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: Bruce Johnson and colleagues

Study Title: Clinical Validation Study for Noninvasive Cardiopulmonary Management Device

Sponsor: Analog Devices, Inc.

Clinical Research Organization: MCRA

Protocol version number and date: 1.1 – September 28, 2020

Research Question and Aims

Hypothesis:

It is hypothesized that the ADI CPM Monitoring System (test device) will be able to measure:

a) Respiration rate and relative changes in tidal volume in healthy human volunteers with enough accuracy and precision to validate the intended use of the system.
b) Thoracic impedance with enough precision and consistency with respect to reference measurements to validate the intended use of the system.

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 tidal volume (rTV) derived by the CPM System*
3) Validate consistency in measurement-to-measurement and day-to-day changes in median Thoracic Impedance (TI) as well as position-dependent Delta Impedance (ΔZ) derived by the CPM System

*Secondary Objectives***
1) Confirm the accuracy of the skin temperature and ECG capabilities of the CPM System

Outcome Measures:
Primary Outcome Measures
1) Accuracy of CPM System calculated RR versus reference device*
   - Correlation coefficient between reference and test device
   - RMSE accuracy
2) Accuracy of CPM System calculated rTV as compared to reference device calculated TV*
   - Correlation coefficient between reference device and test device within subjects
   - Average correlation coefficients across subjects for rTV for immediate and long timeframes between measurements
3) Standard deviation of the difference between reference measured impedance and CPM measured impedance across multiple measurements
4) Average of within-subject standard deviation (STD) of TI values from test device for short term measurements

*Secondary Outcome Measures***
1) ECG and skin temperature confirmation
   - Confirm that ECG characteristics align with those from bench results using a simulator
   - Confirm that skin temperature readings align with those from bench results

** Note that in the pathologic cohort of subjects, RR and rTV are NOT designed to be a primary method of validating the CPM System but are included in the data collection and analysis protocols.*

*** Note that the secondary objectives and outcome measures only apply to the pathologic cohort of subjects and 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 Cardio-Pulmonary 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.

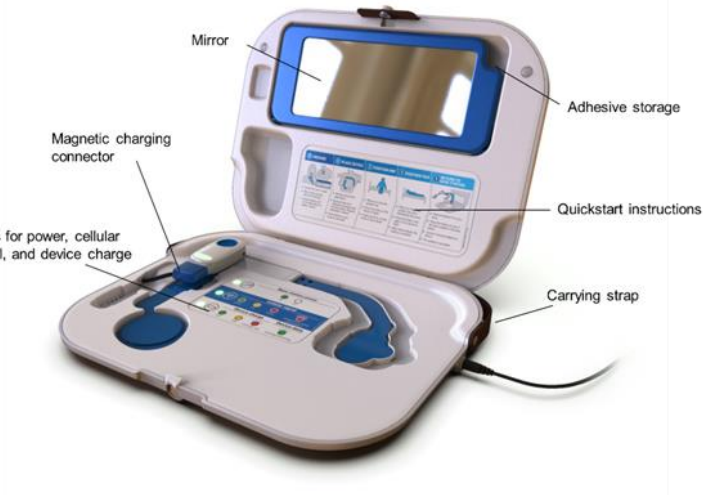
Studies such as MultiSENSE in 2017 have demonstrated, using a large cohort of patients implanted with a CRTD device, that it is possible to predict clinical decompensation (in this case, related to heart failure) using a combination of relevant parameters that include heart sounds, thoracic impedance, 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.

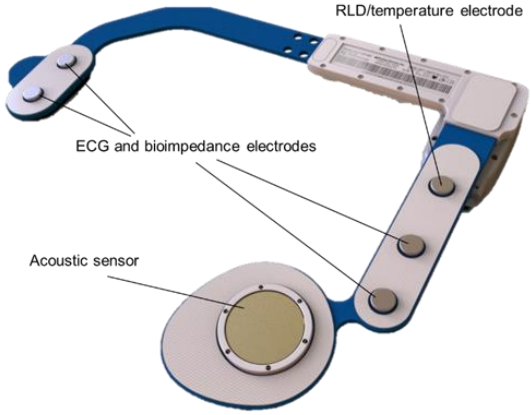
The ADI At-Home CPM System acquires physiological data and derived measurements associated with the presence and progression of cardiopulmonary conditions, including S3 heart sound, respiratory rate and relative changes in tidal volume, changes in thoracic impedance, and electrocardiogram abnormalities. The end goal of the product is to collect, derive and transmit these measurements to the clinical care team daily and 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, and thoracic impedance) clinically, using both pathologic patients in the intended use population as well as healthy volunteers who will follow respiration patterns (changing rate and depth) mimicking those observed in patients with cardiopulmonary conditions.

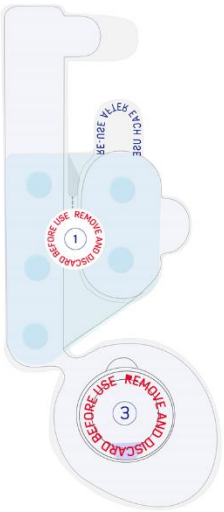
Description of Investigational Device:
The ADI At-Home CPM (Cardiopulmonary Management) System is a non-invasive device that measures and trends a variety of biological parameters. The device is battery-operated and biocompatible. The device is placed on the left chest area with one adhesive “island” 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.

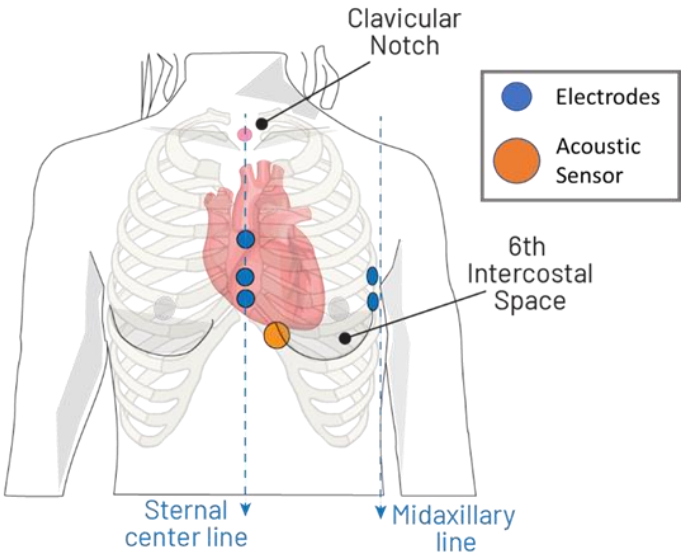
The device uses adhesive patches to adhere to the body. These use a gentle silicone adhesive with five hydrogel pads embedded (which align with the metal electrodes on the device). The device-side of the adhesives are composed of hook and loop material (like baby diapers) which allow the adhesives to 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 base station hardware or alignment tool. Additionally, to ensure consistent placement position, the device will either be worn for the entire duration of the study to avoid changes in the device position throughout the visit (healthy cohort), or a skin marker will be used to locate the device for each placement (pathologic cohort).









Intended Use:
The ADI At-Home CPM (Cardiopulmonary Management) System is intended for adults undergoing monitoring for cardiopulmonary conditions under the direction of a licensed medical professional to measure, record, and periodically transmit physiological data.

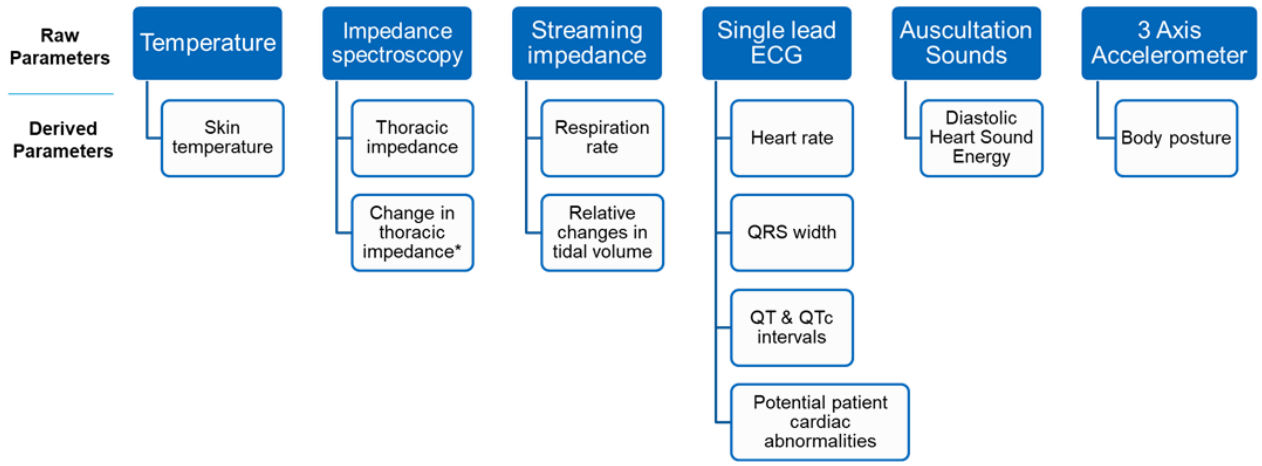
The ADI At-Home CPM System is indicated for patients:

- Taking diuretic medication
- Living with heart failure
- Recovering from a coronary artery disease-related event
- Chronic Obstructive Pulmonary Disorder

The ADI At-Home CPM System is contraindicated for:

- Those patients requiring attended, in-hospital monitoring for life threatening arrhythmias

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, QT and QRS widths, and cardiac abnormalities 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 raw impedance spectroscopy and streaming impedance measurements and the respective derived parameter measurements from each of these raw parameters. Raw and derived ECG and temperature parameters will also be confirmed.



Respiration Rate and 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 50 samples per second.

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

Thoracic Impedance and Delta Impedance Derivation:
The CPM System collects impedance spectroscopy at a variety of frequencies in two positions (usually Supine and Fowler/sitting upright).

The magnitude of thoracic impedance, at 100kHz excitation frequency, is computed as the median of impedance in each body position. The impedance is derived from two different body positions and is displayed as Thoracic impedance (median of impedance in the position with lower tilt) and the change in thoracic impedance (the difference between those two positions, reported as "ΔZ").

Reference Devices:
The MGC Diagnostics Ultima CPX metabolic cart will be used as a reference device to measure reference tidal volume and respiration rate (as well as ECG in the pathologic cohort). This device includes capnography and spirometry in addition to a pneumotachograph function.

The UFI Model 2994D THRIM (Tetra-Polar High-Resolution Impedance Meter) will be used as a reference device to validate the Thoracic Impedance measurement.

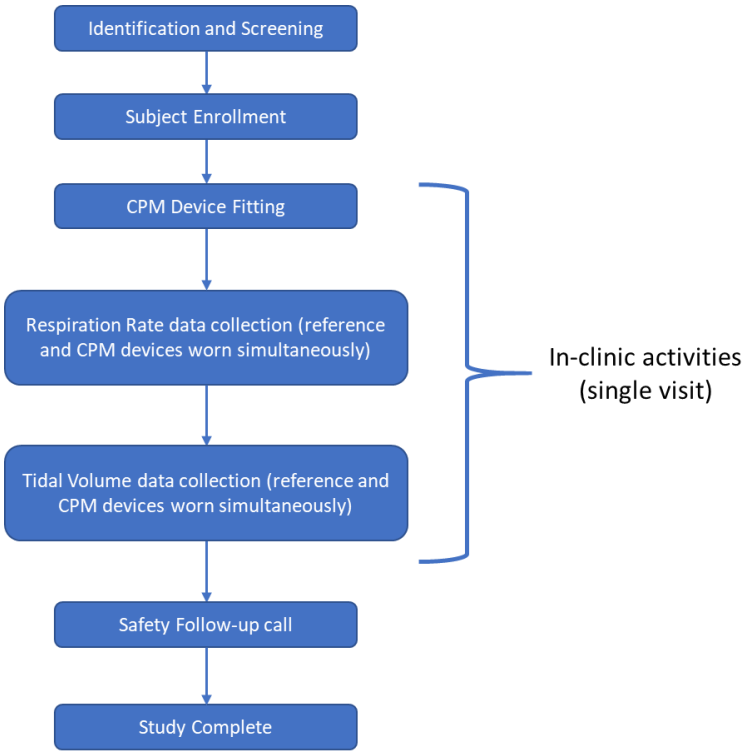
A clinical grade non-contact IR temperature sensor will be used to gather skin temperature data.

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

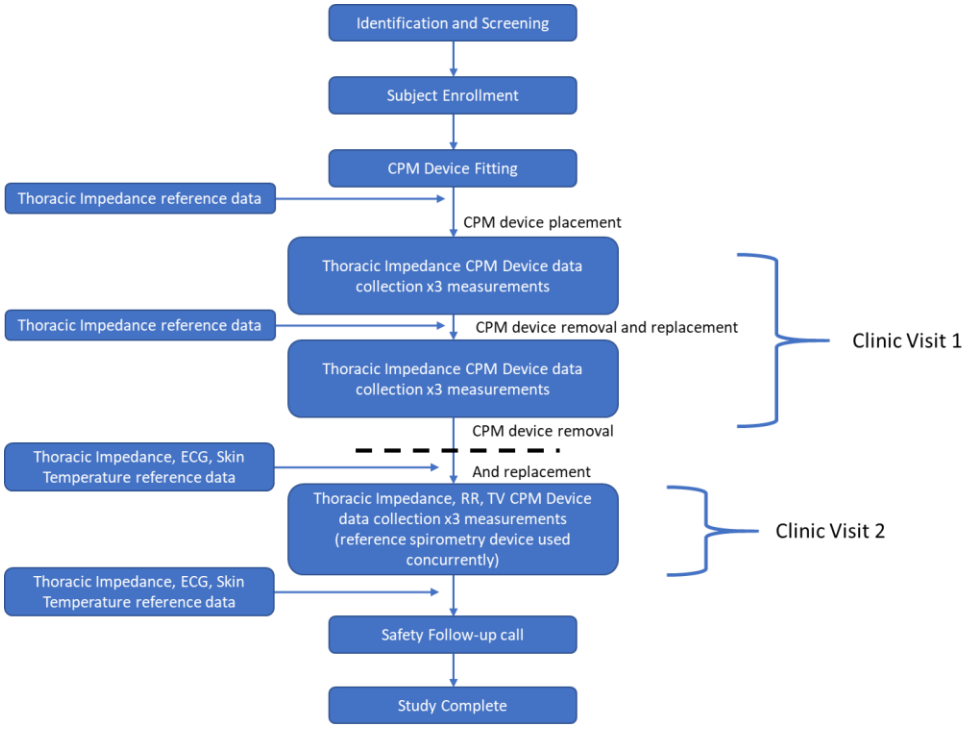
Study Design and Methods

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 study with two study arms/cohorts – one of healthy adult patients, one of pathologic patients who fit into the intended use population of the CPM System. The study is non-significant risk, since the CPM Device is noninterventional and noninvasive. The study is designed to validate the accuracy of the respiration rate and relative tidal volume as well as the precision of the thoracic impedance measurement of the CPM system. All participants, regardless of the study arm they are a part of, will be fitted with both the CPM Device as well as reference devices.

Healthy Cohort Study Activities



Pathologic Cohort Study Activities



Study Population and Sample Size:

Healthy Cohort

The target population for this cohort 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.

Pathologic Cohort

The target population for this cohort is adult patients who have been diagnosed with cardiopulmonary conditions. These can include chronic pulmonary conditions, chronic cardiac conditions, and those who are taking diuretic medications, living with heart failure, Chronic Obstructive Pulmonary Disorder (COPD), or recovering from coronary-artery disease related events. The goal is to recruit a participant population with a range of body types and BMIs and an approximately even split of genders as well as conditions outlined above (e.g. at least 5 each of COPD, HF, recovering from a coronary artery disease related event, and taking diuretic medication).

The minimum sample size for this study is 20 subjects per cohort (40 participants total), who will all complete the entirety of exercises included in the respective cohort's study protocol.

Study Duration:
Healthy Cohort

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.

Pathologic Cohort
The duration per participant will be two supervised sessions of approximately one hour each. These two study sessions will take place within one day and will be separated by at least one hour. At least one safety follow-up call will occur within one week of the in-clinic session.

It is expected that the entire study duration, from the enrollment of the first participant to the completion of the final participant's site visit, will be approximately 12 weeks total, with 6 weeks allotted per cohort.

Device Training and System Configuration
Prior to the enrollment of the first subject, the study sponsor (Analog Devices) 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. For the pathologic cohort, this will be based initially on a review of the individual's medical records. If an individual meets all the inclusion/exclusion criteria of either cohort then 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 PI and research team using the criteria specified in this protocol, initially from Dr. Johnson's laboratory database of potential participants. Pathologic participants can be identified either while they are admitted in the hospital, or when they return to Mayo Clinic for a scheduled physical or follow up visit, or from Dr Johnson's laboratory database of research participants who are diagnosed with cardiopulmonary disorders. IRB approved letters, flyers, and postings on the Mayo website may also be used in recruitment for both 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 GP 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. Pathologic patients will also be asked to complete the HIPAA Authorization to Use and Disclose Protected Health Information. 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

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:
Healthy Cohort
Patients will be recruited and begin the study as they are identified and consent to the study. Recruiting will end when 20 patients have initiated the study. 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. Each exercise will last approximately 2 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 Fowler and Supine. Reference respiration data will be taken concurrently with the CPM device measurement.

Item	Respiration Rate	Tidal Volume	Mode	Duration
1	Natural (baseline)	Natural (baseline)	Doctor Setup, App	3 min
2	6 BPM	Natural	Patient, App	2 min
3	10 BPM	Natural	Patient, App	2 min
4	15 BPM	Natural	Patient, App	2 min
5	20 BPM	Natural	Patient, App	2 min
6	25 BPM	Natural	Patient, App	2 min
7	30 BPM	Natural	Patient, App	2 min
8	35 BPM	Natural	Patient, App	2 min
9	40 BPM	Natural	Patient, App	2 min
10	15 BPM	Natural (~500mL peak-to-peak)	Patient, App	2 min
11	15 BPM	Shallow breaths (< 500mL p2p)	Patient, App	2 min
12	15 BPM	Deep breaths (> 500 mL p2p)	Patient, App	2 min
13	10 BPM	Extremely deep “yoga” breaths (> 750 mL p2p)	Patient, App	2 min

A single metered breathing app or metronome will be used to pace respiration rates throughout the study. The same breathing measurement 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 10-13 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) and the streaming data quality looks questionable, the measurement must be repeated and the adhesives replaced to ensure good contact. 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.

Pathologic Cohort
Patients will be recruited and begin the study as they are identified and consent to the study. Recruiting will end when 20 patients have initiated the study. One participant will participate in the study at a time, with the duration of each of two visits lasting approximately one hour (the total commitment for any given participant being approximately 2 hours spread over the course of one day).

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 reference bioimpedance device will be placed on the participant and a reference measurement will be taken. These electrodes will be worn for the entire duration of the study, even between visits, in order to ensure placement consistency, although reference and test impedance measurements will never be taken concurrently and reference measurements will never be taken with the CPM Device on the participant to avoid device interference. The reference bioimpedance device

electrodes will be placed within 2 cm from the CPM Device's electrode placement on the left chest of the participant. After disconnecting the reference device from the electrodes, 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). A skin marker will be used to mark around the device in order to later place it in the exact same location. On the CRF, the time that the CPM Device is placed on the chest for the first time will be denoted.

A Baseline measurement will then be taken 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 measurement should proceed with two positions; the first half of the measurement should be in a sitting-upright "Fowler" position, and the second half should be in a lying-flat "Supine" position.

In reference to the table below, subjects will be instrumented with the ADI device and laboratory-based reference impedance device along with a mouthpiece connected to a pneumotachometer and gas analyzer (only for the last three measurement items). In addition, they will be instrumented with an ECG for the indicated items.

The exercises below will then be followed, with the time of the start of each exercise recorded in the CRF. Each exercise will last approximately 2 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). Reference bioimpedance will be denoted at the beginning of each measurement in both a sitting and laying down position, following the CPM Device measurement flow. All CPM Device measurements include both a Fowler and a Supine portion.

Participants will be asked to breathe normally throughout the course of all measurements, including during the final three measurements which include the use of a device that tracks respiration rate and tidal volume. Reference devices to measure skin temperature and ECG will also be used during clinic visit two, before and after the CPM Device usage.

Subjects are to be instrumented with both the ADI device and reference impedance, mouthpiece, pneumotach, sampling line for O2 and CO2, ECG, and skin temperature.

Item	Description	Device/Mode	Duration
1	Baseline reference TI measurement*	Bioimpedance reference	1 min
2	Baseline measurement	CPM/Baseline Setup, App	3 min
3	Reference TI measurement	Bioimpedance reference	1 min
4	Application 1/Measurement 1**	CPM/Patient, App	2 min
5	Application 1/Measurement 2	CPM/Patient, App	2 min
6	Application 1/Measurement 3	CPM/Patient, App	2 min
7	Reference TI measurement	Bioimpedance reference	1 min
8	Application 2/Measurement 1	CPM/Patient, App	2 min
9	Application 2/Measurement 2	CPM/Patient, App	2 min
10	Application 2/Measurement 3	CPM/Patient, App	2 min
t = 1 hour			
11	Reference skin temperature, ECG data	Reference temperature, ECG devices	1 min

12	Reference TI measurement	Bioimpedance Reference	1 min
13	Application 3/Measurement 1; RR/TV measurement	Reference spirometer, CPM/Patient, App	2 min
14	Application 3/Measurement 2; RR/TV measurement	Reference spirometer, CPM/Patient, App	2 min
15	Application 3/Measurement 3; RR/TV measurement	Reference spirometer, CPM/Patient, App	2 min
16	Reference skin temperature, ECG data	Reference temperature, ECG devices	1 min

* Measurements with the bioimpedance reference device refer to the length of time that it takes to get a stable thoracic impedance reading in both a sitting and lying down position.
**Measurements with the CPM Device refer to one entire reading of the CPM System, which takes approximately 2 to 3 minutes and includes both sitting and lying down in each measurement.

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 away from the skin during a measurement (as noted by a participant) and the streaming data quality looks questionable, the measurement must be repeated. The IFU can be followed for troubleshooting tips regarding issue with data quality. The device may have to be replaced, the skin moisturized, or the adhesive on the device replaced. Adhesives will be replaced between each placement of the test device. Any note regarding measurement issues and steps taken to resolve these issues must be noted in the CRF.

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, bioimpedance 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:
20 healthy and 20 pathologic adult volunteers will be recruited for this study (a total of 40). More subjects than this will likely have to be approached for potential participation.

Subject population (children, adults, groups):
Healthy Cohort

The subject population will include healthy adult volunteers (over the age of 18).

Pathologic Cohort
The subject population will include those diagnosed with cardiopulmonary conditions who are over the age of 21. This can include those who are taking diuretic medications, living with heart failure, Chronic Obstructive Pulmonary Disorder (COPD), or recovering from coronary-artery disease related events.

Inclusion Criteria:
Healthy Cohort
- Adults over the age of 18 and who are willing and able to give informed consent
- Willing 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

Pathologic Cohort
- Adults over the age of 21 and who are willing and able to give informed consent
- Willing to participate in all activities related to this study, including wearing a capnography device, thoracic impedance reference device, and the CPM wearable device
- Those who**:**
    - Are taking diuretic medication
    - Are living with heart failure
    - Have chronic obstructive pulmonary disorder (COPD)
    - Are recovering from a coronary-artery disease related event.
- Volunteers of any race, any gender
- Range of physiques

Exclusion Criteria:
Healthy Cohort
- Injury or skin disturbance in the area of the test device
- Pregnant
- Currently smokes cigarettes
- Has known respiratory conditions 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)

Pathologic Cohort

- Under the age of 21
- Cognitive or physical impairment sufficient enough to interfere with informed consent or successful completion of the protocol
- Injury or skin disturbance in the area of the test device
- Pregnant
- Have life-threatening arrhythmias which require hospital admission and constant monitoring
- Has other self-reported health conditions that could interfere with 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.*

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		
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	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

MAYO CLINIC

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.

Healthy Cohort Data Analysis:

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 preliminary tests using publicly available databases and internally collected data, the root mean squared error on respiration rate for our system ranges between 0.5 and 0.8 bpm. For an average respiration rate of 20bpm, this is equivalent to 2.5 to 4% error. We expect the relative error of the tidal volume performance to be similar. For these purposes, we will use a worst-case scenario of a standard deviation of 10%. Using the paired-difference equivalence test power formula, we calculate the number of subjects n needed to demonstrate that the 2 device measurements are equivalent ($\delta = 0$) within 10% ($B = 0.10$). To obtain a 2-sided alternative with 90% power we set $z\alpha = 1.96$, and $z\beta = 1.65$. We can then calculate the required $n = 13$. This suggests that with 13 subjects we would be able to demonstrate equivalence (with 90% power) if the differences in the measurements between the CPM Device and the reference spirometers are within 10%. However, to better reflect a broader patient population and since we might be under-estimating our error, we plan to enroll 20 subjects.

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 tidal volumes from the CPM System will be derived from the CPM analytics engine as described previously in the protocol, and the equivalent parameters will be recorded from the reference device output.

For pairs of measurements collected continuously with the CPM and capnography device, scatter plots with the 45-degree line of agreement superimposed will be constructed from paired observations from the two sources along with Bland-Altman plots of the data. The mean absolute error (MAE) and the root-mean-square error (RMSE) estimates of agreement will be calculated for each comparison, as well as correlation coefficients. The standard deviations of each of the agreement measures will also be computed. The R^2 value for the tidal volume measurement will also be calculated.

Endpoints:
- Respiration Rate RMSE < 2 BPM between reference and test device at 8-40 BPM
- Relative Tidal Volume Precision has an R^2 value > 0.5

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 30 seconds of consecutive impedance measurement samples. This QC-validated measurement data of 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
Tidal volume as measured by home-care ventilators have been shown to have a partial Spearman correlation of as low as 0.59 when compared against a reference data logger (Stagnara et. al, Respiratory Care, June 19, 2018). As this variability is deemed acceptable for ventilator products in the market that require greater accuracy for delivery of pre-set tidal volume, an accuracy of R^2 value > 0.5 (R > 0.7) is deemed sufficient for its intended use.

Pathologic Cohort Data Analysis:

Power Statement:
Study Population Justification:
The CPM System intended patient populations are highly overlapping. Patients with heart failure tend to have several comorbidities including Chronic Obstructive Pulmonary Disease (COPD), and Coronary Artery Disease (CAD) and the vast majority of them are on oral diuretics to control their congestion. According to Medicare Advantage reporting data for 2017, 58.1% of heart failure patients were on furosemide (one of few common types of diuretics), 46.8% of HF patients had COPD, and 35.5% of HF patients had ischemic heart disease.

Similarly, COPD patients also tend to have several comorbidities including HF. For example, 39% of COPD patients have cardiovascular disease, over 25% of COPD patients have ischemic heart disease and over 18% have HF.

In addition, the focus of our study is to determine the precision of the impedance measure provided by the CPM system. We believe that the precision of the measurement itself is not dependent on the disease state and impedance measurements are commonly used by many medical devices (including patient monitors) on a variety of patient populations.

These statistics show a significant overlap between the populations that the CPM system is indicated for and our technical analysis shows that the performance should not depend on the underlying disease state. Hence, we believe that there is no need for splitting our study population into subgroups.

Sample Size Justification:
Based on preliminary data, the standard deviation (σ) of the thoracic impedance for an individual subject did not exceed 5.1 Ω when placement was controlled. Using the paired-difference equivalence test power formula, we calculate the number of subjects n needed to demonstrate that the 2 device measurements are equivalent ($\delta = 0$) within 6 Ω (B = 6). To obtain a 2-sided alternative with 90% power we set $z\alpha = 1.96$, and $z\beta = 1.65$. We can then calculate the required n = 10. This suggests that with 10 subjects we would be able to demonstrate equivalence (with 90% power) if the differences in the measurements between CPM Device and the reference device are within 6 Ω. However, we know that our estimates of the standard deviation might be inaccurate since they are based on a small sample of data and did not include the same patient population. To account for that potential error, we plan to enroll 20 subjects.

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:
Thoracic Impedance from the CPM System will be derived from the CPM analytics engine as described previously in the protocol, and the equivalent parameters will be recorded from the reference device output.

For pairs of measurements collected continuously with the CPM and reference device, scatter plots with the 45-degree line of agreement superimposed will be constructed from paired observations from the two sources along with Bland-Altman plots of the data. The mean absolute error (MAE) and the root-mean-square error (RMSE) estimates of agreement will be calculated for each comparison, as well as correlation coefficients. The standard deviations of each of the agreement measures will also be computed. The R^2 value for the tidal volume measurement will also be calculated.

Endpoints

Thoracic Impedance Precision (primary)

- Std < 6 Ohms from measurement to measurement (short term) within a subject
- Std of Z to reference X < 6 Ohms for short- and long-term measurements

Respiration Rate Accuracy (secondary)

- RMSE < 2 bpm between reference and test device

Tidal Volume Accuracy (secondary)

- R^2 value > 0.5

Thoracic Impedance Endpoint Justification

To determine the required precision for an impedance monitor to detect trends of worsening cardiopulmonary conditions, we looked into clinical standards. The ESC guidelines for the diagnosis and treatment of HF[1] recommend that patients with an unexpected weight gain of >2kg in 3 days should increase their diuretic or alert their healthcare team. Using this as the guide for the change to be detected, we looked into the corresponding impedance change per kg of weight gain in patients with cardiopulmonary conditions. Gudmundsson *et al.* reported a change of 2.3 kg and 4.8 ohms (~2.1 ohms/kg) in the weeks preceding a major HF event[2]. Note that those changes were reported using an implantable device which might be different from the thoracic impedance measured by the CPM system. Early data collected by the CPM project team show that an increase in 1kg corresponds to a 2.32 ohms decrease in the thoracic impedance. For the purpose of estimating the required precision, we will assume a 2ohms/kg change.

If we define an event per the ESC guideline for weight changes, (>2kg/3days), and using the conversion factor above, we get a change of 4 ohms in 3 days. In order to estimate the precision needed for the CPM system, we assume an even slower change of 4 ohms in 5 days. In order to detect a change of 4 ohms over 5 days for a patient with a known baseline, the required precision is 6.1ohms. We will set the desired precision for the CPM system at 6ohms.

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 30 seconds of consecutive impedance measurement samples. This QC-validated measurement data of 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.

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[1] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008 Oct;29(19):2388-442. doi: 10.1093/eurheartj/ehn309. Epub 2008 Sep 17. Erratum in: Eur Heart J. 2010 Apr;12(4):416. Dosage error in article text. Erratum in: Eur Heart J. 2010 Mar;31(5):624. Dosage error in article text. PMID: 18799522.

[2] Gudmundsson K, Lyngå P, Rosenqvist M, Braunschweig F. Monitoring of Daily Body Weight and Intrathoracic Impedance in Heart Failure Patients With a High Risk of Volume Overload Decompensation. Clin Cardiol. 2016 Aug;39(8):446-52. doi: 10.1002/clc.22547. Epub 2016 May 13. PMID: 27175605; PMCID: PMC6490859.

Relative Tidal Volume Endpoint Justification

Tidal volume as measured by home-care ventilators have been shown to have as high variability as 0.59 when compared using partial Spearman correlation against a reference data logger (Stagnara et. al, Respiratory Care, June 19, 2018). As this variability is deemed acceptable for ventilator products in the market that require greater accuracy for delivery of pre-set tidal volume, an accuracy of R^2 value > 0.5 for the CPM Device is deemed sufficient for its intended use.