CLINICAL PROTOCOL

PR 2022-516

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CLINIMARK Test Plan

Clinical Evaluation of Zynex Monitoring System, Model CM-1600

PR2022-516

COMMERCIAL SPONSOR:
Zynex Monitoring Solutions
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Englewood, Colorado 80112

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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Table 1: List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	Adverse Event
ANP	Atrial Natriuretic Peptide
BI	Bioelectrical Impedance
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CM-1600	Zynex Non-invasive Monitoring System CM-1600
CBV	Central Blood Volume
CRF	Case Report Form
CS	Clinically Significant
ECG	Electrocardiogram
cGMP	Cyclic Guanosine Monophosphate
H	Hypotensive Prone
HD	Hemodialysis
HR	Heart Rate
ICW	Intracellular Water Changes
IRB	Institutional Review Board
kg	Kilogram
L	Liter
lb	Pound
LBNP	Lower Body Negative Pressure
mg	Milligram
mL	Milliliter
NCS	Not Clinically Significant
N	Non-hypotensive Prone
NSR	Non-Significant Risk
PO	Pulse Oximetry
PPG	Photoplethysmography
RH	Relative Humidity
SAE	Serious Adverse Event
SR	Significant Risk
TBI	Total Body Impedance
TI	Thoracic Electrical Impedance
ZMS	Zynex Monitoring Solutions

Summary

Objectives of the Clinical Investigation Plan

The objective of this study is to determine if manual blood loss of up to 500mL of blood and saline re-infusion can be identified using the non-invasive Zynex Monitoring System, Model CM-1600.

[redacted]

Protocol Overview

This is a prospective, single-arm, non-randomized, non-controlled single-center study for the evaluation of the Zynex CM-1600 in 20 healthy adults undergoing a manual blood loss of up to 500mL followed by an infusion of 1 liter of normal saline.

After IRB Approval, 20 volunteer participants, ages 18 years and older with a range of physiques and skin tones, will be entered into a study that is designed to investigate the Zynex CM-1600 non-invasive monitoring system. Participants will be selected for the study using the inclusion / exclusion criteria. After signing the informed consent, participants will complete a health assessment form and undergo a brief health screening.

Each participant will be offered oral fluids and be fitted with non-invasive electrodes and a wrist wearable. The participant will lie supine during the blood draw procedure. Up to 10% of the participant's total blood volume or up to 500mL (whichever is least) of blood will be drawn by a qualified medical professional under normal conditions. A participant's total blood volume is calculated:

- Females: Weight in kilograms x 65 = Total blood volume
- Males: Weight in kilograms x 75 = Total blood volume

The CM-1600 will electronically record bioelectrical impedance (ohms), heart rate, skin temperature (°C), ECG amplitude, and PPG amplitude before, during, and after the blood draw.

No passing criterion exists for this study. This is an investigative study to collect preliminary data on healthy human volunteers.

Study Population

The study population will include 20 healthy adults, aged 18 and older with a variety of physiques and skin tones. The participants must understand the study and agree to participate by signing the informed consent. The participants must be healthy, showing no evidence of medical problems as indicated by satisfactory completion of the health assessment form and passing the health screening. Eligible participants need to meet all of the inclusion criteria and none of the exclusion criteria for participation.

Inclusion Criteria

- Participant must have the ability to understand the parameters of participation and provide written informed consent
- Male or female of any race
- Participant is adult 18 or older
- Participant must be willing and able to comply with study procedures and duration
- In the Principal Investigator's medical judgment, the participant is suitable for a blood draw of up to 500mL
- Participant must weigh at least 110 pounds

Exclusion Criteria

- Any upper extremity amputation
- Females who are pregnant, who are trying to get pregnant, or have a urine test positive for pregnancy on the day of the study
- Participant has a heart condition that may interfere with the Zynex CM-1600 (e.g., pacemakers, defibrillator, irregular heartbeat, dextrocardia, etc.)
- Participant has been diagnosed with chronic fatigue syndrome (also known as chronic fatigue, immune dysfunction syndrome, or myalgic encephalomyelitis)
- Participant requires equipment and/or devices that may interfere with the Zynex CM-1600 (e.g., life-sustaining equipment, other monitoring devices, insulin pumps, or other implanted devices)
- Participant is taking coumadin (warfarin), heparin, or other prescription blood thinners for 7 or more days prior to blood draw
- Participant donated blood within 8 weeks prior to the study blood draw
- Participant has high or low blood pressure on the day of blood draw (high blood pressure is defined as systolic > 180 mmHg or diastolic > 100 mmHg; low blood pressure is defined as systolic < 100 mmHg or diastolic < 60 mmHg)
- Participant has symptoms of an active infection or a temperature $\geq 100\ ^{\circ}F$
- Female with hemoglobin levels of less than 12.1g/dL or male with hemoglobin levels of less than 13.8g/dL
- Participants with self-reported heart or cardiovascular conditions such as:
    - History of cardiovascular surgery
    - History of chest pain (angina)
    - Heart rhythms other than a normal sinus rhythm or respiratory sinus arrhythmia
    - History heart attack/myocardial infarction
    - Peripheral arterial disease
    - Carotid artery disease
    - Unexplained shortness of breath
    - Congestive heart failure (CHF)
    - History of stroke/transient ischemic attack
    - Myocardial ischemia
    - Cardiomyopathy
    - Dextrocardia
- Participants with clotting disorders such as:
    - Hemophilia

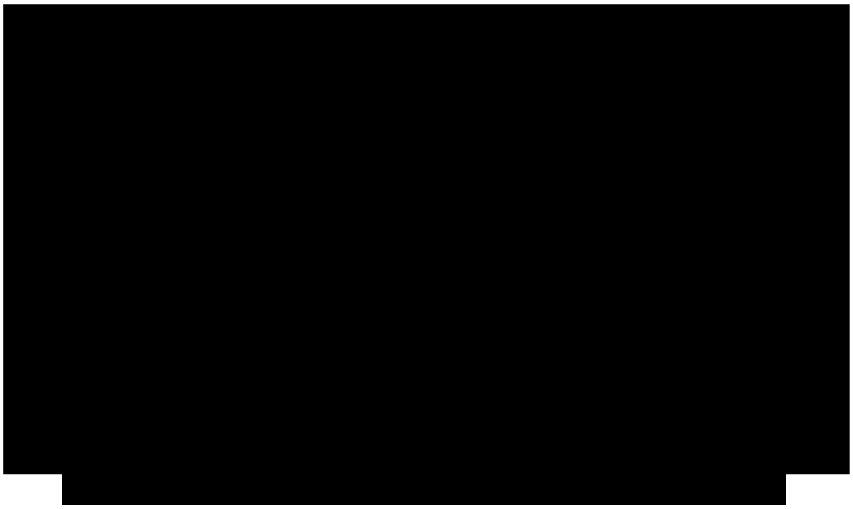
  - History of blood clots
  - History of bleeding problems
  - Bruises easily
- Self-reported health conditions as identified in the Health Assessment Form including:
  - Diabetes
  - Uncontrolled thyroid disease
  - Kidney disease / chronic renal impairment
  - History of seizures (except childhood febrile seizures)
  - Epilepsy
  - History of unexplained syncope
  - Recent history of frequent migraine headache within the last 2 months
  - Recent head injury within the last 2 months
  - History of cancer, with or without chemotherapy within the last 2 months
- Other known health conditions deemed unsuitable for participation by the PI when considered upon disclosure on health assessment form

Duration of Clinical Investigation

It is expected that the data collection for the study will take approximately 8 working days to complete. Individual subject participation is expected to take approximately 3 hours. No additional follow-up is required for the investigation.

Identification and Description of the Investigational Device

The Zynex CM-1600 was developed to provide physicians with a non-invasive way to detect and monitor changes in volume, particularly when fluctuations are anticipated, such as during surgery, in post-op and/or recovery. This monitoring device will identify baseline subject status and detect relative changes using an algorithm to compare and review data trends monitored during surgery, displaying blood volume and blood loss in real-time.



The design configuration for the Zynex CM-1600 includes:

- Compact, all-inclusive unit with display, touch-screen, and electronics
- Power supply
- Wearable
- Wrist strap
- Y-Cable
- Electrodes

Displayed on the screen are:

- Bioelectrical impedance (ohms)
- Heart rate
- ECG amplitude
- PPG amplitude
- Skin temperature (°C)

The values from these parameters become algorithm inputs, which calculate a Relative Index of changes in patients, and a trend graph displays corresponding patient status. The trending graph starts at 100 (baseline data point) and plots changes relative to blood loss.

The CM-1600 is manufactured by Zynex Monitoring Solutions (ZMS). The company maintains a quality system compliant with ISO 13485:2016, Medical Devices -- Quality Management Systems -- Requirements for Regulatory Purposes. The CM-1600 and the enclosed electronics have passed all cleaning and disinfection, biocompatibility, electrical safety, and electromagnetic compatibility testing required for cardiac monitoring devices. Materials are certified to comply with standard material specifications. Formal design of the ZMS CM-1600 was conducted in accordance with the current Good Manufacturing Practices (GMP) requirements set forth in the Quality System Regulations (QSR) promulgated under Section 520(f) of the Food, Drug, and Cosmetic (FD&C) Act; design control procedures under 21 CFR §820 and ISO 13485; other applicable national and international standards and guidance as appropriate; and Zynex's own product specifications and technical drawings, and within the context of the company's design controls and Medical Device File (MDF) that fall under its QMS.

FDA guidance documents, ISO standards, and additional design related documents, including the Device Master Record (DMR)/Medical Device File (MDF), and Device History Record (DHR) reside with ZMS and are available upon request.

Data Acquisition System for the Investigational Device

The data will be collected by the Zynex CM-1600 non-invasive monitoring system.

MediCollector

- Computer with data collection software, able to stream data as it is recorded with the ability to add annotations
- Direct cable connection with the Datex-Ohmeda S/5 Multi-parameter Monitor
- Collects a variety of signals including values displayed by the S5 as well as the raw waveforms
    - Up to 8 signals can be collected

MediCollector –Signal Channels Examples				
#	Name	Description	Freq. of Collection (Hz)	Units
1	SpO2	Oxygen Saturation	0.2	%
2	SpO2_Pulse	Pulse Rate from SpO_2	0.2	beats/min
3	CO_RR	Respiratory Rate	0.2	breaths/min
4	HR_ECG	Heart Rate from ECG	0.2	beats/min

Reference Equipment

- GE Healthcare (Datex-Ohmeda) S5 Compact Monitor (K061185) with M-NESTPR (K993608) or E-PRESTN (K031781) module, and/or other multi-parameter monitor (or equivalent) for ECG /heart rate/SpO_2 /respiratory rate monitoring
- Clinimark data collection system 3900 TruTrak+
- CO-Oximeter: ABL 80 OSM or equivalent (optional)
- Abbott iStat 1 or equivalent (optional)

Safety Equipment

- Portable oxygen tank, mask, and ambu bag
- Blood pressure cuff and stethoscope
- Temperature probe

[redacted]

[redacted]

[redacted]

Risks and Benefits of the Investigational Device and Clinical Investigation

The device under test in this study is considered a non-significant risk device.

Participants engaging in this study are subject to risks that are no greater than, or are similar to, the risks associated with undergoing a blood donation. The risks of blood donation include nausea, lightheadedness, and dizziness, which are temporary and usually brief. The CM-1600 non-invasively monitors and records bioelectrical impedance (ohms), heart rate, ECG amplitude PPG amplitude, and skin temperature (°C).

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 superficially applied to the site and are removed following data collection (less than 1 day).
- 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 participant.
    - See below for discussion of risk associated with the device and use of the device.
- It is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health.

No anticipated risks or adverse device effects need to be assessed. No contraindications exist for use in the proposed study / study population. Any other risks to the participant associated with the device or procedure are unforeseeable at this time.

ECG / Gel Electrodes

Materials (such as the adhesive and/or gel contact) used in the electrodes may cause some skin irritations in some participants. Typical skin irritations present with redness of skin and in some cases of sensitivity as an allergic reaction. Biocompatibility testing for surface contact electrodes is a requirement of the International Organization of Standardization (ISO) 10993-9:2008 Biological Evaluation of Medical Devices. The risk in the use of ECG and other gel electrodes is believed to be minimal.

Pulse Oximetry Sensor

Pulse oximetry sensor placement involves positioning pulse oximetry sensors on the volunteer participant in the same manner that is used on hospitalized patients. The sensors may be warm to the touch. Under normal operating conditions, without electrical abnormalities or 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 participants. Every effort will be made to minimize products with natural rubber or latex, and products containing natural rubber or latex will be identified. The risk involved in the use of pulse oximetry sensors is believed to be minimal.

Finger Prick Lancet

A finger prick blood analysis involves using a lancet to draw a small amount of blood from the tip of a finger. Possible risks from the finger prick procedure include: discomfort, bruising, clotting, and infection.

Peripheral Intravenous Cannula

A peripheral IV cannula will be inserted by a qualified healthcare professional. The possible risks from the IV insertion include: pain, hematoma, clotting, infection, scar formation, and infiltration.

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. Other than being a paid volunteer, no direct benefits to the participants engaging in this study exist. The only alternative to this study is to NOT participate.

[redacted]

[redacted]

[redacted]

Method

This is a prospective, single-arm, non-randomized, non-controlled, single-center study for the evaluation of the Zynex CM-1600 in 20 healthy adults undergoing a manual blood loss of up to 500mL (or 10% BV) and saline re-infusion. Each participant test is expected to take approximately 2.5-3 hours. The overall data collection process is expected to be completed in approximately 8 working days.

The objective of this study is to determine if manual blood loss of up to 500mL of blood and re-infusion of saline can be identified using the non-invasive Zynex CM-1600.

The procedure will be explained to the volunteer, and if he/she agrees to participate, he/she will then sign the informed consent. The participant shall also complete a health screening form, which will be reviewed by a clinician before the test begins.

Participants will lie supine for the application of the devices and for the remainder of the study. Hemoglobin will be measured for inclusion screening with either a finger prick or venous blood draw.

In addition to the study device, a multi-parameter monitor will be utilized to monitor heart rate, cardiac rhythm, blood pressure (not continuously), pulse rate, respiratory rate, and SPO_2 for safety during the test. These observations will be monitored throughout the study, both objectively and subjectively. Should vital signs become unstable, per the clinical judgment of the study staff, the study will be halted immediately.

During the study, data will be continuously recorded electronically. Additional study notes describing conditions of the test, deviations, device issues, and any adverse events will be documented in writing.

Photographs may be taken of the sensor application sites prior to and post sensor application for data collection and analysis purposes and the Sponsor's internal research and development only. Photos may include the upper- and lower body or any other site where equipment has been placed. In order to capture images of the study equipment, it may be unavoidable to photograph the participant's face. In order to protect his/her identity, that person's name and all personal identifiers will be kept confidential at all times.

If the participant refuses to be photographed, it may affect his/her ability to participate in the study.

Reference Equipment

- GE Healthcare (Datex-Ohmeda) S5 Compact Monitor with M-NESTPR (K993608) or E-PRESTN (K031781) module, and/or other multi-parameter monitor (or equivalent) for ECG /heart rate/SpO_2 /respiratory rate monitoring
- Clinimark data collection system 3900 TruTrak+
- CO-Oximeter: ABL 80 OSM or equivalent (optional)
- Abbott iStat 1 or equivalent (optional)

Safety Equipment

- Portable oxygen tank, mask, and ambu bag
- Blood pressure cuff and stethoscope
- Temperature probe

Supplies for Participant

- 16-gauge needles for blood draw (other gauges as necessary)
- Alcohol wipes
- Blood collection bags
- Anticoagulant coated tubing to decrease clotting
- Nasal cannulas
- 1L bags of normal saline
- 18-, 20- and 22-gauge IV catheters
- IV start kit

Investigational Device

- Zynex CM-1600 monitoring system

Procedure

1. Complete equipment set up and checkout prior to starting study.
2. Set and / or synchronize the computer clocks for the CM-1600 and Clinimark data collection systems.
3. Explain the procedure to the participant. Have him/her read the informed consent, review the information with the participant, and answer all questions. Once all questions have been answered, have the participant sign and date the informed consent. Each participant will be given a copy of the consent prior to release.
4. Ask the participant to complete, sign, and date the Health Assessment Form. The clinician or PI will, together with the participant, review the information provided about his/her health history. Based on this review, the clinician will determine to accept or exclude the participant from the study. Continue if accepted into the study.
5. Record participant number and demographic information on the Clinimark CRF and calculate the blood volume.
6. Place the participant into supine position, apply reference ECG leads, and review for normal sinus rhythm or sinus arrhythmia.
7. Take participant's temperature to screen for potential infection prior to study start.
8. Apply NIBP cuff and take reading.
9. Apply PPG sensors and screen for safe SPO_2 to participate in study.
10. Perform hemoglobin inclusion screening.
11. Apply nasal cannula.
12. Cleanse participant's skin with an alcohol wipe, and place the non-invasive electrode pads at participant's left clavicle and left forearm.
13. Set up CM-1600 (See IFUs for proper setup) and begin monitoring session.
14. Verify communication between the devices and data collection system.

15. Start IV (preferably on participant's left hand but either hand or either antecubital site will be acceptable), using 20-22g IV catheter (or other appropriate size) and open line with saline at TKO. Press "Mark Event" on the CM-1600.
16. Record device information for tracking (manufacturer, model number, serial/lot number, hardware/software control information).
17. Participant will rest for 5 minutes while the baseline measurements are recording.
18. After the 5-minute baseline recording is captured, passively raise the participant's legs above his/her heart for 3 minutes and press "Mark Event" on the CM-1600 screen [redacted] when initiating.
19. Passively lower the participant's legs and press "Mark Event" on the CM-1600 when initiating lowering.
20. Wait 5 minutes to return to baseline.
21. Prepare for blood draw using 16g IV catheter (or other appropriate size) primarily from the right arm (left antecubital region is acceptable if right access is not attainable). Just before the blood draw (at needlestick), push the "Mark Event" button on the display.
22. Perform blood draw of 10% of participant's blood volume, up to 500mL, based on body weight and blood volume calculation.
23. Immediately following completion of the blood draw (tubing clamped), press "Mark Event" on the CM-1600 screen.
24. The participant will lie flat for at least 10 minutes while the CM-1600 is still running the monitoring session after the blood draw is complete.
25. Infuse 1 liter of normal saline over 30 – 60 minutes through the IV. Push the "Mark Event" button on the screen at the beginning and end of the saline infusion.
26. Measure vital signs: blood pressure, respiratory rate, ECG, SPO_2, and heart rate.
27. Offer oral fluids and a snack to the participant.
28. Continue to monitor the participant for 30-60 minutes.
29. Measure vital signs: blood pressure, respiratory rate, ECG, SPO_2, and heart rate
30. If normal vital signs are achieved / maintained; the participant is able to walk without compromise; and the participant is not experiencing difficulty eating or drinking, stop the CM-1600 monitoring session and all external reference devices, remove the IV, remove all devices from the subject, and clear the participant to leave.
31. Review any final questions with the participant, and ask if there were any ill effects from the study.
32. Give the participant final instructions for care of the IV site and the blood draw site. Provide phone numbers for questions pertaining to participation in this study, research-related injury, or any adverse reaction post study.
33. Once data collection on the CM-1600 is stopped, the USB data storage can be removed. USB data storage device is to be labeled in accordance with the assigned participant identification number and the continuity of the acquired data is to be verified and/or backed-up. The CM-1600 device and accessories will be wiped down again with a disinfecting wipe. Electrodes will be disposed.
34. Blood disposal will be carried out at the Investigator site and will follow all applicable rules and regulations, including any site-specific procedures.
35. Clinimark will follow up with the participant in 24-48 hours to screen for any adverse events or complications.

Statistical Analysis

This is a prospective, single-arm, hypothesis-generating study early in the clinical development of the Zynex CM-1600; hence, no statistical tests are required and no assumptions are made. Any statistical and data analysis will be performed by the Sponsor.

Sample Size Justification

The objective of this study is to determine if manually controlled and quantified blood loss and saline re-infusion can be identified by the non-invasive Zynex CM-1600. No statistical hypotheses have been generated for this study; therefore, the sample size of 20 participants is empirically determined to be sufficient for an early-phase hypothesis-generating study and is based on clinical judgment rather than statistical considerations.

Analysis Populations

This is a hypothesis-generating study of 20 participants; therefore, all data collected will be used and presented in the study summaries**.**

Statistical Analysis Plan

- The data for this study will be summarized using descriptive and frequency statistics, depending on the nature of the variable. The distribution of continuous variables will be summarized using number and percentage of non-missing data points, means, standard deviations (sd), medians, minimums, and maximums. Ordinal variables will be summarized using categorical methods if the number of observed responses is small (usually fewer than 4) and with medians, minimums and maximums otherwise. Summary statistics for discrete variables will consist of the numbers and percentages of responses in each category.

- A descriptive analysis of the change from baseline will be performed to better understand the magnitude of the changes and variability of the measurements for bioelectrical impedance (ohms), heart rate, ECG amplitude, PPG amplitude, skin temperature (°C), to obtain the relative index (RI).

- A correlation analysis will be performed to gain a basic understanding as to how the Zynex CM-1600 measurements relate to the actual volume of blood loss and saline re-infusion. This is a hypothesis-generating study and is not powered to establish a true relationship; therefore, the results of this analysis will not be presented with statistical significance.

- Adverse events and concomitant medications that are reported during the study will be summarized and presented in a tabular format.

- All available data will be presented and summarized based on the number of participants with available data. Missing data will not be imputed, as no statistical inferences will be made based on the results of these analyses.

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

Prior to the start of participant 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 participant informed consent date. Written IRB/IEC approval and any conditions of approval imposed by the IRB/IEC will be obtained by the Primary 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.

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Monitoring Arrangements

Zynex (Sponsor) 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 Sponsor
- 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.
- A monitoring report is provided at the end of the clinical investigation.

Monitoring Plan

1) Informed Consent
   - Verify that the consent 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) Participant Eligibility
   - Verify that the participant meets all of 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 that all CRFs are completed.
5) Adverse Events
   - Verify that Adverse Events and Serious Adverse Events / UADEs are reported accordingly to the IRB and Sponsor in the required timeframe.
6) Protocol Deviations
   - Verity that protocol deviations are reported accordingly to the IRB and Sponsor in the required timeframe.
7) Electronic Data Review
   - Verify that the filename matches the filename entered on the CRF.
8) Ensure that the Trial Master File is complete.

Data and Quality Management / Confidentiality

A checklist identifying the contents of the Trial Master File / Project folder PFC# 2022-516 will be maintained.

The participant's name and signatures will be recorded on the informed consent, health assessment form, and a participation list. The data collection form will only use a participant number for the day of the test along with participant demographics. A name will not be recorded on the case report form.

Records identifying the participant'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 participant based on participant identification number, 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 participant demographics and participant number may be additionally copied (after de-identification, if applicable), reviewed, and supplied to the Sponsor for the study.

All study records will be stored for at least 2 years post the release of the product or project cancellation. The Investigator will notify the 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

CRF 2022-516

Participant Documents

Provided as separate documents to this protocol:

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

Study Conduct Documents:

- CRF2022-516– Case Report Forms
- Electronic Files – electronic data collected from the devices under test or reference 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 participant enrolled 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, participant identification number, relevant participant demographics, and associated electronic filename(s)
- Evidence that informed consent was signed and dated prior to the participant participating in the study
- Information for participant inclusion or exclusion to the study
- Equipment calibration and communication check out
- Device usage / sensor placement on the participant
- Baseline respiration rate, SpO_2, heart rate and rhythm, blood pressure, and pulse ox data
- 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 complete. Erroneous entries should be crossed out, corrected with the change, and initialed and dated by the individual making the correction. The Investigator(s) or designee will sign and date at indicated places on the data collection form. The Protocol Deviations Report may 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 Report must be signed and dated by the designee and a Sub-Investigator or Investigator. The Principal Investigator must review, sign, and date all serious adverse events. The Investigator or designee will provide a final signature indicating that a thorough inspection of all participant 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. If corrections are made after review and signature by the Principal Investigator, the Principal Investigator will be made aware of the changes, and his/her awareness will be documented by initialing and dating the changes.

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 - Participant 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
- Communications
- Zynex Monitoring Solutions CM-1600 Instructions for Use (Rev 6)

Current revision of documents applies.

Amendments to the Clinical Investigation Plan

Zynex or the site may need to make protocol changes during the study. Such amendments will be documented and reviewed, and changes will be submitted to Zynex for first approval, then to the IRB for approval. Zynex and the site will decide whether or not to continue to enroll participants during this time. 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 wellbeing of human participants may proceed without prior approval of the Sponsor or 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.

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 number, lot number, 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 participant.

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 labeling the device for delivery to the study site. FDA cleared devices do not require special labeling. Investigational devices or their immediate packages 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 that 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/secure with access limited only to approved study staff.

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

Cleaning

Please refer to CM-1600 Instructions for Use.

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.

[redacted]

Informed Consent Process

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

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.

Participant

Equipment is checked out for proper functionality prior to being placed on the participant.

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

A clinician will be present to monitor the participant at all times. Safety monitoring includes ECG, SpO_2, pulse rate, respiration rate, direct observation and communication with the participant.

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 and resulting from insufficiencies or inadequacies in the instructions for use, the deployment, installation, the operation, any malfunction of the investigational medical device, or from usage error.

- **Adverse Event (AE):** Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in participants, 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 participant 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):** An adverse device effect results in any of the consequences characteristic of a serious adverse event.
- **Serious Adverse Event (SAE):** A serious adverse event 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 requires medical or surgical intervention to prevent permanent impairment to body or structure.
- **Severe:** A severe adverse event results in the inability to perform usual activities.
- **Unanticipated Adverse Device Effect (UADE):** A serious adverse device effect is one 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 participant experience an adverse or non-typical event, the investigational staff will assess the situation and determine 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 Zynex 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 results in death of a participant, the event shall be reported to the Principal Investigator, Clinimark Medical Director, Sponsor, and IRB within 24 hours of knowledge of the event.

[redacted]

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
- 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

The 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 withdrawal of 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 of withdrawal of approval.

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

Recall and device
The Sponsor shall notify the FDA and all reviewing IRBs 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 Sponsor 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 the 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 participant's case history and exposure to the device and supporting data, including signed and dated consent, health assessment form, and progress notes during the study. Records should show evidence that informed consent was signed and dated prior to the participant engaging 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. The participant may choose to withdraw from the study at any point. If a participant officially withdraws from the study, the laboratory staff will document the reason for withdrawal in the case report.

Participation in the study may also be stopped at any time by the Principal Investigator or by the Sub-Investigators or Sponsor for the following reasons:

- The participant's failure to cooperate fully (as determined by the Investigator in his or her sole discretion) with the required conduct of this study
- The participant'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 participants will cease in the following cases:

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

No follow-up procedures for withdrawn or discontinued participants are required, unless such is required at the Investigator's discretion.

Consideration for early termination or suspension of the investigation may be related to unanticipated equipment failure or a decision by the Sponsor or the site. Both Zynex 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 may occur because of, but not limited to, inadequate data collection, low participant 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 participants 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 participants and ensure appropriate follow-up for the participant.

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 will provide a detailed written explanation of the termination or suspension. The Investigator will promptly inform the participants and ensure appropriate therapy and follow-up for the participants. The Sponsor will inform the regulatory authorities (if required).

Withdrawal of IRB approval shall be reported to the Sponsor by the Investigator within 5 working days.

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

Attachment A - Protocol Signature Page

Protocol No. PR 2022-516

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 that each participant's informed consent is obtained prior to the start of any study procedure
- Ensuring that 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
- An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

[redacted] _____

Signature of Investigator 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)