BRIEF TITLE: *Belun Ring Validation Study for Assessment of Obstructive Sleep Apnea*

NCT#: NCT03997916

PROTOCOL TITLE:

A validation investigation of the accuracy of the Belun Ring, an innovative single-channel four-signal pulse oximetry, in patients referred to sleep lab for assessment of obstructive sleep apnea (OSA).

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OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE): N/A

VERSION NUMBER:

Version 1.1.

DATE:

7/16/2019

Indicate the origin of this protocol (who conceived of and leads the development of the protocol regardless of funding):

☒ Investigator initiated *(Investigator(s) developed protocol, regardless of funding)*
☐ Industry *(Pharmaceutical, Device, etc.) (Industry developed protocol)*
☐ Federal *(NIH, DOD, etc.)*
☐ Cooperative Group *(SWOG, GOG, etc.)*
☐ Other - *Please specify:*

Funding

Please list the funder of this project. If there is not a funder, please note that your department pays for your time and resources and should be listed here.
Belun Technology Company will give some limited funds for this study around US$15,000. Also, all the Belun Ring devices of different ring sizes and the three HIPAA-compliant laptops will be provided by the Belun Technology Company for free. UH will not be purchasing the Belun Ring devices nor the three HIPAA-compliant laptops for data collection and storage.

Objectives

Aim: To determine the overall accuracy, sensitivity, and specificity of the Belun Ring in evaluating obstructive sleep apnea (OSA) by comparing the device to the attended overnight in-lab polysomnography (PSG) as gold standard

Hypothesis: Belun-Ring, a type 4 portable monitoring device, is overall sensitive and specific for evaluation of obstructive sleep apnea (OSA) when compared to the attended overnight in-lab polysomnography (PSG).

Background

Obstructive Sleep Apnea (OSA) is a disorder characterized by recurrent collapse of the upper airway during sleep. It is estimated that obstructive sleep apnea (OSA) affects 5% of women and 14% of men in the US general population. Severe obstructive sleep apnea (OSA) is associated with significant cardiovascular and cerebrovascular morbidity and mortality.

Currently, attended overnight in-lab polysomnography (PSG) is the gold standard for diagnosing obstructive sleep apnea (OSA). However, polysomnography (PSG) needs to be conducted in a sleep laboratory and scored and analyzed by experienced sleep technologists which can be very expensive, labor-intensive, and time-consuming. Due to high prevalence of obstructive sleep apnea (OSA), there is a significant cost associated with evaluating all patients suspected of having obstructive sleep apnea (OSA) with polysomnography (PSG). Furthermore, there is limited access to attended overnight in-lab polysomnography (PSG) testing in some areas. Type 3 home sleep apnea test (HSAT), though with limitations, is a commonly used alternative method to diagnose obstructive sleep apnea (OSA) in adults based on 2017 guidelines of the American Academy of Sleep Medicine (AASM). Therefore, it is of interest to explore potential alternative testing methods that can reliably determine the apnea-hypopnea index (AHI) with other surrogate markers at a lower cost.

Among the different approaches, obstructive sleep apnea (OSA) evaluation by oxygen saturation (SpO2) and heart rate variation (HRV) may be a promising solution. Sleep apneas and hypopneas are usually associated with a drop of oxygen saturation (SpO2) followed by a rise of oxygen saturation (SpO2) which, in turn, affects the sympathetic and vagal balance resulting in heart rate variability (HRV). Therefore, sleep apnea events may be monitored by analyzing parameters derived from oxygen saturation (SpO2) and heart rate variability (HRV). Indeed, clinical research efforts using oximetry have been attempted over the past few years for evaluation of obstructive sleep apnea (OSA).

Heneghan in 2008 reported the development of an automated algorithm for obstructive sleep apnea (OSA) detection using electrocardiogram (EKG) and oximetry measurements. The

algorithm provides epoch-by-epoch estimates of apnea occurrence and estimates of overall per-subject apnea-hypopnea index (AHI). Using separate thresholds of apnea-hypopnea index (AHI) > or =15 and apnea-hypopnea index (AHI)<5 for defining clinically significant and insignificant sleep apnea, sensitivity, specificity, and likelihood ratios, conditional on positive or negative (but not indeterminate) test results were used to assess agreement between the proposed system and polysomnography (PSG). Sensitivity of 95.8% and specificity of 100% was achieved. Positive and negative likelihood ratios were >20 and 0.04 respectively, with 16.7% of subjects having intermediate test results (AHI 5-14). Regardless of apnea-hypopnea index (AHI), 85.3% of respiratory events were correctly annotated on an epoch-by-epoch basis. Apnea-hypopnea index (AHI) underestimation bias was 0.9/h, and the antilogs of log-transformed limits of agreement were 0.3 and 2.7. Correlation between estimated and reference apnea-hypopnea index (AHI) was 0.95 (P <0.001). It was concluded that a combined Holter-oximeter monitoring compares well with polysomnography (PSG) for identifying obstructive sleep apnea (OSA) in an attended setting and is potentially suitable for home-based automated assessment of obstructive sleep apnea (OSA) in a population suspected of having obstructive sleep apnea (OSA).

In 2012, Poupard reported the development of a new oximetry mathematical analysis, which quantifies amplitude variations of oxygen saturation (SpO2) and heart rate (HR) throughout the night, allowing measurement of the total time in which ΔSpO2 >4% and presented as a new oximetric index named as ventilatory hypoxemic index (VHI). In 106 patients suspected of having obstructive sleep apnea (OSA), ventilatory hypoxemic index (VHI) was compared prospectively with the standard parameters in polysomnography (PSG) such as apnea-hypopnea index (AHI) and oxygen desaturation index (ODI). The criterion for diagnosis of obstructive sleep apnea (OSA) was apnea-hypopnea index (AHI) >15 of sleep during polysomnography (PSG). They observed a significant correlation between the apnea-hypopnea index (AHI) and ventilator hypoxemic index (VHI) ($R = 0.87$, $p < 0.0001$). Using ventilator hypoxemic index (VHI) >15 as the criterion for oxygen saturation (SpO2), oximetry had a sensitivity of 81%, specificity of 98%, positive predictive value (PPV) of 98%, and negative predictive value (NPV) of 84%. Poupard concluded that wavelet-aggregate processing of oximeter data and the relationship between change in oxygen saturation (ΔSpO2) and change in heart rate (ΔHR) show promise as a useful prediction of screening obstructive sleep apnea (OSA).

More recently in 2014, Romem evaluated the reliability and accuracy of Morpheus Ox, a single-channel finger pulse-oximetry photoplethysmography (PPG)-based device, for detection of obstructive sleep apnea (OSA). Among a cohort of 73 patients referred for in-lab evaluation of obstructive sleep apnea (OSA), 65 patients were simultaneously monitored with the photoplethysmography (PPG)-based device while undergoing polysomnography (PSG). Of note, 19 patients had significant cardiopulmonary comorbidities. Using the polysomnography (PSG) as the gold standard, the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), as well as the positive likelihood ratio (+LR) for an apnea hypopnea index (AHI) > 5/h and apnea-hypopnea index (AHI) > 15/h were calculated for the photoplethysmography (PPG). Valid results were available for 65 subjects. Mean age: 52.1 ± 14.2, Male: 52%, and BMI: 36.3 ± 9.7. Positive correlation was found between photoplethysmography (PPG)-derived and polysomnography (PSG)-derived apnea-hypopnea index (AHI) ($r = 0.81$, $p < 0.001$). Compared to apnea-hypopnea index (AHI) > 5/h derived from polysomnography (PSG), the photoplethysmography (PPG)-derived apnea-hypopnea index (AHI) has a sensitivity of 80%, specificity of 86%, positive predictive value (PPV)

of 93%, negative predictive value (NPV) of 68%, and positive likelihood ratio (+LR) of 5.9. Compared to apnea-hypopnea index (AHI) > 15/h derived from polysomnography (PSG), the photoplethysmography (PPG)-derived apnea-hypopnea index (AHI) has a sensitivity of 70%, specificity of 91%, positive predictive value (PPV) of 80%, negative predictive value (*NPV) of 85%, and positive likelihood ratio (+LR) of 7.83. The corresponding areas under the receiver operator curves were 0.91 and 0.9. It was concluded that photoplethysmography (PPG)-derived data compare well with simultaneous in-lab PSG in the diagnosis of suspected obstructive sleep apnea (OSA) among patients with and without cardiopulmonary comorbidities.*

In the 2018 Journal of Clinical Sleep Med October issue, Massie reported the development of a home sleep apnea testing (HSAT) system named NightOwl which consists of a fingertip sensor and a cloud-based analytics software. The sensor acquires accelerometer and photoplethysmography (PPG) data. The software derives actigraphy from the former, and oxygen saturation (SpO2) and peripheral arterial tone among other features from the latter. Data of 101 participants who underwent the attended overnight in-lab polysomnography (PSG) while wearing the NightOwl sensor were collected. In order to establish an external benchmark, all polysomnography (PSG) tests were edited by a somnologist of Younes Medical Technologies Ltd. (YMT) after analysis by the Michele Sleep Scoring System (MSSS). Respiratory event index (REI) derived by NightOwl (NightOwl-REI), the apnea-hypopnea index (AHI) derived by Ziekenhuis Oost-Limburg (ZOL-AHI), and the apnea-hypopnea index (AHI) derived by YMT (MSSS-AHI) were compared. The NightOwl respiratory event index (NightOwl-REI) had a high correlation with the Michele Sleep Scoring System Apnea-Hypopnea Index (MSSS-AHI) ($\rho = 0.87$, $P < 0.001$), which was close to the correlation between the Ziekenhuis Oost-Limburg apnea-hypopnea index (ZOL-AHI) and Michele Sleep Scoring System Apnea-Hypopnea Index (MSSS-AHI) ($\rho = 0.84$, $P < 0.001$). The NightOwl respiratory event index (NightOwl-REI) and Ziekenhuis Oost-Limburg apnea-hypopnea index (ZOL-AHI) had a correlation of 0.77 ($P < 0.001$). After categorization of the apnea-hypopnea index (AHI), the agreement between the NightOwl respiratory event index (NightOwl-REI) and the Michele Sleep Scoring System Apnea-Hypopnea Index (MSSS-AHI) was 0.812 and the agreement between the Ziekenhuis Oost-Limburg apnea-hypopnea index (ZOL-AHI) and Michele Sleep Scoring System Apnea-Hypopnea Index (MSSS-AHI) was 0.743, after double-labeling near-boundary participants. Massie et al concluded that the NightOwl respiratory event index (NightOwl-REI) achieved a close correlation and REI-categorization with the Michele Sleep Scoring System Apnea-Hypopnea Index (MSSS-AHI), especially in light of the significant inter-scorer variability of the analysis of the polysomnography (PSG).

Belun Ring is an FDA-approved (5/29/2019), unique, one-channel, four-signal pulse oximetry device which has the capability of monitoring and analyzing oxygen saturation (SpO2), heart rate variability (HRV), photoplethysmography (PPG) wave form, and accelerometer-derived actigraphy data. An analysis algorithm has been developed using dataset of 5,783 subjects and 8,417 records of overnight sleep over the years. This easy-to-use device not only can calculate an estimated respiratory event index (REI) based on the data acquired, it can also differentiate wakefulness from sleep and perform sleep stage analysis and give REM sleep duration and NREM sleep duration. Furthermore, autonomic nervous system (ANS) activities including sympathetic nervous system activity (SNA) and parasympathetic nervous system activity (PSA) may be measured throughout the monitoring period. Belun Ring measures all these parameters from the proximal phalanx of the index finger of the non-dominant hand. The clip design of the Belun Ring

specifically aimed to minimize sensor motion artifacts and sleep interference of the testing individuals.

Belun Technology Company has conducted two studies in 2017-2018 and has published an abstract of their preliminary findings from Hong Kong at the 2018 APSS meeting. This validation study was conducted in Prince of Wales Hospital in Hong Kong using the original version of the Belun Ring which had no capability of detecting total sleep time (TST). This study excluded patients with a history of congestive heart failure (CHF), stroke, chronic obstructive pulmonary disease (COPD), neuromuscular disorder, or hypoventilation well as those on beta-blockers and calcium blockers. In-lab polysomnography (PSG) signals were recorded simultaneously with device under test and the reference apnea-hypopnea index (AHI) values were manually scored by certified sleep technician according to the American Academy of Sleep Medicine (AASM) Manual for the scoring of Sleep and Associated Events version 2.3. A total of 23 Chinese subjects (17 males, 6 females; 53.2 ± 11.8 years old) were enrolled in the validation and each subject contributed one record of overnight measurement. The time of sleep period was 352.1 ± 47.5 minutes and the distribution of the reference apnea-hypopnea index (AHI) was from 4.1 to 98.3 (38.5 ± 28.3)/hour. The correlation between reference apnea-hypopnea index (AHI) and Sleep Score is r = 0.977 (P<0.001). It was concluded that the overall sensitivity and specificity for the classification of severity of obstructive sleep apnea (OSA) are good, especially in moderate and severe groups. In the subsequent Colorado study (unpublished data), a newer version of Belun Ring with the capability of measuring total sleep time (TST) was used. The correlation between reference PSG-AHI and Belun Ring REI is r = 0.865 using an AHI cutoff of 15 and the overall accuracy was 84.4% with a sensitivity of 80% and a specificity of 88%. The Belun Ring-estimated total sleep time (TST) correlates well with the polysomnography (PSG)-derived total sleep time (TST) with an r = 0.950. In this study, the new version Belun Ring pulse oximeter will be used for evaluation which will be compared with the standard attended in-lab PSG in order to determine the accuracy, sensitivity, and specificity of Belun Ring as an outpatient evaluation for obstructive sleep apnea (OSA).

Inclusion and Exclusion Criteria

	Inclusion Criteria
1.	*All adult patients age 18-80 years old scheduled for overnight in-lab sleep study*
2.	*Provision of signed and dated informed consent form*

	Exclusion Criteria
1.	*Recent hospitalization in the past 30 days*
2.	*Patients on home oxygen, non-invasive ventilator, diaphragmatic pacing, or any form of nerve stimulator*
3.	*Patients with pacemaker, defibrillator, left ventricular assist device (LVAD), or status post cardiac transplantation*
4.	*Patients with baseline heart rate under 50 bpm or over 100 bpm during last clinic visit or prior to study at the sleep lab*
5.	*Patients with unstable cardiopulmonary status judged to be unsafe for sleep study by the sleep tech and/or the on-call sleep physician in the sleep lab on the night of the study*

6.	*Patients who are unable to complete the required study*
7.	*Patients involved in another investigational study*
8.	*Pregnant women*

Number of Research Participants

We will enroll at least 80 subjects in two UH sleep laboratories.

Vulnerable Populations

1. Indicate specifically if you will include each of the following special populations by checking the appropriate box:
   - ☐ **Adults unable to consent**
   - ☐ **Minors (infants, children, teenagers)**
     - ☐ Wards of the state
     - ☐ Foster Children
   - ☐ **Pregnant Women**
   - ☐ **Neonates**
   - ☐ **Neonates of Uncertain Viability**
   - ☒ **Employees of CWRU or UHHS**
   - ☐ **Prisoners**
   - ☒ **Illiterate Individuals**
   - ☒ **Non-English Speaking**
   - ☒ **University Students**
   - ☐ **None**

2. If excluding pregnant women, illiterate or non-English speaking individuals, provide a scientific rationale for the exclusion. Inconvenience or cost is not an acceptable rationale.
   There is unknown risks and benefits of the device to the growing fetus; hence pregnant women are excluded in this study.

3. If the research involves individuals that are included in a vulnerable population, describe the additional safeguards included to protect the rights and welfare of the individuals for each population indicated.
   The illiterate individuals are not excluded as long as they make a mark or able to sign their name in the written informed consent form. Also, the written informed consent form will be read to them verbatim before they give their consent.
   If a Non-English-speaking patient appears to be eligible and would like to participate, a protocol amendment will be submitted to the IRB at that time with the appropriate translated forms. If a patient that speaks another language appears to be eligible for the study and would like to participate, resources will be discussed with the study PI at that time to determine whether appropriate resources exist to accommodate the patient's enrollment.
   Employees of CWRU or UHHS as well as university students will be de-identified during the study.

Recruitment Methods

Note: Attach all applicable recruitment materials to the last section of the Smart form under "Recruitment Materials."

1. Which of the following methods will be used to recruit research participants. – *Select all that apply*
   - ☒ Email
   - ☒ Phone call
   - ☐ Letter
   - ☐ Advertisement (e.g., poster, flyer, etc.)
   - ☐ Social media
   - ☐ Other. *Please specify:*

2. Describe when, where, and how potential research participants will be recruited.
   Non-sleep providers and sleep providers in UH will order polysomnography as they see patients in their respective clinics. Our schedulers in UH Bolwell Building will call and schedule these patients for the standard, overnight, attended, in-lab sleep study, also known as polysomnography. Subsequently and routinely, the schedulers will e-mail a packet of general information to these patients and add the email recruitment form for the Belun Ring Study. On the email recruitment form itself, there is a phone number and email address for patients to call or e-mail if they are interested or if they decide to opt out. If the research team did not hear anything from the patient after 14 days of emailing the recruitment form, the study coordinators will look up the names of the patients in Enterprise software and make follow-up calls on the patients to ask them if they are interested in participating in the research. Prior making follow-up calls, the study coordinators will do a simple chart review using UH Ambulatory Care EMR to screen patients for eligibility and collect demographics data. If a certain patient is found to be eligible, the study coordinators will call that patient using the phone recruitment script and discuss the Belun Ring Study in detail. The study coordinators will also use this phone interview as a time to answer patient's questions and verify patient's eligibility, in case there are unclear information noted during chart review. If patient is eligible and agreed to participate in the research during the phone interview, the patient's name and related personal information will be placed in the linking sheet and a unique identifier will be assigned to that patient.

3. Describe the source (e.g., from what department, EMR, etc.) of the research participants.
   Enterprise software of the UH Sleep Laboratory is the master schedule where we can see the list of patients scheduled for overnight attended in-laboratory sleep study, also known as polysomnography in the 2 sleep laboratories of University Hospitals namely in Bolwell and Beachwood locations.

4. Describe the methods that will be used to **identify** potential research participants.
   Chart review of the patients listed from the Sleep Lab master schedule will also be done to identify which patient meets eligibility criteria. We will use UH Ambulatory Care for the EMR to do chart review.

5. Describe the feasibility of recruiting the required number of suitable research participants within the agreed recruitment period. For example, how many potential research participants do you have access to?
   There are total of 10 beds if we combine the two UH sleep laboratories. Both sleep laboratories operate 7 nights per week except on major federal holidays. One-third of the beds are for pediatric patients and two-thirds are for adult patients. Out of 10 beds, there will be 6 beds reserved for adult patients every night. Considering the possibility of no-show or some patients meeting the exclusion criteria, we are looking into potentially 2-3 research participants per night.

Setting

The sites and locations where the research team will conduct the research is the same as the physical location where research procedures will be performed and they are as follows:

1. *Department of Pulmonary, Critical Care, and Sleep Medicine at 11100 Euclid Avenue, Bolwell-6th floor, Cleveland, OH 44106*
2. *Residence Inn Marriott at 26300 Harvard Road, 4th floor, Beachwood, OH 44122*

However, the main location where the research team will identify and recruit potential research participants will be in Department of Pulmonary, Critical Care, and Sleep Medicine at 11100 Euclid Avenue, Bolwell-6th floor, Cleveland, OH 44106

Consent Process

1. Indicate whether you will be obtaining consent:

☒ Yes ☐ No

If yes, answer the following questions:

1. Describe where the consent process will take place:
   a. *Department of Pulmonary, Critical Care, and Sleep Medicine at 11100 Euclid Avenue, Bolwell-6th floor, Cleveland, OH 44106*
   b. *Residence Inn Marriott at 26300 Harvard Road, 4th floor, Beachwood, OH 44122*

2. The time that will be devoted to the consent discussion:
   15-30 minutes

3. Any waiting period available between informing the prospective subject and obtaining the consent:
   From the time we e-mailed the recruitment form, we will wait 14 days before doing simple chart review and making follow-up calls to prospective subjects. If patients verbalized interest during the phone call interview, they will not sign the written informed consent until the night of their scheduled polysomnography; hence, waiting period from informing prospective subject to obtaining written consent is variable but will most likely be more than 14 days.

4. Steps that will be taken to ensure the research participants' understanding:

Patients can call any study team member and ask questions anytime from the time they have received the e-mail recruitment form to the time they were called by the study coordinators and until the night of their scheduled polysomnography. Study coordinators and sleep technicians will ask patients every now and then if they have any questions. To confirm patients' understanding, we will use teach-back method.

5. Any process to ensure ongoing consent:
No need because the research study does not require follow-up visits. Obtaining written informed consent will be done on the same night patients will get their scheduled polysomnography.

6. The role of the individuals listed in the application as being involved in the consent process:
We will have Sleep technicians who are CITI-trained/ CREC-certified help us in obtaining the written informed consent on the night of the scheduled polysomnography.

7. Steps that will be taken to minimize the possibility of coercion or undue influence to the subjects:
On the night of the patient's scheduled polysomnography, patient will receive the written informed consent form in the Sleep Laboratory. Our CITI-trained/ CREC-certified sleep technicians will discuss the written informed consent form in detail before asking patient to sign it prior the start of the scheduled sleep study. Patient will also receive a photocopy of the signed written informed consent before leaving the Sleep laboratory the following day.

8. Indicate if you will be asking for a waiver or alteration of consent process or documentation (consent will not be obtained, written consent will not be documented)

☒ Yes ☐ No

If yes, indicate which part of the consent process you are requesting to be waiver or altered and the rationale for requesting the waiver or alteration.

☐ I will obtain consent, but not participant's signature
☒ I will obtain consent, but request a waiver for pre-screening purposes
☐ I will obtain consent, but request a waiver of some of the elements of consent (e.g. use of deception)
☐ I will not obtain consent and I am requesting a full waiver of consent

1. Give the rationale for the request of a waiver or alteration of the consent process or documentation:
Once the sleep lab schedulers had emailed the recruitment form, the study team will perform chart review in order to evaluate eligibility criteria of potential subjects and then call subjects using the phone recruitment script. Subjects will only be called after

sufficient time has passed for them to receive and review the email recruitment form which is about 14 days after recruitment forms were e-mailed out.

2. Explain how the research involves no more than minimal risk
There will be no blood tests, radiation exposure, nor surgical/invasive interventions involved.

3. Explain why the waiver or alteration of consent will not adversely affect the rights and welfare of the participants:
Chart review will be performed only within the premises of University Hospitals (UH) Cleveland Medical Center (CMC) where computers are encrypted and protected with firewall and antivirus.

4. Explain why the research could not practicably be carried out without the waiver or alteration of consent.
Chart review is a crucial step in this research study because it is needed for data collection and recruitment of eligible subjects; hence, this research study could not practicably be carried out without the waiver or alteration of consent.

5. If you will obtain consent, but not document consent in writing (e.g. over the phone, verbally, electronic survey, etc.), please describe and provide a rationale.
☒ N/A

6. Describe how you will be documenting that a research participant has consented:
On the night of the sleep study, patients will receive the written informed consent which they will only sign after the CREC-certified sleep technician had explained the study and the consent form in detail. Also, patients have to sign the consent in front of the CREC certified sleep technician who, in turn, will be signing as the witness on the consent form. At the end of the sleep study, patient will be given a copy of the signed written informed consent and another copy goes to the EMR.

**Be sure to upload a consent script or information sheet with your study protocol*

Additional Considerations for Consent Process with Adults
Non-English Speakers *(Please select one)*

☐ I am **not** enrolling non-English speaking individuals in this research study. The following is justification for why non-English speaking individuals cannot be enrolled:

☐ I will be targeting non-English speaking adults
3. Describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study.

4. List the language(s) other than English that will be targeted:

☒ I am **not** targeting non-English speaking individuals. If a non-English speaking individual is eligible for the trial, we will use the following procedures to enroll:

1. Describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study.
   Interpreters will be called on the actual night of the sleep study to help with translation of the English version of the written informed consent.

2. List the language(s) other than English that will be targeted: *Mandarin, Spanish*

Adults Unable to Consent

☒ I am **not** enrolling adults unable to consent in this research study – *please leave the rest of this section blank.*

☐ There is an anticipated direct benefit to the subject. Explain:

☐ There is NOT an anticipated direct benefit to the subject. Explain:

c. Describe the process to determine whether an individual is capable of consent.

d. List the individuals from whom permission will be obtained in order of priority (e.g. durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child).

e. For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in the research.

☐ N/A

f. Describe the process for assent of the research participants. Indicate:

1. Which subjects that are unable to consent will be required to give assent? If not all, explain why.
2. Describe whether assent of the research participants will be documented and the process to document assent.

☐ The subject will be informed about the research to the extent compatible with the subject's understanding.

☐ Subjects will be closely monitored.

☐ The subject will be withdrawn if they appear unduly distressed.

Research Participants Who Are Not Yet Adults (infants, children, teenagers)

☒ I am not enrolling participants who are not yet adults in this research study. – *please leave the rest of this section blank*

1. Will parental permission be obtained from:

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child

☐ Waiver of parental permission

2. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's participation in research.
3. Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.
4. When assent of children is obtained, describe how it will be documented.
5. For children who are pregnant, describe how assent and permission are obtained.
   ☐ N/A
6. Describe how the risk is justified by the anticipated benefit to the subjects.
7. Describe how the anticipated risk-to-benefit ratio is at least as favorable to the subjects as that presented by currently available alternative approaches.

Sharing of Results with Research Participants

☒ Results will **not** be shared with research participants
☒ Results will **not** be shared with research participants' doctors

Study Design

This prospective, single-blind, non-randomized, single-visit study will recruit at least 80 patients who are suspected to have obstructive sleep apnea (OSA) and are scheduled to undergo polysomnography (PSG) in a sleep laboratory for evaluation of obstructive sleep apnea. Patient recruitment starts with e-mailing recruitment forms to the patients who have been scheduled for polysomnography. On the email recruitment form itself, there is a phone number and e-mail address for patients to call or e-mail if they are interested or if they decide to opt out. If the research team did not hear anything from the patients after 14 days of emailing the recruitment forms, the study coordinators will look up the names of the patients in Enterprise software which is the master schedule for all patients going for overnight in-lab polysomnography. Subsequently, the study coordinators will do a simple chart review using UH Ambulatory Care EMR to screen patients for eligibility and collect demographics data. If a certain patient is found eligible, one of our research team will make follow-up call to that patient and determine if patient is interested in participating in the research. During this phone interview, the phone recruitment script will be used to verify the subject's eligibility criteria, discuss the Belun Ring study further, and answer all the patient's questions. If patient is eligible and agreed to participate in the research during the phone interview, the patient's name and related personal information will be placed in the linking sheet and a unique identifier will be assigned to that patient. Then, the list of patient's unique identifier will be e-mailed to the sleep technician prior to the scheduled sleep study. All communication with the sleep technician will be done through UH e-mail addresses within UH premises. On the other hand, if the patient got the e-mail and called the research team to opt out in the trial, that patient will be not be called and no chart review will be done in the EMR for that patient.

On the night of the scheduled polysomnography (PSG), Sleep Questionnaire and 2 copies of the written informed consent will be presented to the patient together with other routine care pre-sleep questionnaires. The Sleep Questionnaire will be completed by the patient prior the start of the polysomnography. Our CREC certified sleep technicians will discuss the consent form in detail

before patient signs it. Questions from the patient will be encouraged, entertained, and answered by our CREC certified sleep technicians. Each patient who consented to the research will undergo a standard polysomnography (PSG) study according to the American Academy of Sleep Medicine (AASM) guidelines in a sleep laboratory. Simultaneously with the polysomnography (PSG), the device of study called Belun Ring will be applied to the patient's non-dominant index finger once the sleep technician has measured the patient's finger size, primed the device, and entered the patient's unique identifier. Belun Ring will derive a respiratory event index (REI) which will be calculated from photoplethysmography (PPG), heart rate, and oxygen saturation analysis. The respiratory event index (REI) will be compared to the Apnea-Hypopnea Index (AHI) calculated from the full polysomnography (PSG) after the manual scoring and staging of the raw data from an experienced CREC-certified sleep technician. All the results of the polysomnography (PSG) will be reviewed and verified by senior member of the study team, Dr. Ambrose Chiang, who will also collect and transfer data to UHRedcap data collection sheet.

The following day after the polysomnography (PSG), one copy of the signed written informed consent will be given to the patient while another copy will be scanned in the EMR. The sleep technician will upload data from the Belun Ring device to the HIPAA-compliant laptop from Belun Technology Company using the patient's unique identifier which the study team will collect and transfer to UHRedcap data collection sheet within 1 week. On the other hand, one of the research team will use the linking sheet in Microsoft Excel to verify the patient's unique identifier with the patient's medical record number (MRN) before collecting and transferring data from Sleep Questionnaire to the UH Redcap data collection sheet. The original Sleep Questionnaire will be scanned into the patient's medical record. All UHRedcap data collection sheets will be submitted to the statistician for analysis.

Study Procedures

No blood tests are needed prior the overnight polysomnography (PSG) study but patients will be given several questionnaires to complete before and after testing with polysomnography (PSG) Overnight standard laboratory-based polysomnography (PSG) will be performed using Sleepworks software on all sites. Sleep will be documented using the electroencephalography (EEG), bilateral electrooculography (EOG), and submental electromyography (EMG). Other routine measurements when performing standard polysomnography (PSG) include the electrocardiogram (ECG), nasal pressure transducer airflow, oronasal airflow (thermistor or thermocouple), thoracic and abdominal respiratory inductance plethysmography (RIP), traditional finger pulse oximeter, body position, bilateral leg electromyography (EMG), video recording, and a surface microphone attached above the sternal notch for detection of snoring. The technician will be attaching all these electrodes and channels to the patient according to the American Academy of Sleep Medicine (AASM) guidelines. Meanwhile, the Belun Ring will be worn on the proximal phalanx of index finger of the opposite hand so that it will not interfere with the measurement of the traditional finger pulse oximeter. After completing the polysomnography (PSG), no need for follow-up visit nor blood tests.

Study Timeline

Once we have the target number of patients, we will stop recruitment.

	Pre-Screening	Visit 1	Visit 2	Wrap Up
Estimated time requirement	15 minutes	15-30 minutes	6-8 hours	1-2 weeks
Data Collection	X			
Phone Call Questionnaire		X		
Study Procedure			X	
Data Analysis				X

Radiation and Radioactive Substances

1. Does the research involve the use of radiation or radioactive substances?
   ☐ Yes ☒ No

ClinicalTrials.gov Information

This study is currently registered on ClinicalTrials.gov with the following Identifier: NCT03997916.

List of Data to be Collected

Note: If using REDCap, all selected identifiers below must be indicated as PHI.

1. Indicate what identifiers you will collect
   ☒ Name
   ☒ Address *(e.g., Zip code, other geographical designation, etc.)*
   ☒ Dates related to an individual *(e.g., Date of admission, birth, surgery, etc.)*
   ☒ Telephone number
   ☐ Fax number
   ☒ Email address
   ☐ Social security number
   ☒ Medical record number
   ☐ Health plan beneficiary number
   ☐ Account number
   ☐ Certificate/license number
   ☐ Any vehicle or other device serial
   ☐ Device identifiers or serial numbers
   ☐ Web URL
   ☐ Internet protocol (IP) address
   ☐ Finger or voice prints
   ☐ Photographic images
   ☒ Other: *Sleep study recording data*

2. List all other data to be collected for the research study *(e.g. laboratory values, physician notes, length of stay, etc.)*
   a. *Age, gender, race, weight, height, and BMI*
   b. *Past medical and surgical histories*
   c. *Concomitant medications*
   d. *Physicians' notes on clinic visits - for chart review to check subject eligibility*

e. *Previous polysomnography (PSG) and home sleep apnea test (HST) in the past*
f. *All subjective information related to current sleep problem including current CPAP use*
g. *SP21256 Sleep Questionnaire*
h. *STOP-BANG score*
i. *UH Pre-sleep Questionnaire – part of routine care prior doing the standard polysomnography (PSG)*
j. *UH Post-Sleep Questionnaire – part of routine care after doing the standard polysomnography (PSG)*
k. *Patient satisfaction survey – part of routine care after doing the standard polysomnography (PSG)*
l. *Arterial blood gas and bicarbonate values if available*
m. *Echocardiogram or cardiac MRI results if needed*
n. *Total sleep time, Sleep latency, SpO2 nadir, oxygen desaturation index (ODI) and overall apnea-hypopnea index (AHI) in the polysomnography (PSG) during the testing*
o. *Total sleep time, SpO2 nadir, and respiratory event index (REI) in the Belun Ring device during the testing*

Data Analysis Plan

RStudio Version 1.1.456 will be used to perform an a priori power analysis for the sensitivity of the Belun Ring REI and PSG AHI diagnoses. At alpha = 0.05, power = 0.95, minimum acceptable sensitivity = 0.825, target level of sensitivity = 0.977, a minimum of 35 obstructive sleep apnea (OSA)-positive patients is required. With an estimated 80% of patients receiving a positive polysomnography (PSG) diagnosis of obstructive sleep apnea, recruitment of 42 patients at minimum is necessary. Because not all recruited patients may complete the overnight PSG, we plan to collect data from approximately 50 patients.

Sensitivity (the proportion of patients correctly diagnosed with OSA) and specificity (the proportion of patients correctly rejected as having OSA) values of sleep scores will be computed, and the area under the receiving operating characteristic (ROC) curve will also be calculated. A sensitivity value of .825 will be considered clinically significant. Pearson correlation will be used to identify the association between OSA and PSG AHI diagnoses. Bland and Altman plots will be generated to demonstrate the degree of identity between the outcomes of the Belun Rung and PSG AHI diagnostic methods.

Additional data such as sleep parameters, stress parameters, and total sleep time will be reported as descriptive analyses (e.g., means and standard deviations).

The primary study endpoint is to investigate the accuracy, sensitivity, and specificity of the Belun Ring in assessing obstructive sleep apnea (OSA) when compared to the gold standard which is polysomnography (PSG). The secondary endpoint is to evaluate the tolerability of the device by the patients.

Confidentiality of Specimens and Banking

Are you storing the specimen(s) for future use for other research projects?

☒ I am **not** collecting specimens in this research project

☒ I am **not** storing specimens in this research project

☐ Yes

☒ No

Confidentiality of Data

1. To maintain the confidentiality of the data:

☒ I will use a unique study identifier (not derived from the participants' personal identifiers) to code individuals' data and I will store this ID log separate from study data.

☐ Other *(please explain):*

2. How are you storing your electronic data?

☒ UH Redcap

☐ CWRU Redcap

☐ CWRU's SRE (Secure Research Environment)

☐ CWRU Box

☐ OnCore

☐ UH Secure Network Drive

☐ CWRU Secure Network Drive

☒ Other *Belun Technology Company will provide 3 HIPAA-compliant laptops free of charge during the entire duration of the research trial. Each sleep laboratory will have 1 HIPAA-compliant laptop from Belun Technology Company which will be used to assign and prime a specific Belun Ring device to a specific subject. All these 3 laptops are HIPAA-compliant and have been approved by UH Research IT prior start of the study. Before the night of the scheduled polysomnography (PSG), the sleep technician will get an email from the study team regarding list of patients who will participate in the study as well as the each patient's corresponding unique identifier. On the night of the polysomnography (PSG), the sleep technician will use the unique patient identifier to identify the subject in the Belun Ring and use the same unique identifier when uploading data from Belun Ring to HIPAA-compliant laptop the following after completion of the polysomnography (PSG).. The study coordinators will transfer all data from the Belun Ring HIPAA-compliant laptop to the UH Redcap data collection sheet. After updating UH Redcap data collection sheets, the study coordinators will delete data from the Belun Ring device and the HIPAA-compliant laptop. During the study, no data will be shared with Belun Technology Company and the latter will not access their laptops until the study is completed. After the study is completed, all the Belun Ring devices and the 3 HIPAA-compliant laptops from Belun Technology Company will be returned to Belun Technology Company. Any lost or damaged Belun Ring device or laptop will not be the financial responsibility of UH nor the patient.*

3. ☒ I acknowledge that paper research data and documents will be stored in a double-locked secure environment in the following location:

Location: ☒ *Office of Dr. Ambrose Chiang and Bolwell-6th floor sleep lab at the Department of Pulmonary, Critical Care, and Sleep Medicine at 11100 Euclid Avenue, Bolwell Bldg 6th floor, Rm 6130, Cleveland, OH 44106*

4. Will data be shared?

☐ N/A

☒ No

☐ Yes

1. List the exact data elements that will be shared:
    1.
2. Describe how data will be sent:

(Please note: if sharing data, please contact your Grants and Contracts Specialist to ensure the proper contracts are in place.)

HIPAA Authorization

If you are going to be accessing PHI (Protected Health Information), indicate how HIPAA authorization will be obtained (check all that apply):

☒ HIPAA authorization is in the consent form

☒ Requesting a full or partial waiver of HIPAA for prescreening

☐ Requesting a full or partial waiver of HIPAA

1. Describe why the study cannot be completed without the specified identifiable information.

We will need to do chart review if there is not enough information about the patient's comorbid conditions. Also, one of the exclusion criteria in this research is involvement of potential subject in another investigational study or recent hospitalization in the last 30 days.

2. If the identifiable information will be used or disclosed by anyone other than the research team, please state who those individuals/entities are and provide justification for the disclosure.

    ☒ Identifiable information will **not** be used or disclosed by anyone other than the research team

    ☐ Identifiable information will be used or disclosed to:

3. Describe how long identifiers will be kept for in relation to study length and data collection and analysis.

Research data will be stored for at least 3 years following study closure or the required length of time required by applicable regulations at that time; whichever is longer.

☒ I assure that protected health information collected for purposes of this research study will not be reused or disclosed to any other person or entity, except as required by law, for

authorized oversight of the research study, or for other research for which the use of disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512

Risks to Research Participants

1. List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and reversibility of the risks. Include the physical psychological, social, legal, and economic risks.
    a. *Risk of breach of confidentiality is prevented by using computers within UH campus and laptops owned by UH as these computers and laptops are encrypted and secured. No transferring of data using USB or text messages will be allowed. Communication between the principal investigator, mentor, and members of the research team will be done through UH-encrypted email or in person in either Dr. Chiang's office or the conference room in Department of Pulmonary, Critical Care, and Sleep Medicine which are both located on the 6th floor of Bolwell building in University Hospitals- CMC.*
    b. *The sensor can be warm to touch occasionally but not hot enough to cause burn.*
    c. *The clip-on sensors may cause some pressure discomfort if the wrong size was applied. The patient may alert the technician so patient can be fitted another size of the Belun Ring.*

2. If applicable, indicate which experimental procedures may have risks to the research participants that are currently unforeseeable.
    ☒ N/A
3. If applicable, describe the risks to others who are not research participants.
    ☒ N/A
4. Describe the availability of medical or psychological resources that research participants might need.
    ☒ N/A

Additional Considerations for Pregnant Women:

5. Indicate which procedures may have risks to an embryo or fetus should the research participant or their partner be or become pregnant.
    ☒ N/A *However, the Belun Ring has not been tested in children or pregnant women.*
    ☐ Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
    ☐ No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
    ☐ Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
    ☐ Individuals engaged in the research will have no part in determining the viability of a neonate.

Provisions to Protect the Privacy Interests of Research Participants

The sleep study will be done in separate rooms in the sleep lab. Privacy will be protected with doors closed.

Potential Benefit to Research Participants

☐ There is potential benefit to research participants.

1. Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

☒ There is **no** direct benefit to research participants.

2. If no direct benefit, state the potential benefit to society or others. *Do not list compensation.*

If the study showed that Belun Ring has high sensitivity and specificity when compared to the gold standard which is the polysomnography (PSG), it can be used as a simple, safe, and inexpensive alternative test to in-lab polysomnography (PSG) testing or as a screening tool prior in-lab polysomnography (PSG) testing. As the device costs less than 10% of a typical home sleep testing device and 1% of an in-lab testing software, its use may revolutionize how obstructive sleep apnea (OSA) is evaluated.

Withdrawal of Research Participants

☒ N/A

If a participant did not sleep for at least 4 hours during the sleep study, patient will be withdrawn from the research without their consent. Nothing needs to be done in such situation as no follow up is needed.

Alternatives to Participation

☒ The alternative is for research subjects not to participate.

If patient wishes not to participate, patient will still get the standard overnight in-laboratory polysomnography (PSG) ordered by his or her physician. There will be no change of care regardless.

Costs to Research Participants

☒ There are **no** costs to research participants or their insurance companies (there are no clinical visits or billable procedures).

Research Participant Compensation

☒ There is **no** compensation or reimbursement for research participants.

☐ There is compensation for research participants.

Describe the schedule, payment method, and payment total of any incentives or compensation that research participants will receive for participation in the research (e.g., gift cards or cash with amount, t-shirts, devices, bags, swag, etc.)

☐ There will be reimbursement for research participants.

Describe the schedule, payment method, and payment total of any reimbursement that research participants will receive for participation in the research (e.g., gift cards or cash with amount, etc.)

Compensation for Research Related Injury

Describe who will pay for the costs of medical treatment and/or compensation in the event of a research related injury:

☐ Funding agency is providing some/all payment for injury
☒ Funding agency is providing no payment for injury
☐ N/A

Provisions to Monitor the Data to Ensure the Safety of Research Participants

1. Describe how often the data will be monitored for completeness, accuracy and adherence to the protocol.

The principal investigator, the mentor, the research coordinator, and the study coordinators will be monitoring data for completeness, accuracy, and adherence to protocol at least 3 times a week. The PI will discuss any discrepancies with the individual that collected the data for prompt resolution.

2. Indicate if there will be a Data and Safety Monitoring Board or Committee:

☒ There will **not** be a formal Data and Safety Monitoring Board/Committee.

☐ There will be a formal Data and Safety Monitoring Board/Committee.

Provide information about the DSMB/C including the contact information of the committee member(s) (as applicable); whether it is independent from the study sponsor; how often it meets; the type of data that will be used; written reports, etc.

Drugs or Devices

☐ This is **not** a drug or device study. The protocol is considered non-therapeutic (non-therapeutic is defined as research not intended to diagnose, prevent, cure, mitigate, treat, etc. a disease or condition) by the FDA. – *You may delete the rest of this section.*

OR

☒ This is a drug or device study. The protocol is considered therapeutic (research intended to diagnose, prevent, cure, mitigate, treat a disease or condition) by the FDA.

1. Is there an active IND (Investigational New Drug) or IDE (Investigational Device Exemption) for the proposed clinical research study?

☐ Yes, provide an official letter of support or proof of approval which identifies the IND/IDE holder and IND/IDE number. *Please attach this in the SpartaIRB smartform*

☒ No, *see question below:*

2. Is the drug IND exempt *OR* is the device (and its use) a non-significant risk device for the proposed study design?

☒ Yes, *please identify the authorized party who made the determination and provide supporting documentation as applicable.*

FDA approved the device on May 29, 2018.

☐ No *NOTE: either an active IND/IDE or an exemption would be required for investigational product use in a therapeutic protocol.*

☐ N/A

3. If the research involves drug(s) or device(s), describe your plans to store, handle, administer and track those drug(s) or device(s) to ensure that they will be used only on research participants and be used only by authorized investigators.
   Each Sleep laboratory will have up to 8 devices of different sizes. Each device has its own cover and docking cradle and will be cleaned with alcohol thoroughly after each use.

Additional Information

N/A

Community-Based Participatory Research

☒ This is **not** a community-based participatory research project – *please leave the rest of this section blank*

☐ This is a community-based participatory research project
Describe the involvement of the community in the design and conduct of the research.

Note: Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) protects, the community participates fully in all aspects of the research process.

International information

☒ This is **not** an international study.

MULTI-SITE RESEARCH (when UH or CWRU is the IRB of Record)

Does this project have multiple sites?

☐ **Yes**

☒ **No** – *please leave the rest of this section blank*

Non-Local Site Information for Multi-Site Studies

*If this is a multi-site study where you are the **lead investigator,** list the following information for each relying site:*

1. Name of site:
2. PI of relying site:
3. Name of IRB contact:
4. Phone number of IRB contact:
5. Email address of IRB contact:

Non-Local Recruitment Methods for Multi-Site Studies

*If this is a multi-site study and research participants will be recruited by methods **not under the control of the local site** (e.g. call centers, national advertisements) describe those methods. Local recruitment methods are described above.*

1. *Describe when, where, and how potential research participants will be recruited.*

- *Describe the methods that will be used to identify potential research participants.*

- *Describe the materials that will be used to recruit research participants.*

Multi-Site Research Communication Plan (when you are the lead investigator)

*If this is a multi-site study where you are the **lead investigator**, describe the processes to ensure communication among sites including:*

☐ *All sites will have the most current version of the protocol, consent document, and HIPAA authorization*

☐ *All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record)*

☐ *All modifications have been communicated to sites, and approved (including approval of the site's IRB of record) before the modification is implemented*

☐ *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*

☐ *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*

☐ *All local site investigators conduct the study in accordance with applicable federal regulations and local laws*

☐ *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy*

*If this is a multi-site study where you are the **lead investigator,** describe the method for communicating to engaged participant sites the following:*

1. *Problems:*
2. *Interim results:*
3. *The closure of the study:*

References

1. Ayasa NT, Pittma S, MacDonald M, et al. Assessment of a wrist-worn device in the detection of obstructive sleep apnea. Sleep Medicine, Vol 4, P435-442, 2003.
2. Chazal P, Heneghan C, Mcnicholas W. Multimodal detection of sleep apnea using electrocardiogram and oximetry signals, Phil Trans. R. Soc. A, (2009) P369-389, 2008.
3. Poupard L, Philippe C, Goldman MD, et al. Novel mathematical processing method of nocturnal oximetry for screening patients with suspected sleep apnea syndrome. Sleep Breath, Vol 10, P 285-290, 2014.

4. Romem A, Koldobskiy D, et al. Diagnosis of Obstructive Sleep Apnea using Pulse Oxiemter Derived Photoplethysmographic Signals. Journal of Clinical Sleep Medicine. Vol 10, P285-290, 2014
5. Berry RB, Brooks R, Gamaldo CE, et al. for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications, Version 2.5, www.assmnet.org, American Academy of Sleep Medicine, Dairen, IL, 2017
6. Berry RB. Fundamentals of Sleep Medicine. Chapter 13 to 18
7. Gu W, Leung L. A NOVEL HOME SCREENING PLATFORM FOR OBSTRUCTIVE SLEEP APNEA THROUGH WEARABLE RING-TYPE PULSE OXIMETER. APSS meeting abstract 0482

Please reference the Investigator Manual for local institutional requirements.