Adults ID# PR 2019-326
- ISO 80601-2-61, first edition 2011-04-01, 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 14155:2011 Clinical investigation of medical devices for human subjects — Good clinical practice
- Clinimark Adverse Events Reporting Document B3000-000-003 (current revision)

Informed Consent Process

- The Principal Investigator or their 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 or their designee uses a investigational device without obtaining informed consent, the Investigator shall report such use to Vital USA 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 subject or legal guardians of 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 or legal guardians of the subject may withdraw the subject 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, 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 Principal Investigator will be contacted as appropriate. Adverse Events are reported through standard Clinimark Procedures, IRB requirements and per Vital USA'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, Vital USA 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, Clinimark Medical Director, Vital USA and IRB within 24hrs of knowledge of the event.

Vital USA 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
- 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 as soon as possible and not later than 10 working days after the Investigator first learns 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 if FDA approval

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

Progress Reports

Vital USA shall submit progress reports to the IRB at least yearly.

Recall and device

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

Final Report

Vital USA shall submit a final report to the IRB with 6 months after termination or completion of the investigation.

Informed consent

Vital USA shall submit to FDA a copy of any report by an Investigator under paragraph (a)(5) of this section of use of an investigational 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 Vital USA had proposed that the IRB consider the device not to be a significant risk device, Vital USA shall submit to FDA a report of the IRB's determination within 5 working days after Vital USA first learns of the IRB's determination.

Other

Vital USA 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 Vital USA 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 Vital USA, 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 Vital USA 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. The subject may choose to withdraw the subject 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 form.

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 Vital USA (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 Vital USA 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 Vital USA. The current subjects will be followed according to the protocol.

If the study is terminated prematurely or suspended by Vital USA /Investigator, Vital USA /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 Vital USA /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 and 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. Vital USA will inform the regulatory authorities (if required).

Withdrawal of IRB approval shall be reported to Vital USA 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

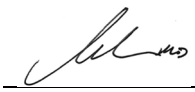
The results of this investigation will not be submitted for publication.

Attachment A - Protocol Signature Page

Protocol No. PR 2019-326

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 participant.

- 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,
- 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, and
- 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

26 APR 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)