CLINICAL STUDY PROTOCOL FOR THE MAKANI SCIENCE RESPIRATION MONITORING SYSTEM

Title:

Comparison of Non-Invasive Respiratory Monitoring System (RMS) to Capnography for Respiratory Rate (RR)

Protocol CP-0004

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Contents

Investigator Approval

Approval will be given electronically via Makani Science's electronic quality management system.

Version History

Version	Date	Author	Description of Change	Justification
A	27-Feb-2024	Michael Chu	Initial Version	New revision based on CP-0001 that addresses feedback from FDA
A	08-May-2024	Michael Chu	Protocol changes	Changed based on feedback from the FDA.

Study Summary

Study Title	Comparison of Non-Invasive Respiratory Monitoring System (RMS) to Capnography for Respiratory Rate (RR)
Study Device	Makani Science Respiration Monitoring System
Study Objective	The study objective is to compare the accuracy of the Makani Science Respiration Monitoring System (RMS) to capnography measurements manually scored by a healthcare professional (reference) for measuring respiratory rate in adult subjects, supporting its indications for use as a non-invasive system intended to monitor a patient's breathing using two Makani Science sensors.
Indications for Use	The Makani Science Respiration Monitoring System (RMS) is a non-invasive system intended to monitor a patient's breathing. It graphically displays respiration versus time and reports an approximate value of respiratory rate. Its measurements are used as an adjunct to other clinical information sources. The Makani Science RMS is intended to be used by healthcare professionals in healthcare facilities and dental offices on adult patients.
Study Design	Prospective, open-label, non-significant risk, single-arm study
Primary Objective	Demonstrate respiratory rate (RR) accuracy of the Makani Science RMS compared to manually scored etCO2 recordings from an FDA cleared capnography device within 3 bpm.
Additional Objectives	• Demonstrate system's ability to recover after motion artifacts. • Demonstrate system's ability to perform while subject is lying on side and in reclined position. • Demonstrate system performance for BMI and biological sex subgroups.
Statistical Endpoints	The primary endpoint is RR accuracy of the Makani Science RMS as compared to manual, clinician-scored etCO2 waveform (capnography), which will be estimated using mean absolute error (MAE). Additionally, bias will be summarized as the actual difference between Makani Science RMS and capnography (Makani Science RMS – capnography).
Primary Analysis	For the primary analysis, accuracy and the associated 95% confidence interval will be calculated. The lower confidence limit will be compared to the performance goal of 3 bpm.
Additional Analyses	• Bias and the associated 95% confidence interval will be calculated. • A Bland-Altman analysis will be performed for the difference in RR between Makani Science RMS and capnography. • Accuracy and bias will be summarized descriptively after artifacts and in different body positions.
Subgroup Analyses	Accuracy and bias will be summarized descriptively by: • Subject BMI (normal: BMI < 25 and overweight: BMI ≥ 25) • Biological sex.

Safety Analysis	Any and all adverse events will be recorded for the duration of the study period. The severity of all adverse events will be assessed based on risk management procedures and will be recorded. Serious adverse events will be recorded.
Inclusion Criteria	• Adult subjects between ages of 22 and 99 years old. • Body mass index between 15 and 40 kg/m^2.
Exclusion Criteria	• Currently has serious symptomatic, cardiac, or pulmonary disease. • History of serious skin irritation (severe rash or blisters) caused by medical adhesives (tape). • Subject cannot lie still on their back for one (1) or more hours. • Subject is unable to give written, informed consent. • Subject is unable to follow instructions.
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Abbreviations

Abbreviation	Term
BMI	Body Mass Index
etCO2	End-Tidal Carbon Dioxide
HCP	Healthcare Professional
MAE	Mean Absolute Error
MKS	Makani Science
RMS	Respiratory Monitoring System
RR	Respiratory Rate

Makani Science Pivotal Clinical Study Protocol

1 Introduction

1.1 Clinical Background

Continuous respiratory monitoring is critical for situations where the patient's breathing is at risk [2, 3, 4]. For example, high risk sedated patients undergoing, or recovering from, medical procedures are at a higher risk of developing respiratory failure and require continuous monitoring [5, 6]. Failure to detect such events in a timely manner can lead to preventable complications and even death, commonly described as "found dead in bed" [7]. Respiratory failure events that occur after medical procedures involving sedatives or opioids are significant contributors to complications, death, and prolonged hospital length of stay [8, 9].

Respiratory rate can be measured by a trained individual counting the number of breaths a patient breathes per minute. This is the standard practice for measuring rate during patient spot checks, but it is has neglected by health care professionals for several different reasons [10]. Breathing can also be measured continuously using certain monitoring systems. However, the current standard of care monitors for respiration, pulse oximetry and capnography, are ill-suited for detecting incipient respiratory failure. A recent study across 16 sites in 1,335 patients receiving parenteral opioid showed that capnography and pulse oximeters were least accurate measure for respiratory depression in these patients [11]. Additionally, both systems have known shortcomings described below.

Pulse oximetry is a measure of a patient's blood oxygenation through an optical sensor. While this type of monitor is ubiquitous and low cost, it is known to be a late indicator of respiratory depression. The Joint Commission Sentinel Event Alert, Issue #49 (now updated to the R3 Report on Pain Assessment and Management Standards), on the Safe Use of Opioids in Hospitals recommends that health care workers should be educated not to rely on pulse oximetry alone because it can indicate adequate oxygen saturation even in patients who are actively experiencing respiratory depression, especially when they are receiving supplemental oxygen [12]. Other important limitations of pulse oximetry include: (1) frequent false alarms; (2) its susceptibility to motion artifact; (3) its poor ability to predict respiratory decline; and (4) insensitivity to early signs of hypoventilation. Moreover, on February 19th, 2021, the US Food & Drug Administration issued a Safety Communication stating that pulse oximetry frequently gives inaccurate readings based on patient's skin color, skin thickness, and temperature [13].

Capnography measures the partial pressure of exhaled carbon dioxide (etCO2) and is widely used for patients under general anesthesia [14]. While this is the standard for monitoring ventilation, use of the system outside the operating room is inconsistent and facilities have been slow to adopt this technology [15, 16]. Additionally, capnography also has limitations, including: (1) delayed response time; (2) frequent false alarms; (3) readings that often are inaccurate and unclear; (4) complicated to use and interpret; (5) accuracy highly dependent on sensor position, which often can be dislodged from the patient's nose; and (6) uncomfortable to wear over time.

While pulse oximetry and capnography can monitor patient respiration continuously, respiratory depression and failure can be best detected by measuring the patient's ventilation (breathing rate and depth) [16]. This is currently done via spot checks by a trained individual in hospital settings [10]. Changes in ventilation can indicate respiratory failure much earlier than the current standard of care [3, 17]. Respiratory rate in particular, is an underutilized ventilatory parameter that can be important in assessing a patient's health [18, 10]. Additionally, a patient's respiration is a dynamic process that changes over time [3, 19]. The ability to monitor changes in breathing patterns can provide better information about the patient and may even permit inference about future adverse respiratory events. Therefore, a need exists for an accurate monitor to provide continuous information on the patient's ventilatory status.

Patient ventilation can be continuously monitored through different methods including direct measurement of flow in line with the airway, through bioimpedance measurements of the chest wall, acoustically through the airways, or by measuring torso movements.

Direct Airway Measurement

The current gold standard for continuous ventilatory monitoring is through capnography measuring respiratory rate using a mask or nasal cannula. Use of capnography is included in many standards and is well accepted by the field. Direct measurement of ventilation from the airway can also be made through other flow-meter type devices, such as the Linshom monitor [20], which hooks onto a capnography mask. Apart from the general problems associated with capnography, direct measurement of ventilation in line with the airway requires access to the patient's mouth or airway, which is not always possible.

Bioimpedance Measurement

The flow of air into and out of the lungs will change the overall impedance of the chest cavity. The change in impedance can be measured by injecting an electrical signal into the body and measuring it's change with breathing. This data can then be used to calculate respiratory rate and volume. Systems like Respiratory Motion's ExSpiron 1Xi monitor uses this method to great effect [21]. However, while this method can provide both respiratory rate and volume, it adds another wire, which tethers the patient to a large, bulky monitor.

Acoustic Measurement

Breathing will generate turbulence in the airway, which can be measured acoustically [22]. Monitoring for breathing sound not only provides respiratory rate information, but can also indicate other patient states, such as wheezing, etc. Equipment like a precordial stethoscope makes it possible to listen to the patient's respiration; however, acoustic systems are very susceptible to motion artifacts and noise, limiting its use to certain environments.

Chest Wall Movement

Patient chest wall and abdomen will naturally move from breathing. Medical professionals are trained to look at the chest wall movement to assess the patient's respiratory status. Quantitatively measuring the chest wall movement can also provide ventilatory information; for example, respiratory inductive

plethysmography (RIP) uses two large bands placed around the patient's torso to measure the change in circumference. A similar technology is PMD Solution's RespiraSense, which uses a piezoelectric sensor to monitor for chest wall movements [23, 1]. While simple to use, these types of systems are prone to motion artifacts. Chest rise and fall can also be monitored using a contactless method via radar (Circadia Health) [24]. This method requires direct line of site to the patient's chest wall and offers the advantage of not adding an additional wire to the patient. However, direct line of sight limits the use case of such a system to environment where the patient's chest is exposed.

While all the methods described above monitor ventilation continuously, they are either cumbersome to use or are subject to certain common environmental factors. The Makani Science Respiration Monitoring System provides a ventilatory monitoring solution that removes the cumbersomeness of wires and a bulky monitor while providing a simple way to monitor respiration that medical professionals are already familiar with (chest wall movement).

1.2 Study Rationale

The purpose of this study is to demonstrate that the Makani Science Respiration Monitoring System (RMS) can accurately measure respiratory rate, compared to manually scored etCO2 recordings from an FDA cleared capnography device.

2 Study Device

2.1 Device Description

The Makani Science RMS (subject device) uses a wireless, wearable sensor that can measure respiratory rate based on the expansion and contraction of the patient's chest (Figure 2-1a). The device uses highly stretchable soft strain sensors to measure torso expansion and contraction from respiration. The change in sensor length is then used to calculate respiratory rate.

Figure 2-1. Representative diagram of the Makani Science RM starting from the sensor placed on the torso (left), Bluetooth communication to the iPad (middle) and image of the Makani Science app displaying the chest wall waveform and respiratory rate.

The concept of using thoracic deflection to calculate the breathing rate is well documented and has been applied with respiratory inductive plethysmography (RIP), commonly used in sleep labs. RIP

measures the change in transverse circumference of the chest using large bands; the changes in chest wall circumference has been shown to have a linear correlation with tidal volume waveform [25]. In a previous publication, it was demonstrated that the concept behind RIP can be preserved even when the measurement length of the chest wall is reduced to a 1 cm length of skin on the torso by using a highly sensitive strain sensor (Figure 2-1b). [26] This significantly reduces the footprint needed for the measurement, making a wearable system more practical.

The Makani Science RMS consists of two disposable "Band-Aid®" size sensors and an iPad, which serves as the monitor. The sensors consist of a Bluetooth-enabled circuit connected to the soft strain sensor; the iPad has a custom app that connects with each sensor via Bluetooth and displays the respiratory rate and waveform. The sensors are attached to the skin with medical grade adhesives, to measure the torso expansion and contraction. A single sensor can be used to capture movement from the abdomen; two sensors can be combined to capture the movement of both the chest wall and abdomen. As the app receives the raw waveforms from the sensors, it will calculate the respiratory rate and display a filtered waveform representing the chest wall rising and falling (Figure 2-2).

The Makani Science RMS is an adjunct device that is to be used simultaneously with another standard respiratory monitoring device (e.g., capnography). The Makani Science RMS will be an FDA Class II device.

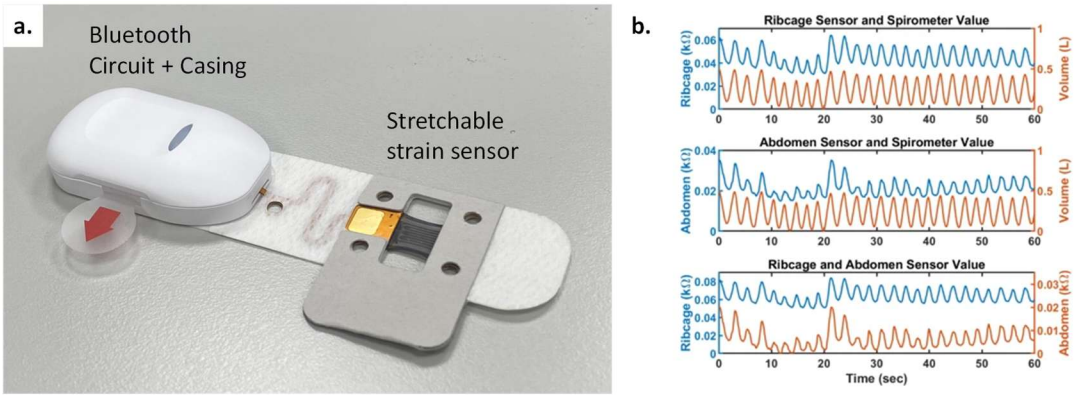

Figure 2-2 (a) Image of the Makani Science RMS sensor (prototype). The Bluetooth circuit and the stretchable strain sensors are labeled within the image. (b) Waveforms showing the ribcage and abdomen rise and fall compared against the tidal volume waveform from a flow meter. [26]

2.2 Indications for Use

The Makani Science RMS is a non-invasive system intended to monitor a patient's breathing. It graphically displays respiration versus time and reports an approximate value of respiratory rate. Its measurement is used as an adjunct to other clinical information sources.

The Makani Science RMS is intended to be used on adults by professionals in healthcare facilities and dental offices.

3 Study Overview

The study objective is to compare the accuracy of the Makani Science Respiration Monitoring System (RMS) to manually scored etCO2 recordings from an FDA cleared capnography device, supporting its indications for use as a non-invasive system intended to monitor a patient's respiration. This will be a prospective, open-label, non-significant risk, single-arm study. This study will use the same type of reference device as Makani Science's predicate device (PMD Solution's RespiraSense) [23, 1].

Participants will follow the protocol-specified breathing procedures and respiratory data will be simultaneously recorded for each participant using: (1) the Makani Science RMS and (2) manually scored etCO2 recordings from an FDA cleared capnography device. Enrollment will be targeted to balance normal (BMI < 25) and overweight (BMI ≥ 25) subjects, biological sex (male and female), and provide a representative range of age.

There will be two investigators present during the study. The first investigator will be a healthcare professional (HCP investigator) responsible for recording the RR from the reference device. This investigator will be blinded to the data from the Makani Science RMS. The second investigator (MKS investigator) will be responsible for recording data from the Makani Science RMS.

3.1 Study Objectives

3.1.1 Primary Objective

- The primary study objective is to demonstrate RR accuracy of the Makani Science RMS as compared to manual, clinician-scored etCO2 waveform (capnography) within 3 bpm.

3.1.2 Additional Objectives

- Demonstrate system's ability to recover after motion artifacts.
- Demonstrate system's ability to perform while subject is lying on side and in reclined position.
- Demonstrate system performance for BMI and biological sex subgroups.

3.2 Study Population

3.2.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to participate in the study:

- Adult subjects between ages of 22 and 99 years old.
- Body mass index (BMI) between 15 and 40 kg/m^2.

3.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study:

- Currently has serious symptomatic, cardiac, or pulmonary, disease.
- History of serious skin irritation (severe rash or blisters) caused by medical adhesives (tape).
- Subject cannot lie still on their back for one (1) or more hour.
- Subject is unable to give written, informed consent.
- Subject is unable to follow instructions.

3.2.3 Subject Enrollment Plan

A representative sample of the target patient population will be enrolled for this study. The intended use population will be adult individuals in ambulatory settings (such as dental office sedation procedures and clinics) outside of the hospital. Thus, the recruitment for this study will target patients from a recuperative care medical clinic where patient conditions should be representative of the population outside of a hospital; additionally, adults outside of the clinic can enroll in the study as well.

Enrollment will be targeted to balance normal (BMI < 25) and overweight (BMI ≥ 25) subjects, biological sex (male and female), and provide a representative range of age.

3.3 Study Data to be Recorded

3.3.1 Subject Baseline Data

The following baseline data will be recorded for each participant.

- Age
- Biological sex
- Weight
- Height
- Abdomen circumference
- Chest wall circumference
- Relevant medical history and medications (See section 3.3.2)

3.3.2 Relevant Medical History and Medications

Relevant medical history and medications will either be collected from the subject's medical files from the clinic or from the subject themselves.

Conditions such as cardiorespiratory conditions, neurological conditions, diabetes, obesity, hypertension, chronic obstructive pulmonary disease, asthma, congestive heart failure, and other relevant conditions will be documented. The following information will be collected:

- Relevant applicable condition and status (active, remission, cured) for each subject.
- If the subject is currently symptomatic. If they are, the symptoms will be documented.
- If the subject is currently on medication. If they are, the specific medication, dosage, and frequency will be documented.

3.3.3 Data for Primary and Secondary Objectives

The following data will be collected for primary and additional endpoint analyses. The data will be recorded manually by the investigators as well as continuously captured via video recording of the monitor's screen and subject torso.

- Manually scored subject respiratory rate from the capnography monitor.
- Concurrent respiratory rate from the Makani Science RMS.

Respiratory rate within a reasonable range for an adult (12 to 20 BPM) is expected to be measured. All respiratory rates will also be verified through benchtop testing. Additionally, RR will also be measured

with the subject in different positions and performing different respiratory maneuvers (coughing and shallow breathing). Additional information on specific positions and maneuvers are listed in **Appendix 1 – Study Procedure**.

3.3.4 Safety Analysis and Adverse Event Recording

The safety analysis shall be performed by recording adverse events (AE) for the study period. The study period is defined as the period from the start of any study procedures to the end of the study follow-up. For this study, the subject's study period is defined as the start of placing the non-invasive Makani Science device on the subject until removal of the device, which defines the subject's study exit.

Information on all adverse events shall be recorded immediately in the source document and in the appropriate adverse event module of the Case Report Form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedure results will be recorded in the source documentation.

All adverse events occurring during the study period will be recorded and reported in the associated Clinical Study Report. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study participation or device is not the cause. The severity of all adverse events will also be assessed based on current risk management procedures and will also be reported in the Clinical Study Report.

Serious adverse events (SAE) that are still ongoing at the end of the study period must be followed-up to determine the outcome. Any serious adverse event that occurs after the study period and is possibly related to study participation will be recorded and reported immediately to Makani Science. Adverse events definitions are detailed in **Appendix 2 – Adverse Events Definition**.

3.3.5 Protocol Deviations

Any deviations from this protocol will be recorded in the associated Clinical Study Report. Potential major deviations will be reported using the following categories:

- **Makani Science RMS failure**
  If the Makani Science RMS fails to operate at any point of the study (e.g., the subject device fails to turn on, turns off, disconnects, shows non-continuous waveforms, or any other unforeseen condition), the troubleshooting protocol in the instruction for use will be followed. If it is determined that the device is no longer operational or the study cannot be continued, the study will be stopped. The investigator will determine whether a new sensor should be applied to complete the study, time permitting. Any data collected prior to the termination of the study, and at the HCP investigator's discretion, can still be used in the primary endpoint of the study.
- **Deviation from normal breathing**
  If the subject's breathing becomes noticeably abnormal (e.g., erratic, coughing, etc.), it will be the HCP investigator's discretion to determine whether that abnormal breathing has affected the reference monitors and whether the data from the abnormal period should be discarded. Additional detail can be found in section 4.5.3.
- **Subject is unable to follow instructions**

If the investigator determines that the subject is unable to follow instructions, the study will be terminated. Any data collected prior to the termination of the study, and at the HCP investigator's discretion, can still be used in study analyses.

- **Study time limit reached**
  If the study time limit is reached, and the protocol could not be completed for the study. The data collected will be used for analysis. Any required data not recorded will be marked as missing and an explanation will be provided.
- **Failure to record baseline information**
  If the investigator fails to record the subject baseline information or has reason to believe the subject baseline information is not accurate, the investigator will follow up with the subject or clinic via phone to obtain the information. The deviation will be recorded.

3.4 Risk Analysis

3.4.1 Risks

The subject device does not have known direct major risks to the health and safety of the subject. There is no SAE anticipated for this study.

Anticipated minor risks include:

- Minor skin irritation in certain participants from the adhesive used in the Makani Science RMS sensor.

3.4.2 Minimization of Risks

Precautions that will be taken to avoid risks related to the study include:

- Well-defined clinical study protocol, including specific inclusion and exclusion criteria to enroll appropriate subjects in the trial.
  - Subjects with significant and extreme skin reaction to adhesives will be excluded from the study.
- Use of approved medical grade materials and adhesives designed and tested to current FDA consensus biocompatibility standards.
- Explanation of potential study risks and adverse events to each subject, and
- Ensuring that each subject fully understands the Informed Consent process and has provided their written consent prior to proceeding with any study procedures.

4 Study Design

This is a prospective, open-label, non-significant risk, single-arm study. Participants will follow the protocol-specified breathing procedures and respiratory data will be simultaneously recorded for each participant using (1) the Makani Science RMS and (2) manually scored etCO2 recordings from an FDA cleared capnography while the subject breaths normally. Enrollment will be targeted to balance normal (BMI < 25) and overweight (BMI ≥ 25) subjects, biological sex, and provide a representative range of age. All testing with the Makani Science RMS will be performed according to the final draft of the Makani Science RMS instruction for use with the final design and app.

4.1 Performance Goal

The primary study objective is to demonstrate that the performance of the Makani Science RMS is equivalent to the reference (capnography) within 3 bpm. Additionally, this study will use the same type of reference device (Capnography monitor) as our predicate device.

4.2 Study Procedure

The final Makani Science device, algorithm, and instructions for placing the sensor will be followed for this procedure. Additionally, the subject will also be monitored by a multi vital sign monitor (Philips IntelliVue MP50). This represents the same environment the patient will be in for most outpatient procedures (i.e., lying in the supine position with multi-vital monitor attached). Thus, this protocol captures a realistic use case of the Makani Science RMS.

The subject's respiration will be monitored simultaneously by the Makani Science RMS and the reference device. Respiratory rate will be recorded for each subject as they breathe normally (free spontaneous breathing) in the supine position. Additionally, respiratory rate will also be recorded with the subject in different position and performing different respiratory maneuvers to simulate artifacts. Details for the steps of the study procedure are provided in **Appendix 1 – Study Procedure**.

4.3 System Verification and Calibration

4.3.1 Subject Device

This study will use the final design (sensors, software, and algorithm) of the Makani Science RMS. Sensors may be reused during this study. Any Makani Science sensors that have been used will be reprocessed and undergo the same inspection and testing done during factory assembly to ensure that the performance is equivalent. The sensors will be documented and tracked through the clinical study.

4.3.2 Reference Device

The reference device used for this study will be a Philips InvelliVue MP50 multi-vital monitor with the capnography module. This is an FDA cleared monitor and will be calibrated for all vital signs prior to use.

4.4 Data Acquisition

Respiratory data will be simultaneously recorded for each participant from: (1) the Makani Science RMS and (2) a capnography device. A video camera will also be continuously recording the values from the monitors present as well as the movement of the subject's chest. All subject baseline data will be recorded prior to the start of the study by the investigators.

The HCP investigator will be recording the respiratory rate in 60 second intervals from the Philips IntelliVue MP50 monitor and will be blinded to respiratory rate information from the Makani Science RMS. The MKS investigator will be recording respiratory rate during the same 60 second intervals from the Makani Science RMS.

Data from both the Makani Science system and the Philips IntelliVue MP50 vital monitor will be recorded electronically as applicable. Data from the Philips IntelliVue MP50 vital monitor may be recorded continuously over time via an ethernet cable to an open-source software (VitalSignsCapture by Xeonfusion) as a comma separated value format [27]. Data from the Makani Science RMS monitor will

be downloaded as a CSV file. The electronically recorded data will not be used in the final primary endpoint analysis of this clinical study but will as used for future studies.

4.4.1 Clinician Scored Capnograph Recording (Reference)

Data from the Philips InvelliVue MP50 monitor will be assessed and recorded by the HCP investigator. The investigator will be counting each waveform from the etCO2 for a duration of 60 seconds; they will be blinded to any respiratory rate values reported on the monitor. The accuracy of the data will be determined by the HCP investigator. Basic guidelines for handling artifacts are listed in section 4.5.3. If the investigator has reason to believe that the capnograph was not functioning properly, the data from that 60 second period will be discarded. The HCP investigator will not be required to interpret the actual etCO2 values.

4.5 Data Handling

4.5.1 Data Storage

All data recorded by the investigators will be assigned a de-identified file name and input digitally as an excel file format. Notes taken during the study, including subject baseline information and any deviations from the protocol, will be scanned, and assigned a de-identified file name. Video recording of the monitor screen will also be assigned a de-identified file name. All the files will then be uploaded onto an external memory drive and kept in a secure, locked, location.

4.5.2 Data Processing and Quality Control

The HCP investigator will be a qualified healthcare professional who can manually count the etCO2 waveform from the capnograph for respiration rate. During the study, they will be asked to assess for and record any abnormal breathing events, which will be reported [28, 24]. The HCP investigator will be blinded to all Makani Science RMS information so that they remain unbiased while making the measurement and decision on artifacts.

The respiratory rate data will be inputted electronically as an excel file with the columns as time, manually counted respiratory rate, and respiratory rate from the Makani Science RMS. The processed data will be provided for statistical analyses. Table 1 shows an example of the data format.

Table 1. Example of the table provided for final analysis

Time (HH:MM:SS)	Manually Counted Capnography RR (BPM)	Makani Science RR (BPM)
3:01:51	5	4
3:02:56	5	5
3:03:55	6	5
3:04:58	6	6

If there is reason to believe that an error has occurred, the video recording of the session will be reviewed and new values for respiratory rate will be recorded and verified.

4.5.3 Identifying and Handling Respiratory Deviations during Primary Objective

Capnographs are prone to artifacts from the environment (i.e., motion, etc.). Thus, it is pertinent to define a set of criteria for identifying any artifacts in the reference data. This process will heavily rely on the experience and discretion of the HCP investigator present recording the capnography waveform from the subjects. Criteria for identifying artifacts are as follows:

- **End-Tidal CO2 Waveform**
  The waveform should show clean repeated patterns for the duration of the monitoring segment (60 seconds). Appearance of incomplete or multiple waveforms should be identified as artifacts.
- **General subject condition**
  Visual assessment of the subject's visual breathing pattern should be periodically made. This will help confirm that the subject is comfortable and breathing normally. If there are any indication that the subject is breathing outside of their normal state during the study (i.e. coughing, apnea, etc.), the healthcare professional should note the artifact during the study.

Determination of artifacts during the study will be at the sole discretion of the HCP investigator, who will be blinded to the Makani Science RMS data. If they have reason to believe that the data from the reference device has been affected by the artifact (i.e. subject coughing or system malfunction), then any data recorded will be discarded.

4.6 Statistical Endpoints and Analyses

Full statistical analysis details and statistical considerations will be provided in the Statistical Analysis Plan (SAP) for this pivotal study.

4.6.1 Study Endpoints

The primary endpoint is RR accuracy of the Makani Science RMS as compared to manual, clinician-scored etCO2 waveform (capnography). Accuracy will be estimated using mean absolute error (MAE).

An additional endpoint, bias, will be summarized as the actual difference between Makani Science RMS and capnography (Makani Science RMS – capnography).

4.6.2 Primary Analysis

For the primary analysis, accuracy and the associated 95% confidence interval will be calculated. The lower confidence limit will be compared to the performance goal of 3 bpm.

4.6.3 Additional Analyses

- Bias and the associated 95% confidence interval will be calculated.
- A Bland-Altman analysis will be performed for the difference in RR between Makani Science RMS and capnography.
- Accuracy and bias will be summarized descriptively after artifacts and in different body positions.

4.6.4 Subgroup Analyses

Accuracy and bias will be summarized descriptively by subject BMI (normal: BMI < 25 and overweight: BMI ≥ 25) and biological sex.

4.6.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. This information includes:

- Age
- Biological sex
- Weight
- Height
- BMI
- Abdomen circumference
- Chest wall circumference
- Relevant medical information (i.e., relevant disease, active symptoms, and current medication)

4.6.6 Sample Size Estimation

The study will target a total of 30 subjects with a maximum enrollment of 40 subjects. This will ensure adequate data for the primary and subgroup analysis.

4.7 Ethical and Regulatory Considerations

4.7.1 Role of Makani Science as Study Sponsor

As the study sponsor, Makani Science, Inc. has the overall responsibility for conducting the study, including any applicable national requirements. In this study, Makani Science will have certain direct responsibilities and may delegate others to qualified consultants. This protocol and any amendments will be documented and maintained at Makani Science.

4.7.2 IRB Approval

Prior to conduction of this study, investigator review board (IRB) approval will be received by Advarra.

4.7.3 Informed Consent

Informed consent forms will be obtained from all participants of the study prior to start of study conduction.

4.7.4 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study. A unique subject de-identification code will be assigned and used to allow identification of all data reported for each subject. Any video recorded will not include any identifiable material (i.e., subject face or any tattoos).

Study data may be made available to third parties, e.g., in the case of an audit, provided the data is treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that the study data is published.

5 Appendices

5.1 Appendix 1 – Study Procedure

Respiration rate will be measured concurrently using capnography and the Makani Science RMS.

5.1.1 Study Material

- Makani Science RMS
- Philips IntelliVue MP50 Vital Monitor + Sensors
- Computer with VitalSignsCaptureMP Software available (Optional)
- Ethernet Crossover Cable (Optional)
- Scale
- Tape measure
- Camera (3x)
- USB drive and USB to iPad adapter
- Resting/massage tables or bed

5.1.2 Study Procedure

1. The procedure will be explained to the subject and consent will be acquired.
2. The subject baseline information will be collected.
3. The subject will be asked to lay in the supine position.
4. The subject's skin will be cleaned with alcohol wipes.
5. The Philips IntelliVue MP50 vital monitoring sensors will be placed on the subject. This includes:
   5.1. ECG
   5.2. Capnography
   5.3. Pulse oximeter
6. The Makani Science sensor will be applied onto the subject.
7. The subject will be asked to breathe quietly for approximately 1 hour.
8. Respiratory rate will be recorded simultaneously from the Makani Science RMS and the capnograph monitor approximately every 2 minutes.
   8.1. The HCP investigator will count the number of etCO2 waveforms on the capnograph monitor for a 60 second duration.
   8.2. The MKS investigator will record the respiratory rate reported by the Makani Science RMS for the same duration.
9. The subject will be asked to perform common breathing artifacts (coughing and shallow breathing). The subject Respiratory rate recorded after each artifact has been performed.
   9.1. The Subject will be asked to cough. 30 seconds after the cough, the respiratory rate will be recorded for a 60 second duration. This will be repeated three times.
   9.2. The subject will be asked to perform shallow breathing for 30 seconds. 30 seconds after the shallow breathing, the respiratory rate will be recorded for a 60 second duration. This will be repeated three times.
10. The subject will be asked to change position and breath for an additional 5 minutes for additional body positions. Respiratory rates will be collected during this entire duration.

- The subject will be roll onto their right side and breath for 5 minutes.
- The subject will be asked to roll onto their left side and breath for 5 minutes.
- The subject will be reclined slightly and breath for 5 minutes.

11. All sensors will be removed and the subject will be presented with their compensation.

5.1.3 Follow up Assessment

- No follow up assessment is required.

5.2 Appendix 2 – Adverse Events Definitions

Adverse Event (AE):

Any unintended medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether related to the study medical device.

Serious Adverse Event (SAE):

An adverse event when the subject outcome is:

a. Death
b. Life-threatening
c. Hospitalization (initial or prolonged); including emergency room visits that do not result in admission to the hospital but were evaluated for one of these other serious outcomes
d. Disability or permanent damage
e. Required intervention to prevent permanent impairment or damage
f. Other serious important medical events (if serious event does not fit the other outcomes, but event may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes (i.e., seizures/convulsions that do not result in hospitalization)

Note that planned hospitalization for a pre-existing condition, or a procedure required by the study protocol without serious deterioration in health, is not considered a serious adverse event.

Device-Related Adverse Event (DRAE):

An adverse event or effect related to the use of the investigational or study medical device.

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