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Clinical Investigation Plan
Respiratory Rate Validation Study – Mindset Medical Informed Vital Core Application
PR 2024-593

Commercial Sponsor
Mindset Medical
12439 N 32 Street
Phoenix, AZ 85032

Document Ownership Document is in accordance with Code of Federal Regulations for Non-Significant Risk Investigations and ISO 14155:2020 where applicable

Function, Title	Name	Signature	Date
Element Boulder, Study Manager	Blair Holman, MS		25 June 2024

Document Approver The document approvers are listed below:

Function, Title	Name	Signature	Date
Element Boulder, Medical Director & Principal Investigator	Monica Rabanal, NP		25 June 2024
Element Boulder, Quality Assurance Manager	Gil Monos		25 June 2024
Mindset Medical Representative, Senior Director, Clinical Operations	Sarah Schermer	Sarah Schermer	06 / 25 / 2024
Mindset Medical Representative, VP of Quality Assurance	Shannon Gentry		06 / 25 / 2024

Revision History

Revision	Date	Revision Description
Version 1.0	25 June 2024	Initial Revision

Author

Blair Holman, MS
Study Manager
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80 Health Park Drive Suite 20
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Ethics Committee Review

Salus Institutional Review Board
2111 West Braker Lane, Suite 100 Austin, TX 78758

Study Procedure

Respiratory Rate Validation Study – Mindset Medical Informed Vital Core Application
Study ID# PR 2024-593

Sponsorship / Providing Funding for This Study

Mindset Medical
12439 N 32nd Street
Phoenix, AZ 85032

Principal Investigator & Medical Oversight

Monica Rabanal, NP
Medical Director
80 Health Park Drive
Louisville, CO 80027

Sub-Investigators

Blair Holman, MS
Clinical Study Manager
80 Health Park Drive
Louisville, CO 80027

Study Site

Boulder Element (Formerly Clinimark), Site ID# 001
Avista Adventist Hospital Plaza, Medical Office Building II
80 Health Park Drive Suite 20
Louisville, CO 80027

Element Statements

Confidentiality

The information contained in this document is confidential and is intended for the use of clinical investigators. It will not be copied by or distributed to persons not involved in the clinical investigations of Mindset Medical unless such persons are bound by a confidentiality agreement with Element Boulder or Mindset Medical.

Impartiality

Element Boulder is committed to maintaining impartiality of laboratory and study activities. Personnel are trained on processes and protocols are followed to ensure conformity of the activities. Commercial, financial, and other pressures are not allowed to compromise the impartiality of laboratory activities. This includes those risks that arise from lab activities, lab relationships, or from the relationships of its personnel.

The risk of Impartiality is mitigated by conducting this study according to the mutually agreed upon protocol, contractual arrangements, and standards or guidance documents if applicable.

Sponsorship

Sponsorship/funding of this study is provided by Mindset Medical. Mindset Medical has retained the services of Element Boulder to perform study conduct activities on paid participant volunteers as identified in the contractual agreement.

Glossary

- **CIP** - Clinical Investigation Plan
- **FDA** – Food and Drug Administration
- **IRB** – Independent Review Board
- **ISO** – the International Organization for Standardization
- **NIST** – National Institute of Standards and Technology, **NIST** is the federal technology agency that works with industry to develop and apply technology, measurements, and standards.
- **Reference** – established accuracy used for clinical evaluations of other instruments
- **Device Under Test (DUT)** – the device being clinically evaluated
- **ECG** - Electrocardiogram. Electrical rhythm of the heart
- **NSR** – Non-Significant Risk
- **PPG** – Photoplethysmography, optical method used to detect blood volume changes in the microvascular bed of tissue
- **bpm** – beats per minute, in regards to heart or pulse rate
- **BPM**– Breaths per minute, in regards to respiratory rate
- **$EtCO_2$** – End Tidal Carbon Dioxide
- **RR** – Respiration/Respiratory Rate
- **PR** – Pulse Rate
- **ROI** – Region of Interest
- **A_{RMS}** - Accuracy Root Mean Square

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

Where:

- A_{RMS} is the accuracy root mean square.
- DUT is the test device during sample i.
- Ref is the Reference Respiratory Rate ($EtCO_2$) during sample i.
- n is the number of points.

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Respiratory Rate Validation Study – Mindset Medical Informed Vital Core Application
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Summary

Objectives of the Clinical Investigation Plan

The purpose of this study is to conduct a Respiratory Rate accuracy validation comparing the Mindset Medical Application to the Reference, an FDA cleared End Tidal Carbon Dioxide monitor (GE Datex-Ohmeda) by manually scoring the collected waveform for data analysis.

The procedure, data collection methods, and data analysis follow:

- **ISO 14155:2020** Clinical investigation of medical devices for human subjects – Good clinical practice (as appropriate).
- Code of Federal Regulations for Nonsignificant Risk Devices

The testing will be conducted in order to obtain a full data set for validation on a minimum of 65 participants. Multiple developmental phases may be conducted and will be reviewed for readiness for continuation to validation. A first developmental phase of 5 participants will be performed. If modifications are warranted, the initial data sets will be used for algorithm development. The full validation set will be collected independent of developmental data sets.

Background

Respiratory Rate is an important physiological measurement in the healthcare setting. The gold standard in Respiratory Rate is based off of an airway measurement using end tidal carbon dioxide ($EtCO_2$) respiratory rate.

The medical device studied under this protocol will be the noninvasive and investigational Mindset Medical Informed Vital Core Application-RR (IVC App, IVC), a web-based application. All appropriate preliminary testing on the device has been successfully performed and demonstrates safety and efficacy for use in human studies prior to Element Boulder's receipt of the devices.

The Informed Vital Core Application is a web-based software application that utilizes existing optical camera technology embedded in a smartphone, tablet, laptop, desktop computer, or camera enabled device to capture an individual's physiological parameters including respiration rate (RR). RR is measured using a non-contact method - no measurement device is physically connected to the patient. The patient looks directly into the camera when it is active. The IVC-RR App software uses proprietary software algorithms to detect landmarks on the individual's shoulders and chest and track the motion corresponding to each inhalation. The IVC-RR App's Vital Core Algorithm additionally applies signal extraction (including image segmentation, shoulder location identification, shoulder movement extraction), signal estimation, and analysis to respiration and accurately estimate RR.

In the proposed commercial application, the IVC Application is delivered to the patient through a unique, one-time-use URL. When the URL is clicked, the default web browser opens on the patient device to launch and run the IVC-RR App. The measured RR data is transmitted and saved into the Mindset Medical Cloud Database using Hypertext Transfer Protocol Secure (HTTPS) methods.

Since the IVC App is a web-based application, it can easily be utilized at a patient's home without the need for a trained clinician, or in hospitals (replacing vital signs carts), physician offices, or clinics. The IVC App will guide a user through the workflow of collecting the measurements.

Protocol Overview

After IRB approval, a minimum of 65 volunteer test participants will be enrolled for the final validation study population. A minimum of 5 volunteer test participants will be enrolled for the initial development study. A maximum of 120 participants will be enrolled. All participants will be ≥ 22 years of age. The study population will be diverse in race, age, gender, BMI, skin tone, and health conditions.

The procedures will be explained to the volunteer test participant and an Informed Consent will be signed by the participant. A health form and health screen will be conducted prior to the start of the test.

Participants will be seated to apply the devices and remain seated for the remainder of the study. Each participant will be connected to a commonly used End Tidal Carbon Dioxide monitor (GE Datex-Ohmeda). The Device Under Test will be set up according to the Instructions for Use and the URL delivery will be initiated by the study staff. The end tidal carbon dioxide (EtCO2) manually scored waveform will determine performance of breathing rate metrics (Reference). Each participant will be instrumented with a mouthpiece or a nasal cannula that allows for measurement of the EtCO2. Participants will also be connected to a 3-lead ECG (reference for pulse rate) and pulse oximeter in order to monitor the participant's vital signs for safety purposes.

The first data sets will be recorded at the participant's natural breathing rate. The study will commence by equipping the patient with the reference device. Once a stable natural breathing rate is attained, the study staff will access the URL, and the IVC-RR App will be activated. After the data set at the participant's natural breathing rate, guided breathing rates will be approximately 8, 10, 15, 20, 25, and 30 breaths per minute; with some natural variation from these exact numbers and tailored to the participant's capabilities, such that the rates will increase or decrease by 5 from the natural breathing rate. A paced audible breathing app will be used for the volunteer participants to follow during inspiration and exhalation periods that result in specific breathing rates.

The breathing pattern on the app will be set to begin near the natural breathing rate of the participant and continue to go down by 5 bpm intervals until reaching the breathing rate of 8 bpm. After that, data collection will pick back up at the rate above the participant's normal breathing rate and continue upwards until reaching 30 bpm or as high as the participant can tolerate up to 30 bpm.

It is expected that some of the participants may not be able to be evaluated over the entire range as some participants may not be able to breathe at the lower and higher breathing rates. In this case, additional data may be recorded at their natural breathing rate and/or other ranges that are comfortable for the participant. Once stable breathing at specified rate is achieved data will be collected for one to two minutes per breathing rate plateau. Between plateaus, the participants using a mouthpiece are allowed to take the mouthpiece out and relax. Participants with comorbidities will be monitored to ensure they return to their baseline EtCO2 value between data sets.

The respiration rate will be measured simultaneously with the Reference and the Device Under Test (DUT). During the stable plateaus at each breathing rate, the DUT will be initiated by the study staff to take a measurement, which takes 60 seconds to calculate and report a breathing rate value. Multiple 60 second measurements may be taken per breathing rate plateau. The Reference device is recorded continuously.

To 'Pass' this test, the Mindset Medical Application must demonstrate a respiratory rate Accuracy root-mean-square (A_{rms}) of ≤3 breaths per minute when compared to the Reference $EtCO_2$ manually scored waveform.

Study Population

The study population will include a minimum of 65 adults, ages 22 years and older. A maximum of 120 subjects will be enrolled. A minimum of five participants will be enrolled in an initial development phase, with a minimum of 65 participants completed for the validation phase.

The study population is carefully designed to represent the intended population for the intended use. The study population will be diverse in race, age, gender, BMI, skin tone, and health conditions. The health conditions will constitute inclusion of healthy controls (to allow testing over the full range of breaths per minute) and disease comorbidities (to represent comorbidities such as COPD, CHF, Asthma, Diabetes, Hypertension, and Obesity).

The participants must understand the study and consent to participate by signing the Informed Consent Form. Participant enrollment and participation in this clinical study is based on meeting the inclusion criteria and none of the exclusion criteria, a satisfactory health screen, and the participant and data demographics needed for the study.

Inclusion Criteria

- Participants must have the ability to understand and provide written informed consent or have legally authorized representative consent to participate
- Participant must be ≥22 years of age
- Participant must be willing and able to comply with study procedures and duration
- Participants or legally authorized representative must be able to read or write in English

Population Criteria to be Included

Gender Goals

- At least 30% of the participants will be male
- At least 30% of the participants will be female

Body Mass Index (BMI) Goals

- At least 33% of the participants will be with BMI between 25.0 to 29.9 kg/m2 (overweight)
- At least 33% of the participants will be with BMI ≥ 30.0 kg/m2 (obese)

Skin Tone (Fitzpatrick scale) Goals

- At least 15% of participants will have a light skin tone (Fitzpatrick Scale 1 or 2)
- At least 15% of participants will have a medium skin tone (Fitzpatrick Scale 3 or 4)
- At least 15% of participants will have a dark skin tone (Fitzpatrick Scale 5 or 6)

Race and Ethnicity Distribution Goal – The study will attempt to enroll a race/ethnicity distribution similar to population demographics consistent with the 2020 US Census Data

Health Conditions / Disease Comorbidities

- At least 5 participants will have a history of smoking
- At least 2 participants each with the below chronic conditions (self-reported):
  - COPD
  - CHF
  - Asthma
  - Hypertension
  - Diabetes

Exclusion Criteria

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

- Participants who refuse or are unable to sign an informed written consent for study
- Participants evaluated by the Investigator and Clinical Staff and found to be medically unsuitable or have self-reported health conditions that are currently unstable as identified in the Health Assessment Form and Health Screening

- Compromised circulation, injury, or physical malformation of the sensor Region of Interest (ROI) which would limit the ability to test ROI needed for the study. (Note: Certain malformations may still allow participants to participate if the condition is noted and would not affect the particular areas utilized.)
- Participants with severe contact allergies to standard adhesives, latex or other materials found in pulse oximetry sensors, ECG electrodes, or other medical sensors (self-reported)
- Other known health condition, should be considered upon disclosure in health assessment form

Each participant test is expected to take approximately 1-2 hours. It is expected that the data collection will take 2-3 weeks for final validation. The development and validation phases may not be continuous. There is no additional follow-up required for the investigation.

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Objectives of the Clinical Investigation Plan

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Identification and Description of the Investigational Device

Informed Vital Core Application is a web-based software application that utilizes existing optical camera technology embedded in a smartphone, tablet, laptop, or desktop computer to capture an individual's physiological parameters including respiration rate (RR). RR is measured using a non-contact method - no measurement device is physically connected to the patient. The patient looks directly into the camera while it is active. The IVC-RR App software uses proprietary software algorithms to detect landmarks on the individual's shoulders and chest and track the motion corresponding to each inhalation. The IVC-RR App's Vital Core Algorithm additionally applies signal extraction (including image segmentation, shoulder location identification, shoulder movement extraction), signal estimation, and analysis to respiration and accurately estimate RR.

In the proposed commercial application, the IVC Application is delivered to the patient through a unique, one-time-use URL. When the URL is clicked, the default web browser opens on the patient device to launch and run the IVC App. The measured RR data is transmitted and saved into the Mindset Medical Cloud Database using Hypertext Transfer Protocol Secure (HTTPS) methods.

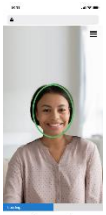

Figure 1: The Mindset Medical Informed Vital Core Application – The Device Under Test

The intended purpose of the Device Under Test is spot check, non-invasive monitoring on the adult population. The software application accompanying acquisition software will be provided by Mindset Medical.

The Mindset Medical Application is for investigational use only and has not been cleared by the FDA.

Instructions for use, storage and handling can be found in the Instructions for Use.. Device model numbers, software version, serial numbers, date(s) of use, and subject ID number(s) for the equipment used will be recorded on the Case Report Forms.

The safety of the IVC App has been well determined during the recent testing of the PR indication and the corresponding documentation is stored in the DHF. The addition of the RR indication does not change the basic safety profile and can be considered safe for use in human studies prior to Element Boulder's receipt of the device. The safety documentation may be requested at any time by the Element Boulder staff if it is required.

Data Acquisition System for the Investigational Device

The data from the investigational devices/smartphone will be collected by a trained member of Element Boulder, separate from the Element Boulder automated data collection system.

Preliminary Investigations and Justifications of the Study

Mindset Medical is dedicated to developing and applying innovative electronic medical solutions that improve patient care in multiple clinical settings. As part of the product development, Mindset Medical retained the services of Element Boulder to conduct a respiratory rate accuracy study.

Risks and Benefits of the Investigational Device and Clinical Investigation

The devices under test in this study are considered non-significant risk devices. 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.
    - The Mindset Medical Application is a non-contact, non-invasive software.
- 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 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.

Hair on the body may need to be shaved in order for the adhesives to work properly. Shaving the electrode site(s) may cause skin irritation or cuts.

Blood Pressure Cuff

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

Through literature searches of other studies, we found the complications of taking repeated blood pressures were temporary and involved either bruising/rash; for example, petechiae rash (less than 2.2%), skin redness/lines (0.8%), or tingling/discoloration in the extremity wearing the cuff while the cuff is inflated (0.1%).

It is possible that the test subject may experience an allergic reaction to the material in the cuff. However, cuffs used in this trial utilize standard material that has undergone skin sensitivity testing. The blood pressure cuff is used during the initial health screen and for any follow up as necessary.

Sensors

Sensor placement involves positioning sensors on volunteer subjects 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. Hair on the body may need to be shaved in order for the adhesives to work properly. Shaving the sensor site may cause skin irritation or cuts.

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 the sensor is believed to be minimal.

Mouthpiece and Nose clip/Nasal Cannula

The mouthpiece, nose clip, and nasal cannula are made of soft, flexible plastic so as to minimize the discomfort level as much as is reasonably possible. Materials may cause some skin irritations. Insertion and removal of a nasal cannula may cause nasal irritation, discomfort, or pain.

General Electrical Hazards

Electrical hazards are a potential risk with all electrical equipment. The equipment used in this study has been designed to meet applicable safety standards. The equipment will be safety and functionally tested prior to subject use. The possibility of any electrical hazard is extremely remote.

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.

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Design of the Clinical Investigation

Method

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

The testing will be conducted in order to obtain a full data set for validation on a minimum of 65 participants. Multiple developmental phases may be conducted and will be reviewed for readiness for continuation to validation. A first developmental phase of 5 participants will be performed. If modifications are warranted, the initial data sets will be used for algorithm development. The full validation set will be collected independent of developmental data sets.

This study is a comparative, single-center, non-randomized comparative study in a minimum of 65 participants for the final validation. Each participant test is expected to take approximately 1-2 hours. Typically, up to 6 to 8 participants will be run per day. The overall study process is expected to be completed in 2-3 weeks for 65 participants. The development and validation phases may not be continuous.

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 screen will be conducted prior to the start of the test.

Participants will be seated to apply the devices and remain seated for the remainder of the study. Each participant will be connected to a commonly used End Tidal Carbon Dioxide monitor (GE Datex-Ohmeda). The Device Under Test will be set up according to the Instructions for Use and the URL will be initiated by the study staff. The end tidal carbon dioxide (EtCO2) manually scored waveform will determine performance of breathing rate metrics (Reference). Each participant will be instrumented with a mouthpiece or a nasal cannula that allows for measurement of the EtCO2. Participants will also be connected to a 3-lead ECG (reference for pulse rate) and pulse oximeter in order to monitor the participant's vital signs for safety purposes.

The first data sets will be recorded at the participant's natural breathing rate. The study will commence by equipping the patient with the reference device. Once a stable natural breathing rate is attained, the study staff will access the URL, and the IVC app will be activated. After the data set at the participant's natural breathing rate, guided breathing rates will be approximately 8, 10, 15, 20, 25, and 30 breaths per minute; with some natural variation from these exact numbers and tailored to the participant's capabilities, such that the rates will increase or decrease by 5 from the natural breathing rate... A paced audible breathing app will be used for the volunteer participants to follow during inspiration and exhalation periods that result in specific breathing rates.

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The respiration rate will be measured simultaneously with the Reference and the Device Under Test (DUT). During the stable plateaus at each breathing rate, the DUT will be initiated by the study staff to take a measurement, which takes 60 seconds to calculate and report a breathing rate value. Multiple 60 second measurements may be taken per breathing rate plateau. The Reference device is recorded continuously.

To 'Pass' this test, the Mindset Medical Application must demonstrate a respiratory rate Accuracy root-mean-square (A_{rms}) of ≤3 breaths per minute when compared to the Reference $EtCO_2$ monitor.

Video and/or Photos

In this study photographs or video may be taken of the study set up during monitor set up for data collection purposes and the Study Sponsor's internal research and development purposes only. This allows the sponsor to analyze the data and observe the monitor set up. Pictures may be taken of any site where we have placed equipment. The study equipment will be photographed, however, in some circumstances it may be unavoidable to not photograph the subject's face. In order to protect the subject's identity, the name will be kept confidential at all times.

A photograph of each patient will be taken will be taken by the IVC App prior to each session and stored in the secure Mindset Medical Cloud Database.

Equipment

Description of MediCollector

The MediCollector software will be used to collect the reference data.

- 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 SpO2	0.2	beats/min
3	CO_RR	Respiratory Rate	0.2	breaths/min
4	HR_ecg	Heart Rate from ECG	0.2	beats/min
5	CO2	CO2 Concentration (RR waveform)	25	%

Safety Equipment

- GE Healthcare Datex-Ohmeda S/5 Multi-parameter Monitor, M-NESTPR (K993608) or E-PRESTN (K031781) module with ECG and/or SpO_2
- GE Healthcare (Datex-Ohmeda) 3900 TruTrak+ (K021955), GE Healthcare S5 Compact Monitor with M-NESTPR (K993608) or E-PRESTN (K031781) module, and/or Nellcor N600x Pulse Oximeter (K123581)
- Portable oxygen tank, mask, and ambu bag
- Blood pressure cuff and stethoscope

Other Equipment

- Skin Pigmentation Assessment (optional) - The Mexameter MX 18, the Melanin Density meter Photonova, Konica Minolta CM-700d, or equivalent

Supplies for Participant

- Mouthpiece and nose clips or nasal cannula for $EtCO_2$ measurement
- Additional equipment for use with the mouthpiece:
  - Ventilation monitoring adaptor with $EtCO_2$ sample line
  - $EtCO_2$ sample line
  - Respiratory bacterial/viral filter (optional)

Reference

- GE Healthcare Datex-Ohmeda S/5 Multi-parameter Monitor, M-COVX (K001814) or E-CaiO (K051092) module (Reference $EtCO_2$)

Investigational Device

- Mindset Medical Informed Vital Core Application with computer, tablet, or phone for data capture transfer

Sponsor Equipment:

- Mindset Medical Provider Platform and login credentials

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

Study Population

The study population will include a minimum of 65 adults, ages 22 years and older. A maximum of 120 subjects will be enrolled. A minimum of five participants will be enrolled in an initial development phase, with a minimum of 65 participants completed for the validation phase.

The study population is carefully designed to represent the intended population for the intended use. The study population will be diverse in race, age, gender, BMI, skin tone, and health conditions. The health conditions will constitute inclusion of healthy controls (to allow testing over the full range of breaths per minute) and disease comorbidities (to represent comorbidities such as COPD, CHF, Asthma, Diabetes, Hypertension, and Obesity).

The participants must understand the study and consent to participate by signing the Informed Consent Form. Participant enrollment and participation in this clinical study is based on meeting the inclusion criteria and none of the exclusion criteria, a satisfactory health screen, and the participant and data demographics needed for the study.

Inclusion Criteria

- Participants must have the ability to understand and provide written informed consent or have legally authorized representative consent to participate
- Participant must be ≥22 years of age
- Participant must be willing and able to comply with study procedures and duration
- Participants or legally authorized representative must be able to read or write in English

Population Criteria to be Included

Gender Goals

- At least 30% of the participants will be male
- At least 30% of the participants will be female

Body Mass Index (BMI) Goals

- At least 33% of the participants will be with BMI between 25.0 to 29.9 kg/m2 (overweight)
- At least 33% of the participants will be with BMI ≥ 30.0 kg/m2 (obese)

Skin Tone (Fitzpatrick scale) Goals

- At least 15% of participants will have a light skin tone (Fitzpatrick Scale 1 or 2)
- At least 15% of participants will have a medium skin tone (Fitzpatrick Scale 3 or 4)
- At least 15% of participants will have a dark skin tone (Fitzpatrick Scale 5 or 6)

Race and Ethnicity Distribution Goal – The study will attempt to enroll a race/ethnicity distribution similar to population demographics consistent with the 2020 US Census Data

Health Conditions / Disease Comorbidities

- At least 5 participants will have a history of smoking
- At least 2 participants each with the below chronic conditions (self-reported):
  - COPD
  - CHF
  - Asthma
  - Hypertension
  - Diabetes

Exclusion Criteria

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

- Participants who refuse or are unable to sign an informed written consent for study
- Participants evaluated by the Investigator and Clinical Staff and found to be medically unsuitable or have self-reported health conditions that are currently unstable as identified in the Health Assessment Form and Health Screening
- Compromised circulation, injury, or physical malformation the Region of Interest (ROI) which would limit the ability to test ROI needed for the study. (Note: Certain malformations may still allow participants to participate if the condition is noted and would not affect the particular areas utilized.)
- Participants with severe contact allergies to standard adhesives, latex or other materials found in pulse oximetry sensors, ECG electrodes, or other medical sensors (self-reported)
- Other known health condition, should be considered upon disclosure in health assessment form

Fitzpatrick Scale

The Fitzpatrick or Monk scale may be used to assess skin tone. The following chart(s) will be used:

Figure 2: The Fitzpatrick Scale

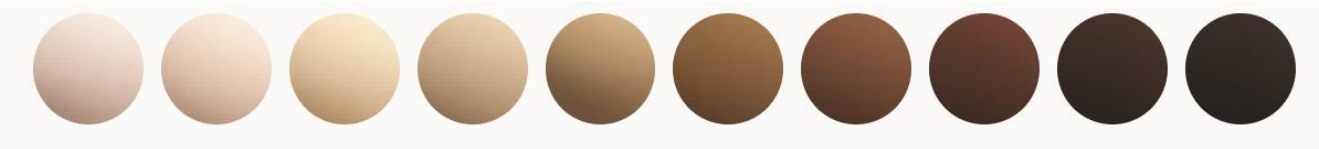

Figure 3: The Monk Scale (MST)[1]

Skin Tone Bins

Skin Tone	Fitzpatrick Scale	Monk Scale
Light	I and II	1-4
Medium	II and IV	5-7
Dark	V and VI	8-10

Mexameter Results Interpretation (Mexameter may be used as necessary)

Mexameter to Fitzpatrick Interpretation of Average Melanin Results	
Type I	0-100
Type II	101-150
Type III	151-250
Type IV	251-350
Type V	351-450
Type VI	451-999

Konica Minolta Results Interpretation, If Used

The Konica Minolta CM-700d may be used for additional skin pigmentation assessment, but its measurements will not be used to determine demographics of the study population. Three measurements will be taken at each of the following:

1. Forehead
2. Inner bicep
3. Sensor Site(s)

Each measurement yields a pair of L* and b* values (CIELAB color space). Each pair will be used to calculate an Individual Topology Angle (ITA) according to:

$$\text{ITAi}=\arctan(Li*-50bi*)180\pi$$

The average ITA=13ΣITAi3i=1 of the three measurements at a site will be used to calculate an ITA for that measurement site. An average ITA will be calculated for each of the measurement sites. These ITA can then later be mapped to skin tone classification scales.

[1] "Developing the Monk Skin Tone Scale." Skin Tone Research @ Google AI, Google, skintone.google/the-scale.

Duration of Clinical Investigation

Each participant test is expected to take approximately 1 – 2 hours. Typically, 6 to 8 participants will be run per day. It is expected that the data collection will take 2-3 weeks for final validation. The development and validation phases may not be continuous. There is no additional follow-up required for the investigation.

Criteria for Study Termination

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

- Study is complete
- Subject withdrew consent. The subject may stop the study for any reason without prejudice
- Withdrawal by Sub-Investigator / Investigator
- Study Stopped due to Technical Problems
- Study may be stopped due to Protocol Deviation
- Study Terminated by Sponsor
- Study Stopped due to Adverse Event
- Development of any cardiac arrhythmia
    - Except respiratory sinus arrhythmia
- PVCs increasing from baseline at health screening or symptomatic

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 for the Final validation of the product. During the development phase, usage and removal of the data is at the sponsor's discretion.

Procedure

Participant Enrollment

1. Explain the procedure to the participant. Have them read the Informed Consent Form and review the information answering all questions. Once all questions have been answered, have the participant sign and date the ICF. Have the participant complete, sign, and date the Health Assessment Form.
    a. Each participant will be given a copy of the consent form prior to release.
2. Study Staff will confirm appropriate signatures on the ICF.
3. The clinician or PI will verbally question the participant about their health history.
4. Apply Reference ECG leads to the participant.
5. Record baseline vital signs (for example: SpO_2, PR or Heart Rate, ECG rhythm, blood pressure, antecubital fossa check, and/or alcohol smell check).
6. Based on the responses to the Health Assessment form and health assessment, record accepted or declined from the study. Continue if accepted into the study.

Setup

7. Complete equipment setup and checkout prior to starting study.
8. Set and / or synchronize the computer clocks for the sponsor and Element Boulder data collection systems.
9. Setup and verify communication between the devices and data collection / measurement systems.
10. Record device information for tracking (manufacturer, model #, serial/lot, hardware/software control info).
11. Record participant information, subject number, and demographics information.
12. Set up Device Under Test and adjust the position of the cell phone camera as appropriate, ensuring the conditions are appropriate for the Device Under Test.
    a. Set up sponsor-provided platform (IVHP) to connect to the DUT for participant data collection.
13. Apply the nasal cannula to the participant or instruct the participant on how to use the mouthpiece.

Data Collection

14. Start data recording for the Reference.
15. Begin the Respiratory Rate evaluation.
    a. Participants will be seated.
    b. Data will be collected for one to two minutes per data set. There will be a sitting time of at least one minute before the marking of the start of each data set. Times will be recorded on the CRF for start and end of each data set.
    c. The data will be continuously recorded electronically from the reference. During the stable plateaus at each level, the DUT will be initiated to take a measurement.
    d. Between data sets, the participant may take out the mouthpiece if in use.
    e. Additional study notes that describe the conditions of the test as well as deviations, device issues, and any adverse events will be recorded in written documentation.
16. The first data sets will be recorded at the participant's natural rate.
17. A range of stable respiratory rates will be elicited from each volunteer test participant. The rates will be approximately 8, 10, 15, 20, 25, and 30 breaths per minute; with some natural variation from these exact numbers and tailored to the participant's capabilities as some participants may not be able to breathe at the lower and higher respiratory rates. A paced breathing app will be used. Once a stable breathing at specified rate is achieved data will be collected for one minute. More than one dataset may be collected, per clinician discretion and assessment and participant capabilities.
    a. The breathing pattern on the app will be set to begin near the natural respiratory rate of the participant and continue to go down by intervals of five BPM until reaching the respiratory rate of 8 bpm. After that, data collection will pick back up at the rate above the participant's normal Respiratory Rate and continue upwards until reaching 30 bpm or as high as the subject can tolerate up to 30 bpm. If the participant's natural breathing rate is lower than 8 bpm, the rate of 8 bpm will be included, and the next rate will be five above the natural rate.
    b. In the case the participant is unable to breathe at higher and lower rates, additional data may be recorded at their natural rate and/or other ranges that are comfortable for the participant.
    c. Study staff will follow the "IVC Clinical Study Instruction Guide – Respiration Rate" for specific device instructions.
18. At the end of the Respiratory Rate evaluation, stop the Reference recording. Remove the nasal cannula or mouthpiece.

Ending Data Collection

19. Take all equipment off and end the data collection, according to sponsor's device IFU.
20. The clinician will review any final questions with the participant and ask if there were any effects from the study. The participant will be released with no further follow-up required.

Statistical Analysis

Element Boulder will perform the statistical analysis for the final validation phase.

Multiple developmental phases may be conducted and will be reviewed for readiness for continuation to validation. If modifications are warranted, the initial data sets will be used for algorithm development. The full validation set will be collected independent of developmental data sets. An interim analysis may be done on a development dataset, following the same endpoint and comparators listed below.

The respiratory rate will be measured simultaneously with the Reference and the Device Under Test (DUT). During the stable plateaus at each level, the DUT will be initiated to take a measurement, which takes 60 seconds to calculate and report a respiratory rate value. The reference EtCO2 waveform during the matching 60 interval will

be scored by counting the respiratory peaks per minute. Multiple 60 second measurements may be taken per respiratory rate plateau, based on clinician assessment and determination. If multiple datasets are completed on a participant, the last one will be used in analysis

The final pairing to be analyzed is Reference manually $EtCO_2$ scored and counted waveforms with the average of the simultaneous 60 second period for the DUT. The Accuracy root-mean-square (A_{rms}) 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, manually scored End Tidal Carbon Dioxide ($EtCO_2$) waveforms. For final validation, the $EtCO_2$ waveform will be scored by counting the respiratory peaks per minute. The clinicians counting the raw $EtCO_2$ waveform will be blinded to the results from the test device.

The endpoint of interest is accuracy as measured by the Accuracy root-mean-square (A_{rms}) difference between the Device Under Test (DUT) and the Reference Respiratory Rate as counted by $EtCO_2$ scored waveform (Ref) for all stable respiratory periods where:

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

Mean bias will also be generated:

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

Acceptance Criteria: Passing requires an A_{rms} of ≤3.0

Mean Absolute Difference (MAD), Deming Regression, and Bland-Altman statistics will also be calculated and reported. Additional analyses will be performed by demographic cohort

1. Age (Participants ≤50 years of age, >50 years of age)
2. Skin Tone (Fitzpatrick Scale 1-6)
3. BMI (Normal Weight, Overweight, Obese)
4. Comorbidity vs No Comorbidity reported
5. Sex (Female and Male)

Sample Size Justification

This study will utilize a sample size of 65 subjects with 7 to 11 respiratory rate plateaus per participant, providing ≥200 data points over the specified breath per minute range.

Success for this study is defined as $A_{RMS} \leq 3.0$. The A_{RMS} statistic measures accuracy of a device under test (DUT) when compared to a reference device (REF) over a range of values. Accuracy, measured by the A_{RMS} statistic, can be affected by both random and systematic components of error. Here we estimate power to obtain an $A_{RMS} \leq 3.0$ for this study through simulation using parameters estimated from two previous studies conducted by Element Boulder. Respiratory rate study 1 composed of 894 data points from 18 study participants. Respiratory rate study 2 composed of 913 data points from 20 study participants. Both studies had respiratory rate targets of 5, 10, 15, 20, 25, 30, 35, 40 and 45 breaths per minute. The A_{RMS} statistics are 2.8 and 1.2 for Study 1 and Study 2 respectively. For more information about the results and standard respiratory rate metrics please refer to 'Summary of Respiratory Rate Data and Results from Element Boulder Studies' dated May 1, 2019. These preliminary data

contain the features of real data, such as within subject correlation that is present due to repeated measurements on the same study participants.

Repeated measures within subjects is a common practice in the pulse oximetry field but is known to potentially lead to within subject correlation, which is accounted for in these power estimates. Linear mixed models (LMM) were used to estimate parameters for each study in order to take into account repeated measures within subjects. DUT was treated as the dependent variable. Subject was treated as a random effect, and REF was treated as a fixed effect. Parameter estimates from the mixed model were used as parameter estimates for simulations. The variance between subjects in the mixed model results were used to model within individual correlation. Residual variance was used to model variance within subjects. The estimated effect of REF was modeled as slope. The simulation model also incorporated mean bias. The simulation model was as follows:

$$DUT_{ij} = m \times REF_{ij} + B + {\sigma^2}_{between} + {\sigma^2}_{within}$$

- m = slope; B = mean bias; σ^2 = variance;
- i = measure; j = individual

Simulations were performed for the studies with a range of 10 to 38 individuals and 1 to 5 measurements at each respiratory rate target of 5, 10, 15, 20, 25, 30, 35, 40 and 45 breaths per minute, for a total of 145 different study size combinations. For each study size, 10,000 simulations were performed and the percentage of simulated studies that passed was taken as the estimate of power for that study size combination. Parameter estimates from study 1 resulted in the most conservative power estimates, and are as follows:

m:0.97039
B: -0.08434
${\sigma^2}_{between}$: 0.4724
${\sigma^2}_{within}$: 7.04

Based on parameter estimates from study 1 the following combinations study sizes would have >80% power to obtain $A_{RMS} \leq 3$: (Subjects x measurements) 27x9, 16x18, 11x27, 10x36. A study design with 30 subjects and 18 measurements per subject has >80% power to obtain $A_{RMS} \leq 3$ given the expectation that the device performs the same as Study 1. Statistical modeling and simulations were performed using R (R 3.5.3 GUI El Capitan build, the R Foundation for Statistical Computing, 2016).

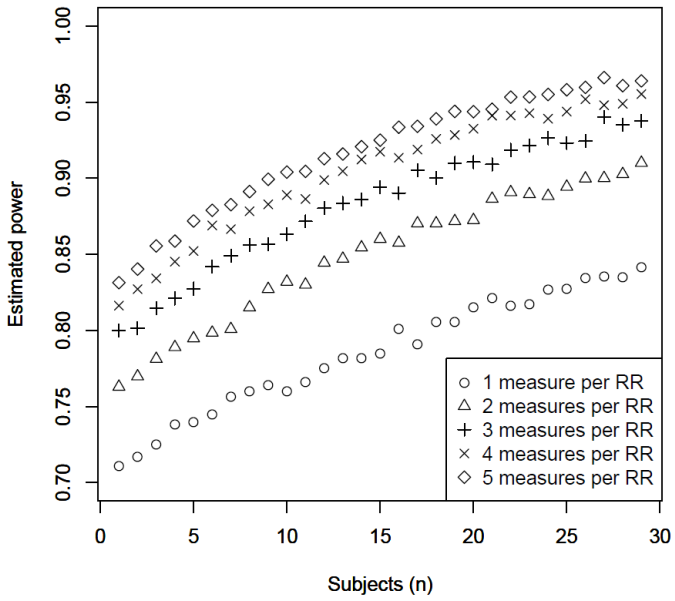

Figure 3 – Plot of estimated power based on the number of subjects and measurements per respiratory rate

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 subject 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.

Monitoring Arrangements

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

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

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

Additionally:

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

Monitoring Plan

1) Informed Consent
   - Verify that the consent form was signed prior to any study procedures being conducted
   - Verify that the staff conducting the consent is listed for approval on the Delegation of Authority Log
   - Ensure that the consent process is documented.
2) Subject Eligibility
   - Verify that the subject meets the inclusion criteria and none of the exclusion criteria.
3) Baseline Data
   - Verify demographic information with the health assessment form
   - Check that informed consent time and date is prior to start of the procedure
4) Verify all CRFs are completed
5) Adverse Events
   - Verify that Adverse Events and Serious Adverse Events / UADEs are being reported accordingly to the IRB and Sponsor in the required timeframe.
6) Protocol Deviations

- Verity that Protocol Deviations are being 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 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# 2024-593.

The participant's name and signatures will be recorded on the Informed Consent and Health Assessment Form. 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: Element Boulder representatives collecting the information and conducting the study, Medical Director for Element Boulder, Regulatory Authorities, 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 off of participant #, 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 commercial sponsor for the study or Contractors associated with Element Boulder 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

Respiratory Rate Validation Study – Mindset Medical Informed Vital Core Application
Element Boulder Study ID# PR 2024-593

Subject Documents

Provided as separate documents to this protocol:

- Informed Consent form (IRB approved)
- Health Assessment Form (Control # F2000-001-001 Rev 14 or current revision)

Study Conduct Documents:

- CRF 2024-593 – Case Report Forms
- Electronic Files – electronic data collected from the systems

Data Collection Forms / Case Report Forms

To ensure the quality and integrity of the data, it is the responsibility of the Investigator(s) or designee to complete the Case Report Forms (CRFs) for each subject who is enrolled to participate in this study. In some cases, the data

collection forms will also be the source document for some information that is not directly collected in the Health Assessment Form. The following information will be recorded on the site's data collection forms (CRF):

- Study date, Subject ID#, 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 vital signs pertinent to the inclusion and exclusion criteria
- 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)
- Device Deficiency 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, 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 Investigator should review, sign and date. The Adverse Events Reporting should be signed and dated by the designee and Principal 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 Files

- Document # B3000-000-003 - Adverse Events and Protocol Deviation Reporting System
- Document # F2000-001-029 - Device Deficiency Form
- Document # F2000-001-016 - Device Accountability Form
- Document # F2000-001-015 - Delegation of Authority
- Document # F2000-001-017 - Investigator Financial Interest Disclosure
- Document # F2000-001-022 - Investigator's Certification Statement
- Document # F2000-001-028 - Subject Enrollment Log
- Document # F2000-001-027 - Site Personnel Training Log
- Document # F2000-001-033 - Site Visit/ Monitoring Log
- Document # F2000-001-034 - Data Clarification Form
- Document # F2000-001-037 - Protocol Deviation Log
- Document # F2000-001-038 - Adverse Events Log
- Document # F2000-001-042 - Adverse Event CRF
- Document # F2000-001-043 - Protocol Deviation Form
- Document # F2000-001-044 - Subject Screening Log
- Document # F2000-001-052 - Device Deficiency Log
- Communications
- Additional documents include: Investigator brochure if provided, PI CV, key staff CV or resumes, Correspondence with IRB, IRB voting list, signed contract (optional), insurance certificates, shipping records, SIV / Monitoring documentation, names and contacts for key staff & sponsor, relevant sponsor correspondence, customer provided documentation, Final report.

Current revision of documents applies.

Amendments to the Clinical Investigation Plan

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

Deviations from the Clinical Investigation Plan

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

Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study must be reported to the Sponsor within 5 working days from awareness of occurrence and reported to the IRB per the deviation reporting policy.

Deviations that do not affect the safety, efficacy, integrity, or conduct of the study will be documented in the case report forms, regulatory binder Protocol Deviation Log as appropriate.

Device Accountability

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

Device Deficiencies

A Device Deficiency Log will be maintained during the study. Upon a device deficiency, a Device Deficiencies Form will be filled out and is also marked on the subject's CRF. Any device deficiency regarding the operation of the device or software or any malfunctions are to be reported to the sponsor. The sponsor will provide a follow up investigation to the deficiency.

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 of the device for delivery to the study site. Investigational devices or its immediate package shall bear a label with the following information: name and place of the manufacturer, packager, or distributor, the quantity of contents, if appropriate, and the following statement per 21 CRF Part 812.5 Labeling of investigational devices:

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

The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

It is the investigator's responsibility to ensure the appropriate labelling is visible and remains intact throughout the life of the study.

The User Manual / Instructions for Use (IFUs) are provided as separate documents from this protocol.

Storage and Accountability

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

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

Statement of Compliance

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

Reference Documents

IRB Approved Informed Consent for Study Title: Respiratory Rate Validation Study – Mindset Medical Informed Vital Core Application
Study ID# PR 2024-593

- 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
- World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects
- ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice

Informed Consent Process

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

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

Safety

Investigators

All experimenters must review the protocol prior to testing 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 the 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.

A clinician will be present to monitor the subject at all times. Safety monitoring includes, SpO_2, pulse rate, respiratory 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 Element Boulder Procedures, IRB requirements and per Mindset Medical SOPs.

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

- Type of effect (ADE, AE. ASADE, SADE, SAE, UADE)
- Date of onset and resolution
- Intensity (mild, moderate, severe)
- Serious (yes/no)

- Relationship to device (unknown, not related, possibly related, probably related, definitely related)
- Anticipated (yes/no)
- Treatment given and / or action taken (procedure stopped, withdrawn from study, no action)

Reporting of Serious Adverse Events and / or UADE

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

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

Sponsor Records and Reports

Records 21 CFR 812.140 (b) 4,5

The following records shall be consolidated in one location and available for inspection and copying by Regulatory Authorities:

- 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 Regulatory Authorities
- 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 Regulatory Authorities, 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 Regulatory Authorities, IRB and the investigator within 5 working days after receipt of the withdrawal approval by the sponsor.

Withdrawal of Regulatory Authorities approval

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

Progress Reports

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

Recall and device

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

Final Report

The sponsor shall submit a final report to the IRB within 6 months after termination or completion of the investigation.

Informed consent

The sponsor shall submit to Regulatory Authorities 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 Regulatory Authorities 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 Regulatory Authorities, provide accurate, complete, and current information about any aspect of the investigation.

Investigators Records and Reporting

Records 21 CFR 812.140 (a)(3)(i)

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

Reports 21 CFR 812.150 (a) 1,2,5,7

The investigator shall prepare and submit the following complete, accurate, and timely reports:

Unanticipated adverse device effects

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

Withdrawal of IRB approval

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

Informed consent

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

Other

The investigator shall, upon request by a reviewing IRB or Regulatory Authorities, 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.

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 an Element Boulder representative (in his or her sole discretion), for whatever cause, that the study should be discontinued.
- A determination by the sponsor (in his or her sole discretion), for whatever cause, that the study should be discontinued

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

- Subject completes all study requirements
- Subject withdraw 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 Mindset Medical and Element Boulder reserve the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of, but not limited to, inadequate data collection, low subject enrollment, or non-compliance with the protocol or other research requirements.

Early termination results when the study is closed prior to the end of the study. A study suspension is a temporary postponement of the study activities related to enrollment. Both are possible for the study. If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol.

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

If the investigator (or IRB/IEC) terminates or suspends the investigation the investigator will promptly inform the institution (if required) and the IRB/IEC, 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. The sponsor will inform the regulatory authorities (if required).

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

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

Publication Policy

The results of this investigation may be submitted for publication.

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Appendix A - Protocol Signature Page

Protocol No. PR 2024-593

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, 54, 56, and 21 CFR 812: or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual.

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

Signature of Investigator

25 June 2024
Date

Monica Rabanal, NP
Investigator Name (print or type)

Principal Investigator
Investigator Title

Element Boulder
Name of Facility

Louisville, CO USA
Location of Facility (City, State, Country)

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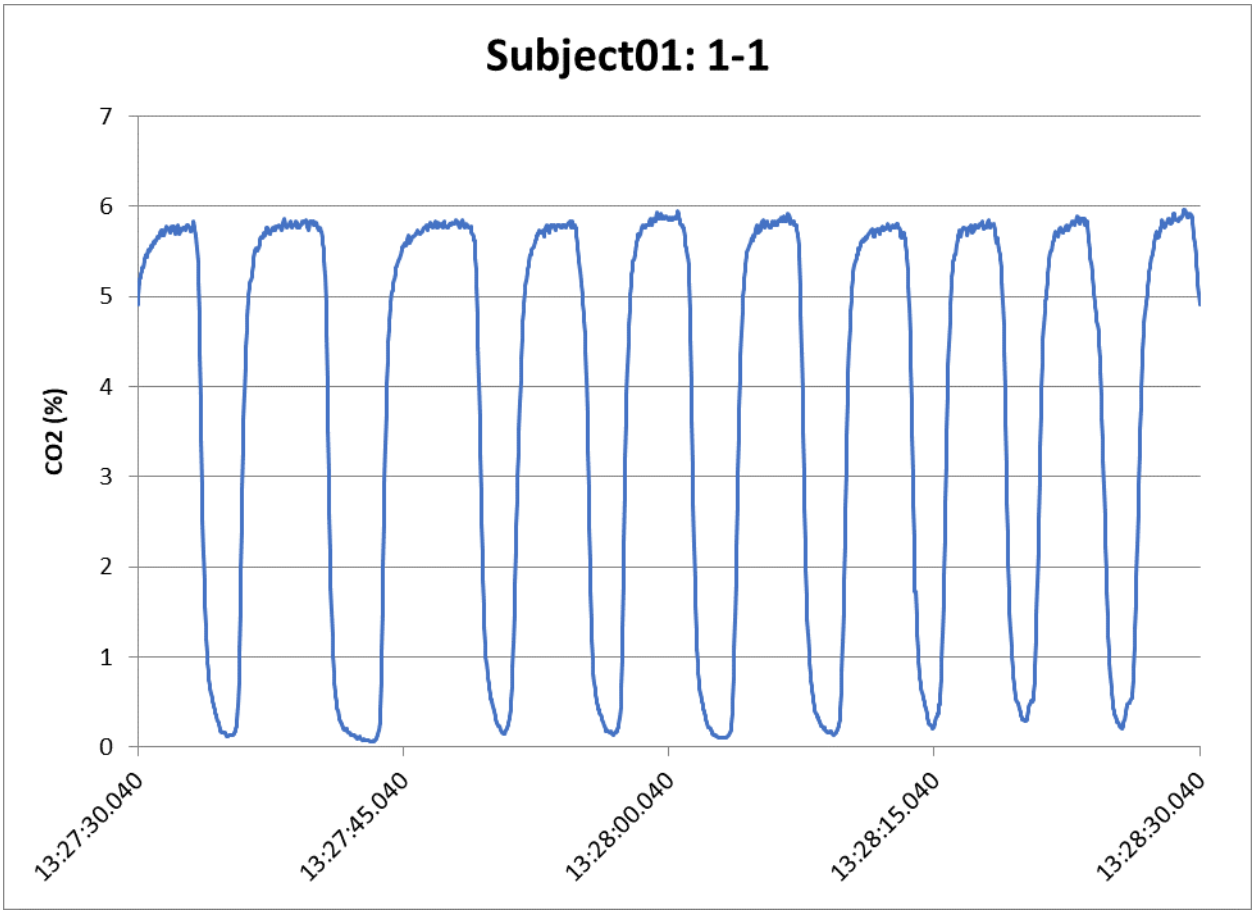
Appendix B: Sample Waveform Scoring Form

Below is an example of the waveform scoring form. The reviewers counting the raw $EtCO_2$ waveform will be blinded to the results from the test device.



Respiratory Rate _____

Scorer Name _____ Date _____

Checked by _____

Date _____