IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points, save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Dr. Bruce Johnson

Study Title: Clinical Validation Study for Noninvasive Cardiopulmonary Management Device (Phase II)

Sponsor: Analog Devices, Inc.

Clinical Research Organization: N/A

Protocol version number and date: 1.0 – February 7, 2022

Research Question and Aims

Hypothesis:

It is hypothesized that the ADI CPM System (test device) will be able to measure in healthy human volunteers:

a) Respiration Rate (RR) with sufficient accuracy
b) Changes in relative Tidal Volume (rTV) with sufficient accuracy

Objectives:

Primary Objectives

1) Validate Respiration Rate (RR) accuracy derived by the Cardiopulmonary Management (CPM) System in the range of 6-40 BPM

2) Validate relative changes in relative Tidal Volume (rTV) derived by the CPM System

*Secondary Objectives**
1) Confirm the ECG capabilities of the CPM System
2) Confirm the Skin temperature capability of the CPM system

Outcome Measures:
Primary Outcome Measures
1) Accuracy of CPM System calculated RR versus reference device
   - Proportion of the error within ± 2 bpm
2) Accuracy of the changes in the rTV calculated by CPM System compared to reference TV
   - Root Mean Squared (RMS) of residual relative error after linear fitting.
   - Correlation coefficient between reference device's TV and test device's rTV within subjects

*Secondary Outcome Measures**
1) Accuracy of CPM System calculated RR versus reference device
   - Bland-Altman analysis
2) ECG capabilities confirmation
3) Confirmation of skin temperature accuracy

* Note that the secondary objectives are NOT designed to be a primary method of validating the CPM System. These objectives and outcome measures are meant to gather more data in a controlled setting since the devices used to measure these specific parameters will already be used in the study.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):
The Cardiopulmonary Management (CPM) System is intended for use in adults undergoing monitoring for cardiopulmonary conditions under the direction of a licensed medical professional to measure, record, and periodically transmit physiological data. One of the main challenges in managing these patients' care with the current standard of care lies in providing health care providers with insight on how patients are trending once diagnosed, and (post-discharge) identifying patients who are at high risk for an adverse event, so that these patients can be treated prior to being admitted or re-admitted to the hospital.

Studies such as MultiSENSE in 2017 have demonstrated, using a large cohort of patients implanted with a CRT-D device, that it is possible to predict clinical decompensation (in this case, related to heart failure) using a combination of relevant parameters that include heart sounds, thoracic impedance, respiration, heart rate, and activity (Boehmer et al., 2017). Measurement and monitoring devices are important tools used to manage these at-risk populations; however, there are limited options that provide multi-parameter and noninvasive patient data collected and analyzed within one device.

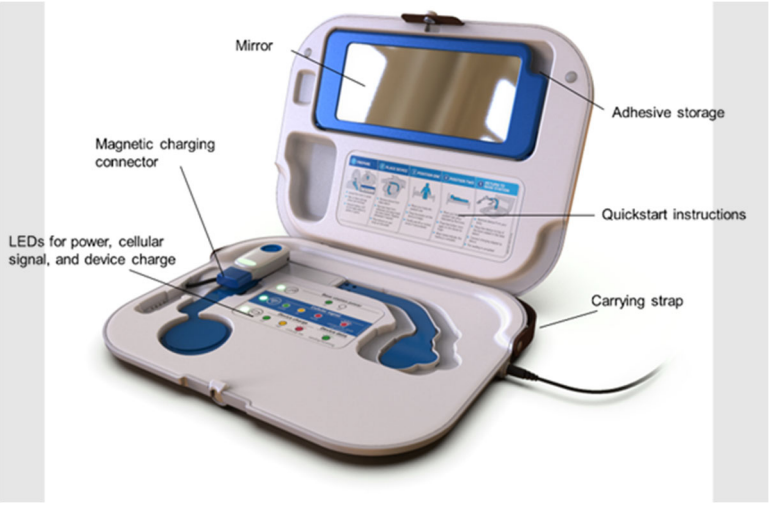
The ADI At-Home CPM System acquires physiological data and derived measurements associated with the presence and progression of cardiopulmonary conditions, including diastolic heart sounds energy, respiration rate and relative tidal volume, changes in thoracic impedance, and electrocardiogram abnormalities. The end goal of the product is to collect, derive and transmit these measurements to the clinical care team daily with high accuracy. These data enable the clinical care team to monitor their patients more closely, potentially resulting in more informed clinical management decisions and reducing the need for hospitalizations. This study

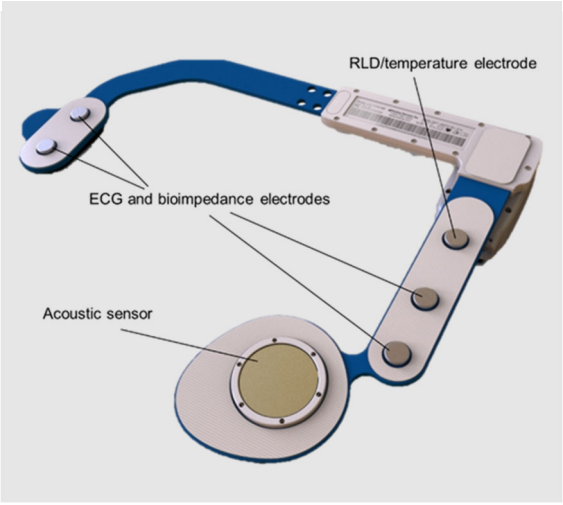
aims to validate the accuracy of several of these parameters (respiration rate, relative tidal volume) clinically, using healthy volunteers who will follow respiration patterns (changing rate and depth) mimicking those observed in patients with cardiopulmonary conditions.

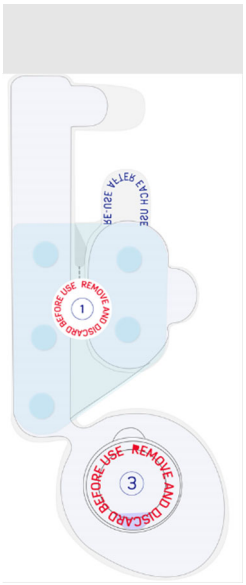
Description of Investigational Device:
The ADI At-Home CPM (Cardiopulmonary Management) System is a non-invasive device that measures and trends a variety of physiological parameters. The device is battery-operated and biocompatible. The device is placed on the left chest area with one adhesive "island" on the sternum and the other island under the left arm (near the mid-axillary line). A round acoustic sensor falls near the apex of the heart, and for those with breast tissue, it is located similarly to the underwire of a bra. The device uses this sensor as well as five electrodes, an accelerometer, and a temperature sensor.

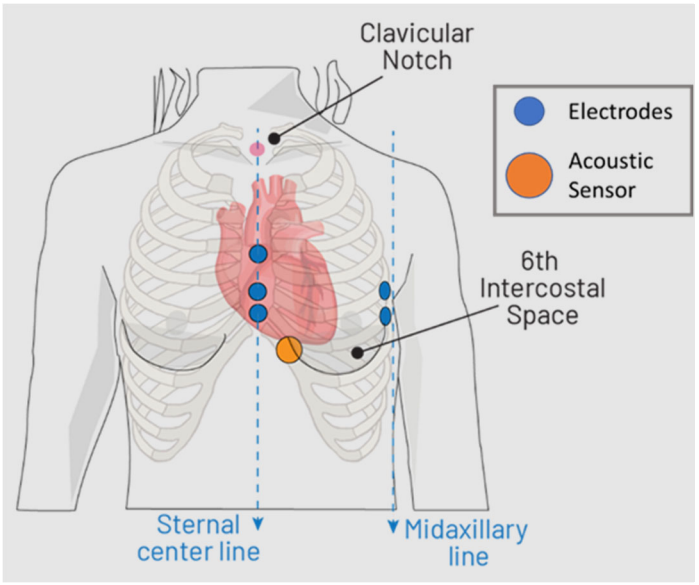
The device uses adhesive patches to adhere to the body. These use a gentle silicone adhesive with five hydrogel pads embedded (which align with the metal electrodes on the device). The device-side of the adhesives are composed of hook and loop material (like baby diapers) which allow the adhesives to be easily replaced when adhesion degrades.

During normal use, the device is only worn for about 5 minutes to acquire a single measurement. It is used with a Base Station that charges and stores the device and sends measurement data to the cloud. The CPM Device also has an alignment tool that is fitted to each patient and aids in proper repeatable placement of the device. In this clinical evaluation however, the study team will place the device on participants and will not use the alignment tool. Additionally, to ensure consistent placement position, the skin will be marked and the device will be placed in aligned with the skin markers every time adhesive is replaced to avoid changes in the device position throughout the visit.









Intended Use:
The ADI CPM (Cardiopulmonary Management) System is a wireless remote monitoring system intended for use by healthcare professionals for spot checking of physiological data in home and healthcare settings.

This can include:

- ECG (including computer generated analysis of possible atrial fibrillation which must be confirmed by a physician with other relevant clinical information)
- Heart Ausculation Sounds
- Skin Temperature
- Thoracic Impedance (including Changes in Thoracic Impedance)
- Respiration Rate and relative changes in Tidal Volume
- Heart Rate
- Diastolic Heart Sounds Strength
- Body Posture (including Tilt Angle)

The device is intended for use on general care adult patients who are 18 years of age or older to provide physiological information. The data from the ADI CPM System are intended for use by healthcare pofessional as an aid to diagnose and treatment.

The ADI CPM System is intended to be used by patients at rest and not performing any activities or movements. This system is for spot checking and does not have continuous monitoring capability. The device does not produce alarms and is not intended for active patient monitoring (real-time).

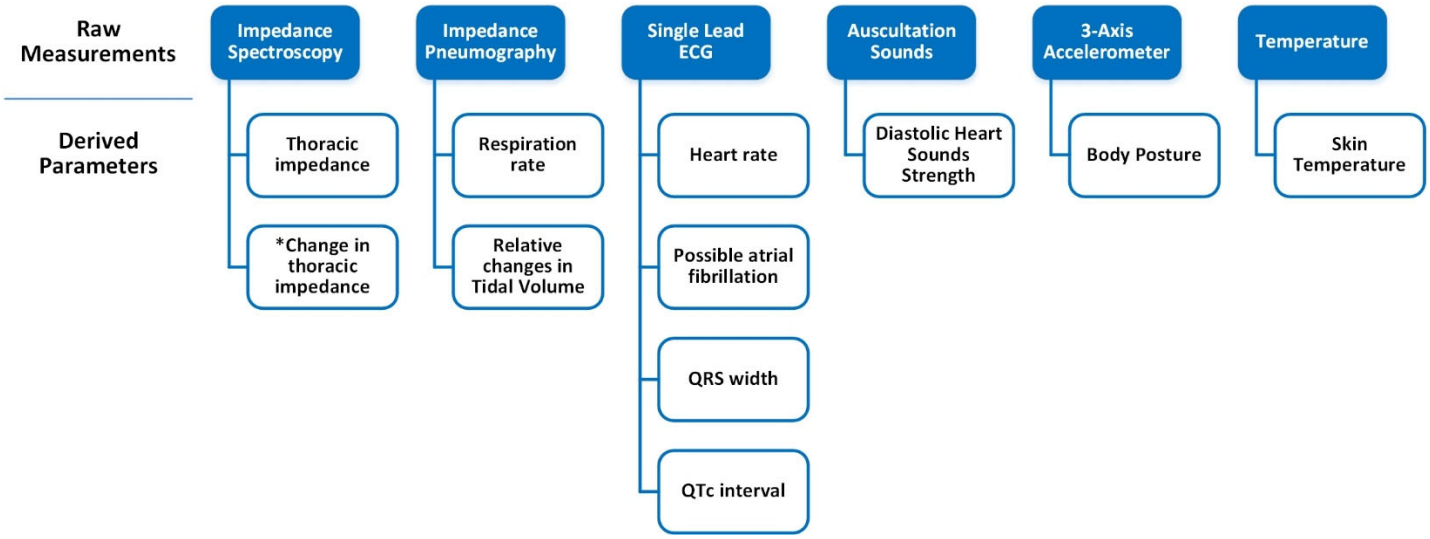
The computer-generated analysis of ECG data displayed by the CPM system is intended for informational use only. The ECG waveform and analysis are meant to supplement currently used methods of rhtyhm classification for the purposes of discriminating atrial fibrillation from sinus rhythm and not intended to replace traditional

methods of diagnosis or treatment. The interpretation of ECG offered by the device are only significant when used in conjunction with a physician overread as well as consideration of all relevant patient data.

The ADI At-Home CPM System is contraindicated for:

- Those patients with life threatening arrhythmias requiring immediate medical intervention.

CPM System Raw and Derived Measurements:
The CPM Analytics Engine derives measurements such as heart rate, respiration rate, relative tidal volume, thoracic impedance, body posture, diastolic heart sounds strength, and possible atrial fibrillation from raw measurement data acquired from the CPM device's sensors and electrodes. The raw measurements taken by the device and their derived parameters are illustrated in the graphic below. For this study, the focus will be on the impedance pneumography and the respective derived parameter measurements from each of these raw parameters.



Respiration Rate and Relative Tidal Volume Derivation:
Streaming of impedance is measured across the left side of the chest using 100kHz excitation frequency and streamed/sampled at a rate of 50 samples per second.

An algorithm is used to process the stream of impedance data and extract changes in impedance caused by breathing (i.e., relative tidal volume). Similarly, the rate of these changes in thoracic impedance is used to calculate the respiration rate.

Reference Devices:
The metabolic cart that provides breath-by-breath tidal volume, such as MGC Diagnostics Ultima CPX metabolic cart, will be used as a reference device to measure reference tidal volume. The capnography device, such as Capnostream 20p Bedside Monitor, or mass spectrometry device will be used as a reference device to record a continuous waveform of partial pressure or concentration of CO_2. This waveform will be annotated by the trained medical professional(s) to establish the reference respiration rate.

A clinical grade temperature sensor or a skin temperature thermistor probe will be used to gather skin temperature data.

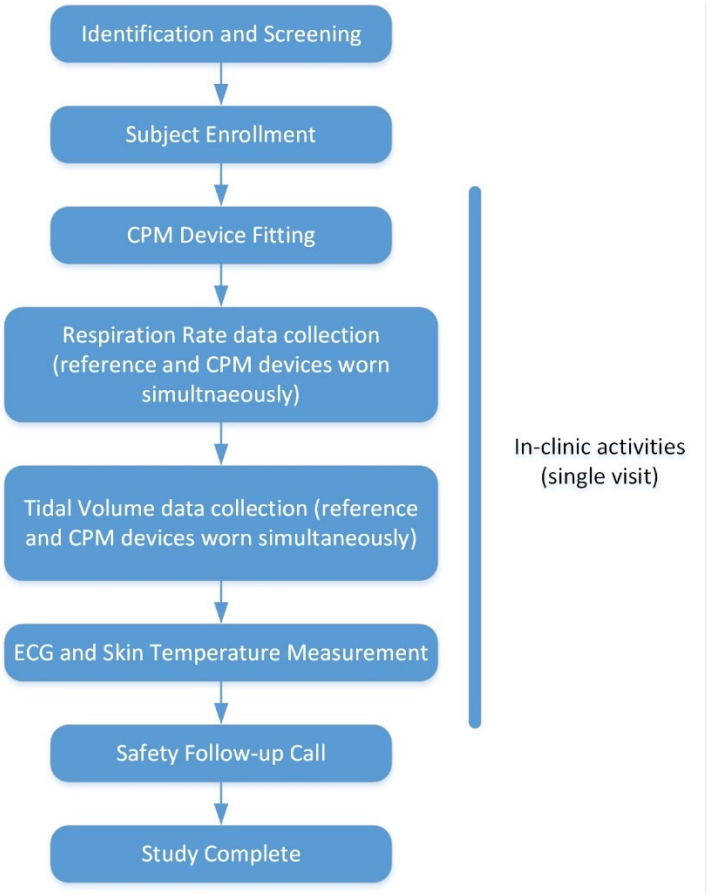
A diagnostic ECG device that provides 3 limb leads ECG simultaneously will be used to collect the diagnostic quality ECG for cardiologists' annotation.

Safety Equipment:
A finger-worn or forehead SpO2 monitor will be used throughout the study exercises to ensure that subjects are receiving enough oxygen during the clinic visit for safety.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:
Study Design:
This study is designed to be a clinical validation study to ready the CPM System for FDA 510(k) submission. This study will be conducted as a prospective non-randomized. The study is non-significant risk since the CPM Device is noninterventional and noninvasive. The study is primarily designed to validate the accuracy of the respiration rate and the changes in relative tidal volume. All participants will be fitted with both the CPM Device as well as reference devices.

Study Activities



Study Population and Sample Size:
The target population is healthy adult volunteers who do not have preexisting heart or lung conditions or illness. The goal is to recruit a participant population with a range of body types and BMIs and an approximately even split of genders.

The minimum sample size for this study is 40 subject who will all complete the entirety of one of the four procedure versions described in the study protocol.

Study Duration:
The duration per participant will be one supervised session of approximately two hours. At least one safety follow-up call will occur within one week of the in-clinic session.

Device Training and System Configuration
Prior to the enrollment of the first subject, the study sponsor (Analog Devices Inc.) will train the study team on the proper setup, fitting, placement, and use of the CPM System. The CPM System Web App will also be configured such that there is a separate user "bucket" specifically for each cohort of this clinical study to ensure data privacy and organization.

The reference device will also be configured as necessary to maintain traceability and facilitate data management and analytics. Study site staff will be trained on the proper configuration, application, and use of the reference and safety devices as per their associated Instructions for Use as they pertain to the metrics required to fulfil the study objectives.

Subject Identification, Recruitment and Informed Consent:
Screening of participants will take place based on the inclusion/exclusion criteria. If an individual meets all the inclusion/exclusion criteria, the investigator or designated study coordinator will approach the potential participant to discuss the details of the clinical study, including the risks and benefits of participating in the research study. Eligible healthy participants will be identified by the principal investigator (PI) and research team using the criteria specified in this protocol, initially from Dr. Johnson's laboratory database of potential participants and through the Mayo Clinic Employee Classifieds. IRB approved letters may also be used in recruitment for the pathologic cohorts.

Enrollment in this study is completely voluntary. At the time of recruitment, participants will be introduced to the study by the research team verbally and in writing. If the participant expresses interest, written consent will be obtained and documented at the time of the discussion by the IRB approved consent designees. Participant information and informed consent will be presented detailing the exact nature of the study as well as any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as they wish to consider the information and the opportunity to question the Investigator, their general practitioner or other independent parties to decide whether they will participate in the study.

Participants who have verbally consented will be asked to complete the informed consent form and return it to the clinical staff before the start of the study. Participants will be provided a copy of the informed consent for their records. No patient data will be collected prior to this. Once the form has been signed, the study can begin.

Written consent will be obtained, documented, and maintained as part of the research records. No identifiable patient information will be maintained, other than a randomly assigned subject number and patient ID that is generated by the CPM System.

Pre-Screening:
Before signing the Informed Consent form, subject will be screened by the study team for eligibility based on the inclusion and exclusion criteria.

Baseline Evaluation:
The following evaluations are required at the time of subject enrollment:

1. Medical history and current status – skin disorders;
2. Medical history and current status – allergies;
3. Medical history and current status – electronic implants;
4. Medical history and current status – cardiopulmonary disorders or illnesses including date of onset, recent hospitalizations and/or treatments, and medications taken;
5. Evaluation of device application site for broken, damaged, or irritated skin or rashes;
6. Demographics information: Age, Gender, Height, Weight, Race, Ethnicity, Occupation

7. Other information: smoking history, alcohol use (self-reported), recreational drug use (self-reported), Caffeinate intake, exercise habits
8. Body temperature via tympanic thermometer.

These assessments will be recorded in the CRF. Subjects who meet all inclusion and none of the exclusion criteria for either of the cohorts will then be able to proceed with the study and will be considered enrolled once measurement capability of the device on the subject has been verified.

Risks and Benefits:
Participating in this study poses minimal risk to participants. The ADI CPM Device is a non-significant risk, noninvasive medical monitoring device. The device is IEC 60601 compliant and meets all standards needed for FDA approval. There is slight risk that the adhesive used on both the reference and test devices will cause mild skin irritation due to prolonged adhesion of the devices as well as hair in the area. If this is case, the participant can decide to stop the study at any time. Hair in this area may also have to be trimmed if initial data collection proves to be a challenge. This will be done by the study team.

This laboratory has used all the listed reference devices for numerous studies, and there are no excessive risks of using these devices.

Finally, there is a slight possibility that performing the breathing exercises outlined in this protocol for the healthy cohort will cause participants to experience shortness of breath, dizziness, or syncope. An SpO2 monitor will be used as a backup safety mechanism in addition to constant supervision of study activities by the study team and the study will be paused if any of these symptoms are noted.

There is always a risk for disclosure of electronic data. The data collected from the devices will be stored on an internal secure server and secure cloud platform. If transport of electronic data is necessary for any reason an encrypted storage device will be used. The research team will be responsible for any data entry. Access to the data will be restricted to only research personnel approved on the IRB application, and the study sponsor. The research team will complete the institution's IRB education requirements for staff assisting with research data. Additionally, the devices used in the study store no identifiable patient information other than Patient ID and upload data to the cloud securely. Smartphones used in the study as well as the cloud repository are password protected and store Patient ID with no patient identifiable information. In other words, all patient data will undergo HIPAA-compliant de-identification.

By taking part in this study, participants will have a chance to aid in the validation of this novel device that will eventually have an impact on those living with cardiopulmonary disease.

Setting:
All study activities will take place at the Mayo Clinic in Rochester, MN in Dr. Johnson's laboratory.

Study Procedures:
Subjects will be recruited and begin the study as they are identified and consent to the study. Recruiting will pause when 40 subjects have initiated the study. If necessary, the recruiting can resume until 60 subjects have initiated the study. Otherwise, the recruiting may end at 40 subjects. One participant will participate in the study

at a time, with the duration of the single study visit lasting approximately two hours (the total commitment for any given participant being approximately half a day at the most).

Upon arrival to the clinic on the day of the study visit, prior to the application of the reference and test devices, skin inspection of the application site will be conducted. The CPM Device will then be applied to the participant's chest as described in the IFU materials supplied with the device (the study team will also have received training on the proper placement of the device prior to the initiation of the study). This device will be worn for the entirety of the clinic visit (without removal and replacement). The reference device will also be used for each measurement taken during the visit, concurrently. On the CRF, the time that the CPM Device is placed on the chest will be denoted.

A Baseline measurement will then be initiated using the CPM Mobile Application in order to assign a system-generated patient ID to the participant as well as to establish the tilt angle for the following measurements. The first half of the measurement should be in the Fowler, sitting-upright position, and the second position should be in a Supine, lying-flat position. The reference device will also be used during this time to establish a respiration baseline.

The exercises below will then be followed, with the time of the start of each exercise recorded in the CRF. Four different versions of the exercises (Procedures A-D) will be available that differ only in the sequence of the measurements. The study staff will randomly select a procedure version, using the EDC. Only one procedure version per subject is used. The selected version for each subject will be recorded.

Each exercise will last approximately 4 minutes, or the time that it takes to complete one full measurement with the CPM device in measurement mode (initiated by the CPM mobile app). Within each measurement, participants will move through two positions, both upright and supine. Reference respiration data will be taken concurrently with the CPM device measurement. For each measurement, it is ensured that the reference device recordings are stabilized before initiating the CPM measurement sequence.

For items 1-17, capnography waveform and breath-by-breath reference tidal volume from a metabolic cart will be simultaneously recorded for comparison. For item 18, a diagnostic ECG and clinical grade temperature sensor data will be collected simultaneously.

<Procedure A>

Item	Respiration Rate	Tidal Volume	Mode	Duration
1	Natural (baseline)	Natural (baseline)	Doctor Setup, App	4 min
2	15 BPM	Natural	Doctor Setup, App	4 min
3	30 BPM	Natural	Doctor Setup, App	4 min
4	40 BPM	Natural	Doctor Setup, App	4 min
5	6 BPM	Natural	Doctor Setup, App	4 min
6	25 BPM	Natural	Doctor Setup, App	4 min
7	10 BPM	Natural	Doctor Setup, App	4 min
8	35 BPM	Natural	Doctor Setup, App	4 min
9	20 BPM	Natural	Doctor Setup, App	4 min
Replace Adhesives				3 min

10	Natural	Natural (~500mL, peak-to-peak)	Doctor Setup, App	4 min
11	Natural	Shallow breaths (~ 250mL)	Doctor Setup, App	4 min
12	Natural	Deep breaths (~ 750 mL)	Doctor Setup, App	4 min
13	Natural	Extremely deep "yoga" breaths (~ 1000 mL)	Doctor Setup, App	4 min
14	15 BPM	Natural	Doctor Setup, App	4 min
15	10 BPM	Natural	Doctor Setup, App	4 min
16	30 BPM	Natural	Doctor Setup, App	4 min
17	25 BPM	Natural	Doctor Setup, App	4 min
18	Natural	Natural, ECG and skin temperatures are measured. (Simultaneous Recording with reference devices)	Doctor Setup, App	4 min

<Procedure B>

Item	Respiration Rate	Tidal Volume	Mode	Duration
1	Natural (baseline)	Natural (baseline)	Doctor Setup, App	4 min
2	30 BPM	Natural	Doctor Setup, App	4 min
3	40 BPM	Natural	Doctor Setup, App	4 min
4	6 BPM	Natural	Doctor Setup, App	4 min
5	15 BPM	Natural	Doctor Setup, App	4 min
6	10 BPM	Natural	Doctor Setup, App	4 min
7	35 BPM	Natural	Doctor Setup, App	4 min
8	20 BPM	Natural	Doctor Setup, App	4 min
9	25 BPM	Natural	Doctor Setup, App	4 min
Replace Adhesives				3 min
10	Natural	Shallow breaths (~ 250mL)	Doctor Setup, App	4 min
11	Natural	Deep breaths (~ 750 mL)	Doctor Setup, App	4 min
12	Natural	Extremely deep "yoga" breaths (~ 1000 mL)	Doctor Setup, App	4 min
13	Natural	Natural (~500mL, peak-to-peak)	Doctor Setup, App	4 min
14	10 BPM	Natural	Doctor Setup, App	4 min
15	30 BPM	Natural	Doctor Setup, App	4 min
16	25 BPM	Natural	Doctor Setup, App	4 min
17	15 BPM	Natural	Doctor Setup, App	4 min
18	Natural	Natural, ECG and skin temperatures are measured. (Simultaneous Recording with reference devices)	Doctor Setup, App	4 min

<Procedure C>

Item	Respiration Rate	Tidal Volume	Mode	Duration
1	Natural (baseline)	Natural (baseline)	Doctor Setup, App	4 min
2	40 BPM	Natural	Doctor Setup, App	4 min
3	6 BPM	Natural	Doctor Setup, App	4 min

4	15 BPM	Natural	Doctor Setup, App	4 min
5	30 BPM	Natural	Doctor Setup, App	4 min
6	35 BPM	Natural	Doctor Setup, App	4 min
7	20 BPM	Natural	Doctor Setup, App	4 min
8	15 BPM	Natural	Doctor Setup, App	4 min
9	10 BPM	Natural	Doctor Setup, App	4 min
Replace Adhesives				3 min
10	Natural	Deep breaths (~ 750 mL)	Doctor Setup, App	4 min
11	Natural	Extremely deep “yoga” breaths (~ 1000 mL)	Doctor Setup, App	4 min
12	Natural	Natural (~500mL, peak-to-peak)	Doctor Setup, App	4 min
13	Natural	Shallow breaths (~ 250mL)	Doctor Setup, App	4 min
14	30 BPM	Natural	Doctor Setup, App	4 min
15	25 BPM	Natural	Doctor Setup, App	4 min
16	15 BPM	Natural	Doctor Setup, App	4 min
17	10 BPM	Natural	Doctor Setup, App	4 min
18	Natural	Natural, ECG and skin temperatures are measured. (Simultaneous Recording with reference devices)	Doctor Setup, App	4 min

<Procedure D>

Item	**Respiration Rate**	**Tidal Volume**	**Mode**	**Duration**
1	Natural (baseline)	Natural (baseline)	Doctor Setup, App	4 min
2	6 BPM	Natural	Doctor Setup, App	4 min
3	15 BPM	Natural	Doctor Setup, App	4 min
4	30 BPM	Natural	Doctor Setup, App	4 min
5	40 BPM	Natural	Doctor Setup, App	4 min
6	20 BPM	Natural	Doctor Setup, App	4 min
7	25 BPM	Natural	Doctor Setup, App	4 min
8	10 BPM	Natural	Doctor Setup, App	4 min
9	35 BPM	Natural	Doctor Setup, App	4 min
Replace Adhesives				3 min
10	Natural	Extremely deep “yoga” breaths (~ 1000 mL)	Doctor Setup, App	4 min
11	Natural	Natural (~500mL, peak-to-peak)	Doctor Setup, App	4 min
12	Natural	Shallow breaths (~ 250mL)	Doctor Setup, App	4 min
13	Natural	Deep breaths (~ 750 mL)	Doctor Setup, App	4 min
14	25 BPM	Natural	Doctor Setup, App	4 min
15	15 BPM	Natural	Doctor Setup, App	4 min
16	10 BPM	Natural	Doctor Setup, App	4 min
17	30 BPM	Natural	Doctor Setup, App	4 min

18	Natural	Natural, ECG and skin temperatures are measured. (Simultaneous Recording with reference devices)	Doctor Setup, App	4 min

To ensure synchronization between reference device's time and CPM system's time, timestamps from each device will be recorded at the beginning of each CPM reading. Additionally, a pre-determined maneuver can be performed on or before item #1, and on or after item #18 during upright position, and corresponding clock time in the reference devices will also be logged.

A single metered breathing app or metronome will be used to pace respiration rates throughout the study. The same breathing pacing method will be used across all patients. It is assumed that actual respiration rates will differ slightly from those described in the protocol. Higher and lower respiration rates may be tailored slightly to accommodate the abilities of participants. During both phases of varying respiration rate (items 1-9 in above table) and varying tidal volume (items 10-17 in above table), both respiration rate and tidal volume will be tracked from the reference device.

Readings will not be considered "successful" or "complete" unless all CPM device errors are resolved prior to the device streaming mode. In the case that a contact or tilt error cannot be resolved, the measurement must be repeated until the data quality is deemed sufficient. If the device begins peeling off of the skin during a measurement (as noted by a participant or by a study staff) and the streaming data quality looks questionable, the measurement must be repeated and the adhesives replaced to ensure good contact. It is recommended that if the electrode contact issues are cumulatively encountered three times, adhesives must be replaced to restore good device attachment to the body. The IFU can be followed for troubleshooting tips regarding issues with data quality. The device may have to be replaced, the skin moisturized, or the adhesive on the device replaced. Any note regarding measurement issues and steps taken to resolve these issues must be noted in the CRF. If the above actions were not taken, the relevant readings should be excluded based on the deviation of the study protocol.

The recorded capnography waveforms, simultaneously acquired with the CPM readings for Items 1-17, will be interpreted by clinicians in a blinded fashion to provide the measured respiration rate as a reference. After time synchronization between the capnography and the CPM system, the sponsor will provide the clinicians with segments in the continuous capnography waveform corresponding to the duration of the CPM system readings. Clinician(s) will then be asked to annotate and provide the reference respiration rate.

Discontinuation/withdrawal of participants from the study:
Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- An adverse event which requires discontinuation of the use of the study device or results in an inability to continue to comply with study procedures (e.g. severe skin irritation)
- Consent withdrawn

Reasons for withdrawal will be recorded. Some data may be excluded from participants who withdraw from the study, at the discretion of the PI and sponsor. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has been resolved.

Malfunctioning or Broken Investigational Devices:
In the case that the study device malfunctions or breaks for any reason before the completion of the baseline, a new device will be fitted and assigned to the participant, the old device will be replaced by this one, and the full procedure will be followed as written. In the case that a CPM device malfunctions or breaks for any reason after the baseline measurement has been taken, the procedure below will be followed:

1) Markings are made using skin-compatible marker to relocate a new device after the malfunctioning one is removed;
2) Malfunctioning device is removed from the skin;
3) New device is fitted, placed according to markings, and a new baseline reading is taken (a new patient ID will be assigned in the app);
4) Protocol continues as normal, starting from the dataset on which the device malfunctioned;
5) A note is made in the CRF of:
    a. the exact nature of device malfunction;
    b. the time that the device was replaced;
    c. the measurement on which the device malfunctioned (e.g. metered breathing at 30BPM);
    d. and the new device ID and patient ID.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

This research study will be conducted in Dr. Johnson's laboratory in the Joseph building at St. Mary's hospital. The laboratory is equipped with all necessary equipment to perform human physiology experiments in a safe and secure environment. The study team has a long history of conducting Mayo IRB approved research protocols involving controlled breathing exercises in healthy participants. All personnel involved with this study have completed human subject protection certification such as CITI training. The combined expertise of the study team and the Sponsor will ensure that this research project is conducted safely and completed in a timely manner. This study has no financial implications for Mayo Clinic other than person hours required to recruit patients and run the study. All materials related to the CPM System (under test) used in the study will be provided by Analog Devices, and the reference devices and materials (SpO2 monitor, spirometry device, metabolic cart, ECG devices) will be supplied by Dr. Johnson's lab.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual:
40 healthy adult volunteers (up to 60 healthy subjects, if necessary) will be recruited for this study. More subjects than this will likely have to be approached for potential participation.

Subject population (children, adults, groups):
The subject population will include healthy adult volunteers (over the age of 18).

Inclusion Criteria:
- Adults over the age of 18 and who are willing and able to give informed consent
- Willing and able to participate in all activities related to this study, including trimming chest hair and wearing a reference device and the CPM wearable device
- Volunteers of any race, any gender
- Range of physiques
- Healthy

Exclusion Criteria:
- Injury or skin disturbance in the area of the test device
- Allergies or sensitivities to silicone/acrylic-based adhesive
- Pregnant
- Currently smokes cigarettes
- Has known respiratory conditions that might prevent them from following the study procedure such as:
    - Flu
    - Pneumonia/bronchitis
    - Shortness of breath/respiratory distress
    - Respiratory or lung surgery
    - Emphysema, COPD, lung disease
- Has self-reported heart or cardiovascular conditions such as chest pain, AFib, CHF, cardiomyopathy, or other conditions that could interfere with cardiopulmonary function
- Has other self-reported health conditions that could interfere with the breathing patterns and exercises detailed in the protocol (including wearing a capnography mask)

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is

cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☐ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

MAYO CLINIC

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number		
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	X
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.		
Social Security number		
Medical device identifiers and serial numbers	X	
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		

Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement:

Population Justification:

We have determined that healthy volunteers should be sufficient to validate the metrics of tidal volume and respiratory rate, due largely to the fact that healthy volunteers are able to breathe through a range of respiration rates and tidal volumes without putting their health at risk. Using the intended use population, who are generally ailing, struggling to breathe normally, and elderly, we would likely not be able to cover the full range of measured values with as much standardization as we would like to in this protocol. The mode of operation of the device and its use does not change whether a subject is healthy or part of our intended use population, and thus we believe that whether this data comes from healthy or ill volunteers does not matter in this case.

Sample Size Justification:

Based on prior studies data, the mean error (e.g., bias) of the respiration rate across 6 and 40 bpm ranges between -0.02 and -0.16 bpm, and the standard deviation of the error ranges between 1.74 and 3.31 bpm. To demonstrate the mean error is less than ±1 bpm, we will use a worst-case scenario of the mean error of -0.16 bpm with a standard deviation of 3.31 bpm. For two-sided hypothesis testing with significance level (alpha=0.05) and with 90% power (beta=10%), the minimum sample needed across 6-40 bpm is 202. Given that 9 readings will be collected per each participant, the minimum number of subjects is 23.

In addition, based on the prior study, the root mean squared residual relative errors after linear fitting ranges between 25.2 and 30.4%. To demonstrate that the root mean squared residual errors after liner fitting is less than 35% based on the hypothesis testing Chi-squared test with significance level (alpha=0.05) and 95% power (beta=5%), the minimum sample needed is 136. Given that 8 readings will be collected per each participant, the minimum number of subjects is 17.

However, to better reflect a broader patient population and since we might be under-estimating our error, we plan to enroll 40 subjects (up to 60 subjects, if necessary).

Data Analysis Plan:

Demographics:

A table will be constructed with counts and percentages of the number of subjects who were screen failures, the number of subjects enrolled in the study, the number of subjects withdrawn from the study before study completion, and the number who completed the study. For those subjects who withdrew before completion of the study, counts and percentages of the reasons for withdrawal will be tabulated. The continuous demographic characteristics at screening will be summarized for all subjects enrolled in the study using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations). The categorical baseline characteristics will be summarized for the study participants using frequency counts and percentages.

Effectiveness and Endpoint Analyses:
Respiration rate and relative tidal volume from the CPM System will be derived from the CPM analytics engine as described previously in the protocol, and the equivalent parameters and study data will be recorded from the reference device output. The reference respiration rate will be derived by trained medical professional annotating the number of breathing cycles in the recorded capnography waveform in the time period corresponding to the CPM readings.

For pairs of respiration rate calculated by the CPM and the reference, Bland-Altman analysis will be conducted to evaluate the accuracy of the respiration rate.

For pairs of relative tidal volume (rTV) calculated by the CPM system and tidal volume measured by the reference device, the correlation coefficient and R^2 value for the tidal calculated. In addition, the root mean squared of the residual errors after linear fitting will be calculated to characterize the relative errors of the relative tidal volume.

Endpoints:
Respiration Rate Accuracy
- 85% respiration rate error $\leq \pm 2$ BPM between reference and test device at 6-40 BPM

Relative Tidal Volume Relative Accuracy
- Root Mean Squared (RMS) of residual error after linear fitting $\leq 35\%$

Respiration Rate Endpoint Justification
The Respiration Rate is derived by the CP Analytics Engine from impedance measurements taken by the CPM device for a one (1) minute period. The CP Analytics Engine performs a quality control (QC) check for at least 30 seconds of consecutive impedance measurement samples. This QC-validated measurement data of at least 30 seconds results in a maximum computational accuracy of 2 BPM for the respiration rate. Consequently, an accuracy of 2 BPM is deemed sufficient for the CPM Device's intended use.

Relative Tidal Volume Endpoint Justification
Relative Tidal Volume as measured by an implanted device have shown to have day-to-day variability ranges between 10% and 14% in terms of coefficient of variation (Boehmer et al., *Journal of Cardiac Failure*, vol. 18, no. 8S, Aug, 2012). In addition, breath-to-breath tidal volume variability ranges from 18% to 43% depending on the underlying pulmonary disease conditions (Kuratomi et al. *Japanese Journal of Medicine*, vol. 24, no. 2, May, 1985), which further supports that day-to-day variability can be as high as 14%. Given this physiological day-to-day variability, it is considered that as high as 35% (about 2.58 times, $Z_{99.5\%}$, of 14%) of change can be

considered physiologic unless other clinical information strongly indicates otherwise. To correctly indicate the change greater than 35%, the relative error less than 35% is deemed sufficient to trend and indicate clinically significant change of rTV.