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Validation of the DreamKit plethysmography-derived respiratory effort signal against esophageal pressure

Protocol ID: SRC_SLE_Sparkle EP 2_2021_11315

Version 1

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FINAL

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Version History

Version No.	Amendment No.	Version Date	Summary of Changes	Rationale
1.0	N/A	12 May 2021	Initial release	N/A

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Sponsor Sign-Off

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June 24, 2021

Jessie Bakker, PhD; Associate Director of Clinical Affairs — Date

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CFR	Code of Federal Regulations
CPAP	Continuous positive airway pressure
CRF	Case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HSAT	Home sleep apnea test
ICH	International Conference on Harmonization
IRB	Institutional review board
OSA	Obstructive sleep apnea
PCCAB	Pulmonary and Critical Care Associates of Baltimore
PI	Principal Investigator
PPG	Photoplethysmography
PSG	Polysomnography
SADE	Serious adverse device event
SAE	Serious adverse event
SpO_2	Blood oxygenation saturation
UADE	Unanticipated adverse device event
UP	Unanticipated problem
US	United States

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1. STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

2. PROTOCOL SUMMARY

2.1. Synopsis

Study Title & ID:	Validation of the DreamKit plethysmography-derived respiratory effort signal against esophageal pressure SRC_SLE_Sparkle EP 2_2021_11315
Project Name:	Sparkle
Study Description:	This study has been developed in order to demonstrate the validity of the DreamKit respiratory effort signal against the gold-standard measurement of respiratory effort, esophageal pressure.
Endpoint:	The primary endpoint is the intraclass correlation coefficient of the peak-to-peak breath amplitude sequences extracted from the DreamKit and esophageal manometry respiratory effort signals over a range of respiratory effort generated during periods of occluded inspiration, end-expiratory breath holds, increased inspiratory resistance, increased expiratory resistance, and unresisted shallow breathing.
Hypothesis:	We hypothesize that the lower-bound of the 95% confidence interval for the correlation of breath amplitude sequences extracted from the DreamKit and esophageal manometry respiratory effort signals will be ≥0.5, indicating at least moderate agreement between the signals.
Study Population:	Up to 20 participants will be enrolled in this study in order to complete data collection in n=10. Inclusion Criteria: • Aged ≥18 years; • Fluent in English; • Able to provide informed consent. Exclusion Criteria: • Contraindication to esophageal pressure monitoring, including a sensitive gag reflex (determined by a positive response to the screening question "do you sometimes or often gag while brushing

	your teeth?"), dysphagia, nasal obstruction, and/or esophageal disorder likely to impact placement of the balloon; • Pregnancy or planned pregnancy during the study • History of allergic reactions to medical adhesives; • Known allergy to lidocaine; • Known seizure disorder; • Severe medical condition (controlled or uncontrolled) impacting breathing including neuromuscular disease, chronic obstructive pulmonary disease, respiratory failure or insufficiency, or requirement for oxygen therapy; • Chronic cardiopulmonary or renal disease, including a history of irregular heart rhythms; • At risk for excessive bleeding including use of anticoagulants; • An employee, or spouse of an employee, of a company that designs, sells, or manufactures sleep related products (including Philips); • An employee, or spouse of an employee, of PCCAB.
Study Design:	This is an interventional study performed in a single center for algorithm validation.
Study Visit(s) Summary & Duration:	Visit 1 • Consent, medical history, anthropometrics, skin assessment. Visit 2 • Respiratory effort data collection (esophageal manometry alongside the DreamKit device) under various breathing conditions.

2.2. Schedule of Activities

Procedures	Performed by	Visit 1 (office)	Visit 2 (lab)
Informed Consent	PI or designee	X	
Medical History & Anthropometrics	PI or designee	X	
Skin pigmentation assessment	Study coordinator	X	
Enrollment	Study coordinator	X	
Data Collection & Monitoring	PI or designee		X
AE Monitoring	Study coordinator	X	X
Participant Compensation & Study Dismissal	Study coordinator		X
AE Monitoring phone call	Study coordinator		[1-2 days after Visit 2]

3. INTRODUCTION

3.1. Background

Home sleep apnea test (HSAT) devices are increasingly used to diagnose obstructive sleep apnea (OSA).[1] Potential advantages of taking the diagnostic process from the hospital to the home include reduced cost; increased access; reduced wait times; higher patient turnover; increased patient comfort; and the collection of data that is more representative of a patient's usual sleep. Drawbacks of the HSAT model include the reduced number of signals compared with polysomnography (PSG); reduced patient/provider contact thereby limiting the opportunity for OSA education/support; and increased possibility of configuration error or signal loss leading to the requirement for further testing.[1-3] Research has demonstrated that a lab-based diagnostic approach is not superior to a home-based approach in terms of self-reported daytime sleepiness, quality of life, blood pressure, and subsequent adherence to continuous positive airway pressure (CPAP) measured over four weeks.[4] Development of a simpler HSAT device may be beneficial in terms of maximizing the collection of good quality signals, while also increasing ease of use and patient comfort. The DreamKit device has been designed to meet these needs.

The DreamKit device is a single-use adhesive patch containing an accelerometer and pulse oximeter, linked to nasal pressure cannula. From these three sensors, the following signals can be monitored or

derived: nasal airflow, blood oxygen saturation (SpO_2), pulse rate, respiratory effort, sleep time, and head position. The adhesive patch containing the pulse oximeter is designed to be placed on the forehead, connected to adhesive nasal pressure cannula placed over the nasal bridge and directly below the nostrils. Data are stored in the flash memory on the device, and can be uploaded to a computer upon completion of the recording.

4. OBJECTIVES

4.1. Primary Objective, Endpoint, and Hypothesis

The objective of this study is to validate the DreamKit plethysmography-derived respiratory effort signal against the gold standard, esophageal pressure, in ten healthy participants during a single in-laboratory daytime visit.

The primary endpoint is the intraclass correlation coefficient (ICC) of the peak-to-peak breath amplitude sequences extracted from the DreamKit and esophageal manometry respiratory effort signals during periods of occluded inspiration, end-expiratory breath holds, increased inspiratory resistance, increased expiratory resistance, and unresisted shallow breathing. We hypothesize that the lower-bound of the 95% confidence interval for the correlation of breath amplitude sequences extracted from the DreamKit and esophageal manometry respiratory effort signals will be ≥0.5, representing at least moderate agreement between the signals.[5]

4.2. Exploratory Objectives

Our exploratory objectives are:

- To repeat the analysis for the primary objective for each participant individually.
- Within the periods of occluded inspiration (representing obstructive apneas) and end-expiratory breath-holds (representing central apneas), to categorize each respiratory effort signal as being above or below a threshold of 10% of the baseline amplitude derived from normal (relaxed) breathing, in order to calculate sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve for the detection of obstructive events (overall and for each participant individually).
- Within the periods of increased inspiratory and expiratory resistance (representing obstructive hypopneas) and unresisted shallow breathing (representing central hypopneas), to calculate the area under the ROC curve in order to assess the agreement between the respiratory effort signals across all possible thresholds.

- To compare the number of breaths/minute between esophageal manometry and the DreamKit device during relaxed breathing, fast breathing, slow breathing, occluded inspiration, increased inspiratory resistance, increased expiratory resistance, and unresisted shallow breathing.
- To evaluate the phase relationship between esophageal manometry and the DreamKit device during relaxed breathing, fast breathing, slow breathing, occluded inspiration, increased inspiratory resistance, increased expiratory resistance, and unresisted shallow breathing.

4.3. Claims and Intended Performance

The proposed intended use statement for DreamKit is as follows, with the parts relevant to this study bolded (wording may change before regulatory submission):

> *The DreamKit device is a physiologic data recorder intended to collect and record data for use by clinical software used in polysomnography and sleep disorder studies for the diagnosis of sleep related breathing disorders.* ***The Plethysmography-Acquired Respiratory Effort (PARE) algorithm provides a respiratory effort signal acquired from the DreamKit photoplethysmography signal that correlates with traditional respiratory effort signals used in polysomnography.*** *The DreamKit with PARE provides the information required to detect apneas and hypopneas and classify these respiratory events as central, mixed, or obstructive. It is intended for adult use and can be used in a hospital, clinic, or patient home.*

5. STUDY DESIGN

5.1. Overall Design

This is an interventional study performed in a single center for validation purposes, with all data collection occurring within a single visit.

Up to 20 participants will be enrolled, in order for up to ten to complete data collection. Completion of the protocol by an individual participant will require an office visit of approximately one hour followed by a laboratory visit of approximately three hours during the day, to take place within a four week period. If convenient, the two visits may be combined. Total enrollment duration for an individual participant will not exceed four weeks; it is estimated that the entire study duration will not exceed six months.

5.2. Scientific Rationale for Study Design

5.2.1. Data collection from healthy participants during wakefulness

The purpose of this study is to compare two continuous signals and demonstrate that the DreamKit respiratory effort signal aligns with the esophageal pressure signal. We chose to collect data during wakefulness in order to coach participants through various breathing maneuvers that mimic a range of

respiratory patterns characteristic of sleep-disordered breathing, as described in Section 9.1.3. The breathing maneuvers were designed to manipulate the rate, amplitude, and phase of the signals as much as possible, in contrast to collecting the data during sleep, which would have led to recordings with mostly relaxed breathing interrupted by respiratory events that may not represent the full range of apneas, hypopneas, and RERAs. In addition, overnight esophageal manometry is now performed very rarely as it is not well-tolerated during sleep. The decision to collect data during wakefulness means that there is no need to target those with diagnosed sleep-disordered breathing, whose breathing during wakefulness is not disordered.

The study design we have adopted here is analogous to the requirements for validating a pulse oximetry signal per ISO 80601-2-61, in which ten healthy participants are required to breath a gas mix that results in oxygen saturation ranging from 70-100%, in order to validate the pulse oximeter against oxygen saturation determined by the gold-standard of arterial blood samples.

5.2.2. Identification of the comparator

Esophageal manometry is now rarely included in PSGs; instead, the 'clinical standard' for assessing respiratory effort is belts worn around the thorax and abdomen. It is important, however, that any estimate of respiratory effort is compared against the gold-standard, which in this case is esophageal pressure. Referring to the pulse oximeter example described above, comparison to esophageal pressure rather than thoracic/abdominal belts is akin to comparison to arterial blood samples rather than a previously-validated pulse oximeter.

5.2.3. Adoption of respiratory effort amplitude as the primary endpoint

The three characteristics of a continuous signal are amplitude (in this case, respiratory effort in pressure units of cmH_2O), frequency (in this case, breathing rate), and phase (in this case, time alignment of the two signals). The most clinically-relevant of these characteristics is amplitude, as the only component of the respiratory effort signal taken into account when scoring PSGs and HSATs is whether or not respiratory effort is present or absent during apneic events or whether there is reduction in respiratory effort that is proportional to the flow reduction during hypopneic events (AASM scoring criteria; Version 2.6). We will undertake exploratory analyses of respiratory rate (breaths/minute) and phase (time alignment).

5.2.4. Analysis of the primary endpoint breathing conditions

Attempting to breathe against an occluded airway is an essential characteristic of an obstructive apnea, while cessation of breathing following expiration is characteristic of a central apnea. Attempting to breathe against a resistor limiting the flow during inspiration or expiration characterizes respiration during an obstructive hypopnea or respiratory-effort related arousal (RERA), while unresisted shallow breathing is characteristic of a central hypopnea. Our primary analysis will therefore be based on breathing conditions representative of every respiratory event that relies on the respiratory effort signal per the AASM scoring

manual (Version 2.6). Additional manipulations of the signal (relaxed, fast, and slow breathing) will be used for exploratory analyses.

5.2.5. Identification of performance target

We adopted a performance target of 0.5 for the ICC of respiratory effort amplitude between the DreamKit and esophageal manometry signals in order to demonstrate 95% confidence of at least moderate agreement between signals.[6]

5.3. End of Study Definition

The study will be considered complete when participants are no longer being examined or the last participant's last study visit has occurred.

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

6. STUDY POPULATION

6.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

- Aged ≥18 years;
- Fluent in English;
- Able to provide informed consent.

6.2. Exclusion Criteria

Subjects shall be excluded if any of the following are present:

- Contraindication to esophageal pressure monitoring, including a sensitive gag reflex (determined by a positive response to the screening question "do you sometimes or often gag while brushing your teeth?"), dysphagia, nasal obstruction, and/or esophageal disorder likely to impact placement of the balloon;
- Pregnancy or planned pregnancy during the study (self-reported);
- History of allergic reactions to medical adhesives;
- Known allergy to lidocaine;
- Known seizure disorder;

- Severe medical condition (controlled or uncontrolled) impacting breathing including neuromuscular disease, chronic obstructive pulmonary disease, respiratory failure or insufficiency, or requirement for oxygen therapy;
- Chronic cardiopulmonary or renal disease, including a history of irregular heart rhythms or dyspnea;
- At risk for excessive bleeding including use of anticoagulants;
- An employee, or spouse of an employee, of a company that designs, sells, or manufactures sleep related products (including Philips);
- An employee, or spouse of an employee, of PCCAB.

6.3. Enrollment

Participants who sign the informed consent form will be screened for eligibility at Visit 1. Participants meeting all enrollment criteria will be enrolled into the study.

6.4. Screen Failures

Participants who are consented to participate in the study, but who do not meet one or more criteria required for participation, are considered screen failures. Minimal information will be collected for such participants, including demographics, screen failure details, eligibility criteria, and any AEs.

Re-screening is possible if, in the opinion of the PI or their designee, the reason for the original screen fail is likely to have changed and will not impact participant safety or data integrity. Re-screened participants should be assigned the same participant number as for the initial screening.

6.5. Strategies for Recruitment and Retention

The participants will be of both sexes, with a wide body mass index (BMI) range, in order to support generalizability of results. Due to the small sample size, no firm parameters for these measures have been determined *a priori*.

It is anticipated that racial/ethnic minorities will represent at least 30% of the sample.

All participants will be enrolled within the US. Recruitment will be the responsibility of the site, and will take place through a local university newspaper and online advertisements. As this study involves only two visits, it is not likely that participants will drop-out or be lost to follow-up before study completion. No specific strategies for retention are required.

7. STUDY INTERVENTION

The DreamKit device is a non-released, investigational product. The previous generation device, SomnaPatch, is released (K183625); however, the device has been modified from this version.

The device consists of a forehead patch containing the oximeter and accelerometer, and a nasal patch for connection to the cannula. The nasal pressure signal is not required for calculation of respiratory effort, and the presence of the nasal cannula during testing will interfere with the equipment required for esophageal manometry. We will therefore use a version of the device that does not include the nasal cannula. Although this prototype device will differ from the final released version, there is no difference in function with regards to the respiratory effort signal.

Additional Philips devices include the Threshold IMT breathing trainer, the Threshold PEP positive expiratory pressure device, and the Alice 6 with Sleepware (which is already in use at the site). All are released products and will be used according to their labeling.

7.1. Acquisition and Accountability

The DreamKit devices will be shipped to the investigator. All devices (used and un-used) will be returned to the Sponsor at the end of the study. An inventory of devices will be maintained.

7.2. Formulation, Appearance, Packaging, and Labeling

The Device Label, User Manual and Operating Manual are included with the IRB submission. Some content of these documents may change before regulatory submission.

7.3. Product Storage and Stability

The DreamKit device should not be used in temperatures above 35 degrees Celsius (95 degrees Fahrenheit).

7.4. Preparation

The DreamKit devices do not require configuration prior to use. The investigator is required to peel off the adhesive backing, and place the forehead patch above the eyebrows in the center of the forehead, after thoroughly prepping the skin.

8. DISCONTINUATION/WITHDRAWAL

8.1. Discontinuation/Withdrawal from the Study

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy;
- Significant study non-compliance;
- If any AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant;

- Any disease progression or medical condition which requires discontinuation;
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- At the discretion of the PI for any reason.

If a participant wishes to voluntarily discontinue from the study, they should contact the site directly. AE monitoring will continue for all participants who voluntarily discontinue the study or are withdrawn from the study by investigators.

Discontinuations, withdrawals, and participants lost to follow up will be replaced. Recruitment will continue until the evaluable dataset is complete.

8.2. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for Visit 2 and is unable to be contacted by the study site staff.

9. STUDY PROCEDURES & EVALUATIONS

9.1. Efficacy Assessments

9.1.1. Phone screening

Recruitment will be the responsibility of the site. Potential participants will be screened over the phone for eligibility, and then scheduled for an enrollment visit.

Phone screening will include questions regarding sex, height and weight (for calculation of BMI), to facilitate the recruitment of participants of both sexes with a wide BMI range.

9.1.2. Visit 1: Office visit for enrollment

Preliminary assessment of eligibility will be performed by the PI or their designee during Visit 1, which is anticipated to take approximately one hour. The PI or their designee will then describe the purpose of the study, all study procedures, and possible risks of participation. After an opportunity to ask questions, consent will be sought by the PI or their designee.

Following consent, an investigator will perform a brief medical history and physical examination, including anthropometric measurements (height; weight; neck, waist, and hip circumferences). The examination will include vital signs (blood pressure obtained while seated according to American Heart Association guidelines,[7] pulse rate, respiratory rate,[8] and SpO2).

Participants will complete the Fitzpatrick skin type questionnaire.[9]

Skin pigmentation will be assessed with a Mexameter probe (C&K Electronic; Köln, Germany) a small hand-held tool held over the skin of the inner arm (an area with minimal sun exposure) for a few seconds that emits three light wavelengths to calculate melanin and hemoglobin content in arbitrary units on a scale of 0-999 (within ±5%).

If the participant is found to be eligible, they will be scheduled for the in-lab visit within four weeks of the enrollment visit. A study physician will advise participants as to whether they should take their prescription medication during the fasting period prior to Visit 2. Note that the office visit (enrollment) and the laboratory visit (testing) may be combined, if logistically feasible.

9.1.3. Visit 2: Laboratory visit for testing

Participants will be asked to attend Visit 2 for daytime testing in the fasting state (no food or drink for four hours). The visit is anticipated to take approximately three hours. Prior to any testing, each participant will be guided through what to expect during the visit. Each participant will be given an opportunity to practice the breathing conditions described below prior to instrumentation.

Insertion of esophageal catheter

The gold-standard measurement of esophageal pressure will be made via a catheter surrounded by a small, sealed balloon placed in the lower esophagus, connected to a pressure transducer (Model 0585; Braebon Medical Corporation; Ontario, Canada). The site PI or their designee will administer local anesthetic in the form of lidocaine topical gel and/or spray to the nose and throat prior to insertion of the esophageal pressure balloon. The esophageal catheter will then be inserted through the nares, and placed in the lower esophagus for the duration of the testing procedures (approximately one hour). Calibration will be undertaken prior to testing.

Although generally well-tolerated, initiation and continuation of esophageal pressure measurement will depend on participant tolerance of instrumentation.

Placement of DreamKit device

The DreamKit device will be configured and placed on each participant per the supplied instructions.

Monitoring of other signals

Vital signs including, at minimum, finger pulse oximetry via the Alice 6 platform will be monitored throughout the data collection period.

Synchronization

Continuous viewing and recording of data from the esophageal catheter will take place via the Alice 6 and Sleepware, which is the system currently in use at the site. The site coordinator will ensure that these signals are free from artefact at initiation, and throughout the data collection period.

Data from the DreamKit device will not be visible in real-time, and therefore it is important to ensure that the DreamKit signals can be synchronized to the esophageal pressure signals post-hoc. At the beginning and end of the data collection period, the participant will be asked to breathe out and hold their breath for approximately three seconds; then take a deep breath in and hold for approximately three seconds; and then finally, tap the DreamKit device to coincide with the peak of inhalation. This process will place a motion artefact on the accelerometry signal timed (approximately) to inhalation observed in the respiratory effort and esophageal pressure signals. The SpO_2 signals collected via the Alice 6 and the DreamKit device may also be used for time-alignment. During data processing, it may be necessary to make a small adjustment to the DreamKit time to match the Alice 6 time, ensuring synchronization of the signals.

Data Collection

Participants will be instructed to undertake the following breathing conditions (all in the supine position):

- End-expiratory breath holds to mimic central apneas: ten breath holds after exhalation, 10-20 seconds in duration.
- Occluded inspiration to mimic obstructive apneas: five periods of occluded inspiration paced at 15 attempted breaths/minute with blocked nose and mouth closed, 10-20 seconds in duration.
- Increased inspiratory resistance to mimic obstructive hypopneas and RERAs: paced at 15 breaths/minute against inspiratory resistance using the Philips IMT device (see details below), for 30 seconds at a time, five times.
- Increased expiratory resistance to mimic obstructive hypopneas and RERAs: paced at 15 breaths/minute against expiratory resistance using the Philips Threshold PEP device (see details below), for 30 seconds at a time, five times.
- Shallow breathing to mimic central hypopneas: partial breaths paced at 15 breaths/minute without resistance, for 30 seconds in duration, five times.
- Slow: paced at 12 breaths/minute; two minutes.
- Fast: paced at 20 breaths/minute; two minutes.
- Relaxed: paced at 15 breaths/minute; two minutes.

The coordinator will allow the participant time to become comfortable and still before beginning each condition, and will note the exact start/end time of each (MM:SS) from the computer used for data collection.

The participant may return to relaxed breathing at any time if they experience discomfort or dizziness.

For the paced breathing conditions, the site coordinator will play a metronome (e.g. www.imusic-school.com/en/tools-online-metronome) set to 24 (slow), 30 (relaxed) and 40 tones per minute (fast), allowing the participant to time each inspiration and expiration to the tones for breathing rates of 12, 15, and 20 breaths per minute.

Increased inspiratory resistance will be achieved with the Philips Threshold IMT breathing trainer, a small, hand-held mouthpiece containing a flow-independent one-way valve[1]. Similarly, increased expiratory resistance will be achieved with the Philips Threshold PEP device, a device which creates positive pressure during exhalation[2]. The pressure of each device can be adjusted in 2cmH_2O increments. During data collection, the coordinator should coach the participant and adjust the pressure of each device when necessary in order to achieve appropriate changes in pressure during increased inspiratory and expiratory resistance conditions. Participants should aim to achieve a change from normal breathing of at least -15mmHg, but ideally -20 to -30mmHg, during the increased inspiratory and expiratory resistance conditions, and ensure a minimal change in esophageal pressure during the end-expiratory breath holds compared to normal breathing. A previous study following similar methodology to simulate apneas found a median change in esophageal pressure compared to normal breathing of -20.1mmHg (quartiles -21.9 to -15.0) with increased inspiratory resistance, -29.1mmHg (quartiles -38.4 to -20.6) with increased expiratory resistance, and 0.1mmHg (quartiles -2.9 to 2.0) with end-expiratory central apnea.[10,11]

The data collection period is likely to be approximately one hour per participant, and will not exceed 1.5 hours. At this time, all equipment will be removed and the participant will be free to leave the laboratory.

Data processing

Using the timing information noted during data collection, an analyst blinded to the DreamKit data will score the esophageal pressure data files in order to identify the periods of occluded inspiration, end-expiratory breath-holds, increased inspiratory resistance, increased expiratory resistance, shallow breathing, slow respiration, fast respiration, and relaxed breathing. Periods of poor pressure signal quality will be excluded from analyses, such as artifact caused by movement, swallowing, or sensor displacement. An independent analyst will then import the DreamKit signal and ensure that the two data sources (Alice 6 and DreamKit) are synchronized following the procedures above. Periods where the DreamKit device indicates poor effort data quality by means of channel fail events will be excluded from analyses.

Follow-up phone call

A follow-up phone call will be placed 1-2 days after completion Visit 2, in order to assess any AEs that may have become apparent in the intervening period.

9.2. Compensation

[1] Philips Threshold IMT: https://www.usa.philips.com/healthcare/product/HCHS730010/treshold-inspiratory-muscle-trainer

[2] Philips Threshold PEP: https://www.usa.philips.com/healthcare/product/HCHS735010/treshold-positive-expiratory-pressure-device/overview

Participants will be compensated $50 for the office visit and $225 for the data collection visit ($275 in total). Participants who opt to discontinue from the study will be prorated at the time of withdrawal.

9.3. Safety Assessments

All study procedures will take place during study visits, under the supervision of the PI. The PI is a physician and all visits will take place at a clinical facility, allowing for clinical intervention if needed. The risks associated with the study are immediate; that is, it is considered highly unlikely that an AE will take place after the completion of a study visit.

If any participants discontinue or withdraw early, for any reason including AEs, the reason will be captured.

10. RISK/BENEFIT ASSESSMENT

10.1. Known potential risks

- There may be discomfort related to insertion and continued placement of the esophageal cannula. This could include a nose bleed, gagging, and/or vomiting.
- Dizziness, lightheadedness, a feeling of nausea, or fainting may occur during the fasting period.
- Dizziness/lightheadedness may occur during the data collection period, particularly during the different breathing conditions.
- The only anticipated AE related to the DreamKit device is skin irritation associated with the adhesive patch.
- There are no anticipated AEs related to the breathing devices (Philips IMT and Philips Threshold PEP), beyond the possible dizziness/lightheadedness described above.
- There are no anticipated AEs related to the Mexameter skin probe.

10.2. Known potential benefits

Participation in this trial will not result in direct benefit to the participant. The information collected from participants will be used to improve product design and function.

10.3. Assessment of Potential Risks and Benefits

- Participants reporting a sensitive gag reflex or dyspnea will not be recruited.
- If a participant experiences any adverse event related to fasting, they may discontinue the protocol and will be provided with food/juice.

- If a participant experiences any discomfort related to dizziness or lightheadedness, they may return to relaxed breathing or discontinue the protocol at any time.
- Participants reporting a history of allergic reactions to medical adhesives will not be recruited.

It is the opinion of the Sponsor and the Principal Investigator (PI) that the benefits of this protocol outweigh the risks.

11. SAFETY MONITORING

11.1. Adverse Events and Serious Adverse Events

11.1.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). When an AE is deemed to be related to the study device, it is termed an adverse device event.

11.1.2. Definition of Serious Adverse Events

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. When a serious AE is deemed to be related to the study device, it is termed a serious adverse device event (SADE).

11.2. Unanticipated Adverse Device Event

An unanticipated adverse device event (UADE) is defined in 21 CFR Part 812.3(s) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects".

Other important medical events which may not result in any of the outcomes above, but which may require intervention to prevent one of the outcomes above, may in the opinion of the investigator, be considered a UADE.

11.3. Classification of an Adverse Event or Adverse Device Event

11.3.1. Severity of Event

All AEs will be assessed by the study clinician using a protocol defined grading system as follows:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

11.3.2. Relationship to the Study or Device

All AEs will have their relationship to study procedures and the study device assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.
- Probably Related – An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- Possibly Related – An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- Unrelated – An AE is unrelated if the cause is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the IRB as indicated. Often, the cause of an unrelated AE is disease progression.

11.3.3. Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

11.4. Adverse Event Assessment and Follow-Up

Within 1-2 days of completing Visit 2, a phone call will allow for the assessment of any possible AEs that may have become apparent in the intervening period. Events will be followed for outcome information until resolution or stabilization

All AEs including local and systemic reactions will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

11.5. Serious Adverse Event or Serious Adverse Device Event Reporting

The study investigator shall complete a SAE or UADE Form and submit to the Sponsor and to the reviewing IRB as soon as possible, but in no event later than 24 hours (for a SAE) or 10 working days (for an UADE) after the investigator first learns of the effect. The Sponsor is responsible for conducting an evaluation of the SAE/UADE and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 24 hours (for a SAE) or 10 working days (for a UADE) after the Sponsor first receives notice of the effect. Thereafter, the Sponsor shall submit such additional reports concerning the effect as FDA requests.

11.6. Device Deficiency

All device deficiencies, use or user errors, and equipment failures will be documented. Use or user errors will be captured as part of the source documentation. Device deficiencies and equipment failures will be kept on a separate log. The serial numbers and type of deficiency/failure will be captured. Unanticipated device deficiencies that lead or may lead to an SAE will be reported to the Sponsor within 24 hours of learning of the event.

11.7. Unanticipated Problems

11.7.1. Definition of Unanticipated Problems

An unanticipated problem (UP) is any incident, experience, or outcome that for which the nature, severity, or frequency is unexpected for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the ICF.

11.7.2. Unanticipated Problem Reporting

The PI will submit to the Sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). Under 812.46(b), the Sponsor shall report the results of such evaluation to the FDA and to all reviewing IRB's and participating investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

12. STATISTICAL CONSIDERATIONS

The statistical analysis plan has been incorporated into this protocol. It is not a stand-alone document.

12.1. Sample Size Determination

Up to 20 participants will be enrolled. The evaluable dataset will consist of data from ten participants.

12.2. Statistical Analyses

12.2.1. General Considerations

The primary and secondary analyses will be performed in the validation dataset only. Descriptive data tables will be provided for all variables of interest. Continuous data will be presented by mean, standard deviation, median, minimum, and maximum observation. Data will be presented in the untransformed and transformed format (if applicable) for each continuous variable. Categorical data will be presented as frequencies and percentages. If formal statistical analysis is required, it will be performed using either SAS® or SPSS® software. Significance tests will be conducted at a two-sided significance level of alpha=0.05.

There are no statistical criteria for terminating the study. No sensitivity analyses are planned, and any deviations from the original statistical plan will be noted in the analysis report.

12.2.2. Participant Disposition

Participant disposition, including the total number of participants enrolled, completed, early terminations and withdrawals, will be presented. A listing will be provided with the reasons for discontinuation.

12.2.3. Demographics and Baseline Characteristics

Participant demographics and baseline characteristics will be summarized for all participants enrolled and for evaluable participants.

12.2.4. Analysis of the Primary Efficacy Endpoint

The primary endpoint is the ICC of the peak-to-peak breath amplitude sequences extracted from the DreamKit and esophageal manometry respiratory effort signals among periods of occluded inspiration, end-expiratory breath holds, increased inspiratory resistance, increased expiratory resistance, and unresisted shallow breathing. We hypothesize that the lower-bound of the 95% confidence interval for the correlation of breath amplitude sequences extracted from the DreamKit and esophageal manometry respiratory effort signals will be ≥0.5.

Among the periods of occluded inspiration, end-expiratory breath holds, increased inspiratory resistance, increased expiratory resistance breathing and unresisted shallow breathing conditions, the peak-to-peak amplitude in the respiratory excursions will be extracted from the esophageal pressure signal and the DreamKit device signal. A correlation coefficient will be generated in order to compare the breath amplitude sequences from the two signals among these data collection periods. First, amplitudes of the DreamKit device signal will be scaled to have the same variance as the amplitudes calculated from the esophageal pressure signal. After this normalization step, amplitudes will be aggregated among all participants, and ICC estimates and their 95% confidence intervals will be calculated based on single measurements, absolute agreement and a 2-way mixed-effects model.[5]

12.2.5. Exploratory Analyses

The methodology described above for the primary analysis will be repeated using data from each participant individually.

Within the occluded inspiration and end-expiratory breath holds (representing obstructive and central apneas, respectively), we will categorize each signal as being above or below a threshold. Each period will be identified as a true positive for obstructive apnea (esophageal manometry scored as occluded inspiration and DreamKit signal above the threshold), true negative (esophageal manometry scored as breath-hold and DreamKit signal below the threshold), false positive (esophageal manometry signal scored as breath hold but DreamKit signal above the threshold), or false negative (esophageal manometry signal scored as occluded inspiration but DreamKit signal below the threshold). This will allow us to calculate the sensitivity, specificity, and area under the ROC curve for the ability of the DreamKit signal to identify obstructive apnea events. The threshold for calculating sensitivity and specificity will be 10% of the baseline amplitude derived from normal (relaxed) breathing. This threshold corresponds to a proportional change in respiratory effort for an apneic event that requires a 90% reduction of flow amplitudes as compared to the baseline respiration.

Within the increased inspiratory/expiratory resistance and shallow breathing periods (representing obstructive and central hypopneas), we will calculate the area under the ROC curve which will provide an aggregate assessment of agreement between the two respiratory effort signals across all possible thresholds. Unlike apneas, the classification of hypopneas as obstructive or central is not based on the presence or absence of respiratory effort (AASM scoring criteria; Version 2.6), and therefore we will not categorize each breathing period on the basis of a respiratory effort threshold.

The respiratory rate will be extracted from each breathing condition except breath holds, and we will provide a Bland-Altman analysis of respiratory rate between the esophageal pressure signal and the DreamKit device.

Finally, to evaluate the phase relationship between the esophageal pressure and DreamKit signals, the peaks in the cross-correlation function will be used to estimate the average phase shift between the two effort signals. All manually scored epochs of relaxed breathing, slow breathing, fast breathing, occluded inspiration, increased inspiratory resistance, increased expiratory resistance, and unresisted shallow breathing will be used for this analysis.

12.3. Safety Analyses

Safety evaluations will be performed by recording clinical AEs at the time originally reported, and they will be followed at regular intervals until resolution. AEs will be provided in data listings.

12.4. Planned Interim Analyses

There are no planned interim analyses.

12.5. Missing Unused and Spurious Data

Imputations methods will not be employed in this study.

12.6. Deviations from the Statistical Analysis Plan

Any deviations from the original statistical plan will be noted in the analysis report.

13. OPERATIONAL CONSIDERATIONS

13.1. Regulatory and Ethical Considerations

13.1.1. Informed Consent Process

Participants will be asked to complete the consent form prior to any study procedures, including screening for eligibility.

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

Study participation is voluntary. Potential subjects, and/or their legal representatives, will be given the most current IRB-approved consent form to read. They shall be provided ample time for review and an opportunity to ask questions about the study. If they agree to participate, they shall sign the consent form and be given a copy of the signed document for their records. Each of these actions/steps will be documented. Only after informed consent has been obtained, may the remaining study procedures begin.

13.1.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to review the written consent form carefully and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.1.3. Study Discontinuation and Closure

Although there are no pre-determined criteria for study closure, the study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and Sponsor, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Insufficient compliance to protocol requirements;

- Data that are not sufficiently complete and/or evaluable.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and/or FDA.

13.1.4. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Each study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

Study participant research data for statistical analysis and scientific reporting will be transmitted to and stored by the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Sponsor.

13.2. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Sponsor, where it may be used for future research. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to data storage may not be possible after the study is completed.

13.3. Safety Oversight

Safety oversight is the responsibility of the PI. It has been determined that a Safety Monitoring Committee, Data and Safety Monitoring Board, Safety Assessment Committee and/or an Independent Safety Monitor is not required for this study.

13.4. Clinical Monitoring

This study will be monitored using a risk-based monitoring approach. It will ensure that documents used to originally record subject data (source documents) are maintained, and to verify that transcribed data are accurately reflected on the study CRFs. All study documentation must be made available for review by the Sponsor or its designees as well as regulatory agencies.

13.5. Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

13.5.1. Data Handling and Record Keeping

The site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants.

13.5.2. Data Collection and Management Responsibilities

Data collection is the responsibility of the staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.6. Study Records Retention

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

13.7. Protocol Deviations

Any and all deviations from the protocol shall be documented upon discovery and reported in the subject's (e)CRFs. Significant deviations shall be reported immediately to the Sponsor.

13.8. Publication and Data Sharing Policy

The results of this clinical study may be submitted for publication. The rights for publication of results from this study remain with Philips. The Investigator must request permission from Philips prior to initiating any publication. Permission must be requested and received in writing. Review and approval of any data, abstract or manuscript is required. Philips reserves the right to delay publication to review the presentation of study methodology, data collection, data analysis, interpretation of data, proprietary information or patented technology. A request for delay and the reason(s) shall be communicated by Philips to the Investigator in writing. Philips ultimately reserves the right to deny any request to publish.

The study does not meet the definition of an Applicable Clinical Trial per the FDA; however, we will voluntarily register the trial on ClinicalTrials.gov.

13.9. Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest (apart from that related to Philips) of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

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15. INVESTIGATOR'S STATEMENT

I agree to conduct the trial as outlined in the protocol in accordance with the Sponsor's guidelines, Good Clinical Practices, the Declaration of Helsinki, and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB. The Sponsor's guidelines include, but are not limited to:

- Provide Philips with current curriculum vitae including a statement regarding relevant experience.
- Provide accurate financial disclosure information to allow Philips to make an accurate disclosure statement as required under 21 CFR, Part 54 for the course of the investigation and for up to one year after its completion
- Provide supervision of all testing of the device involving human subjects.
- If applicable, provide Philips with information regarding past investigations or other research that was terminated, including an explanation of the circumstances that led to the termination.
- Permission to allow Philips and/or regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality. If this study is to be inspected by a regulatory agency, Philips is to be notified as soon as possible.
- Submission of the proposed clinical investigation including the protocol and the consent form to an IRB for approval and the acquisition of written approval for each subject ensuring that the requirements for obtaining informed consent are obtained prior to the use of any test articles.
- Submission of any proposed change in or significant deviation from the protocol to the IRB using a signed formal amendment document prepared by the Sponsor. Any proposed changes or deviations from the protocol require that the informed consent also reflects such changes or deviations and that the revised informed consent be approved by an IRB.
- Documentation and explanation of individual protocol deviations and violations are captured with explanations as indicated.
- Submission of reports of AEs to the Sponsor and IRB as outlined in the protocol.
- Submission of timely progress reports to the IRB and Sponsor at appropriate intervals on a schedule determined by the IRB or Sponsor, as indicated.
- Record keeping: the Investigator shall maintain adequate and accurate records designed to record completion of all study procedures, related observations and other key data (such as safety, compliance and product accountability) pertinent to the investigation on each subject enrolled. The investigator must maintain these records for a period as specified by Philips following completion of the study report.

I agree that all information provided to me by the Sponsor including pre-clinical data, protocols, electronic databases, CRFs, and verbal and written information shall be kept strictly confidential and confined to the clinical personnel involved in conduct of the trial. It is recognized that this information may be related in confidence to the IRB. I also understand that reports or information about the trial or its progress shall not be provided to anyone not involved in the trial other than the Sponsor or other legally constituted authority.

ALAN SCHWARTZ MD

Alan Schwartz MD

Principal Investigator Signature and Printed Name

6/27/22

Date

LATE ENTRY