Belun Ring Platform (BLS-100) Home Sleep Apnea Testing Device with Improved Algorithm for Assessment of Obstructive Sleep Apnea (OSA): A Comparison to in-lab polysomnography

National Clinical Trial (NCT) Identified Number: NCT04885062

Principal Investigator

Sub-Investigator:

Sponsor: Belun Tech Company, Hong Kong

Sleep Labs

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

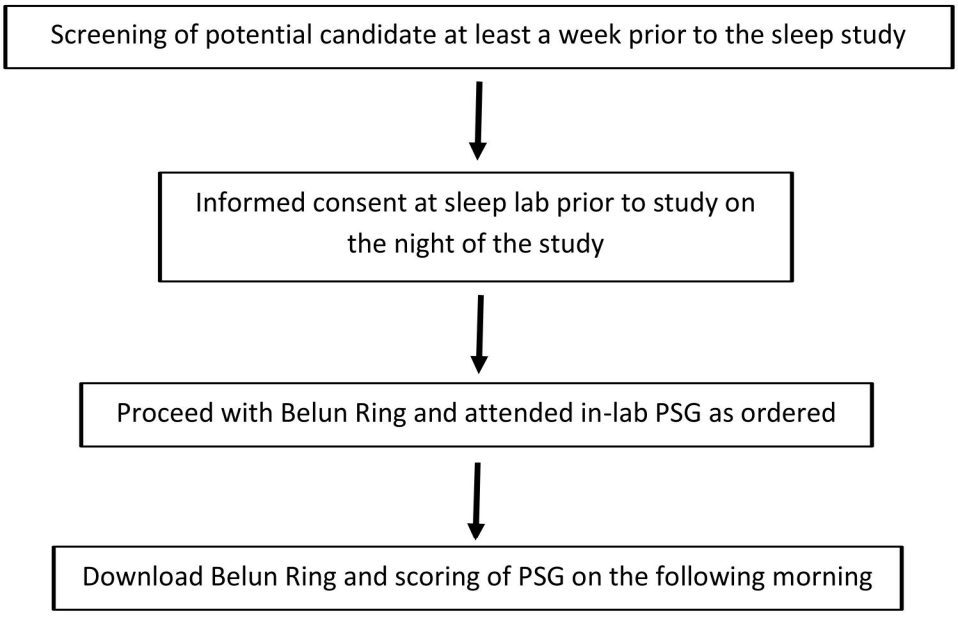
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Belun Ring Platform (BLS-100) Home Sleep Apnea Testing for Assessment of Obstructive Sleep Apnea (OSA): A Comparison against in-lab polysomnography
Study Description:	OSA is commonly diagnosed with either attended in-lab polysomnography (PSG) or unattended home sleep apnea testing (HSAT). The BLS-100 (Belun Technology Company Limited, Hong Kong) is This study investigates the hypothesis that the BLS-100 is a reasonable HSAT device for OSA assessment in patients referred to sleep labs for assessment of OSA whose STOP-Bang is ≥ 3.
Objectives:	• Primary objective: ○ To determine the overall accuracy, sensitivity, and specificity of the BLS-100 in assessing OSA by comparing to the attended in-lab PSG, which is the gold standard • Secondary objectives: ○ To determine the accuracy of BLS-100 sleep stage parameters by comparing to the standard attended in-lab PSG ○ To assess the BLS-100 ANS response parameters derived from heart rate variability (HRV), i.e., the sympathetic nervous system response (SNS) from the low frequency component (LF) and the parasympathetic nervous system response (PNS) from the high frequency component (HF)
Endpoints:	• Primary endpoints: ○ In-lab PSG apnea-hypopnea index using 4% O2 desaturation hypopnea criteria (PSG-AHI4) ○ Belun Ring Respiratory event index using improved algorithm (bREI-1) • Secondary endpoints: ○ PSG Total sleep Time (PSG-TST), Wake time (PSG-WT), NREM time (PSG-NREM), and REM sleep time (PSG-REM) ○ PSG apnea-hypopnea index using 3% O2 desaturation or arousal hypopnea criteria (PSG-AHI3A), PSG central apnea index (PSG-CAI), O2 desaturation index using 4% criteria (PSG-ODI4), O2 desaturation index using 3% criteria (PSG-ODI3), time with SpO2 < 90% (PSG-T90), periodic limb movement of sleep index (PLMI), PLM-arousal index (PLMAI), and overall arousal index (PSG-AI), Average heart rate, EKG ○ Belun Ring TST (bTST), Wake Time (bWT), NREM time (bNREM), and REM time (bREM) ○ Belun Ring Respiratory event index (bREI-2) using original algorithm ○ Belun Ring time with SpO2 < 90% (bT90) ○ Belun Ring ANS parameters: LF, HF, and LF/HF rati ○ ESS, STOP-Bang, Insomnia Severity Index (ISI)

Study Population:	Individuals referred to the sleep lab with clinical suspicion of OSA and a STOP-Bang ≥ 3. This study will aim at recruit a total of 100 consecutive adult individuals with a M:F ratio of 1:1. Those who fail to have at least 4 hours of technically valid sleep based on BLS-100 in a diagnostic study or at least 3 hours of technically valid sleep during the diagnostic portion of a split night study will be excluded from statistical analyses.
Phase:	N/A
Sites/Facilities Enrolling Participants:	
Description of Study Intervention:	The Belun Ring sensor will be applied to the proximal phalanx of the index finger in the non-dominant hand of the participating individuals prior to their sleep onset in the sleep lab and will be removed upon awakening at the end of the sleep period on the following morning. The attended in-lab sleep study will be performed simultaneously in a standard fashion.
Study Duration:	It is estimated that data collection will be completed 6 months from the start of the study. The data analysis and write up will require an additional 6 months. The total duration of the study therefore is estimated at 12 months.
Participant Duration:	The testing will last only for one night.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Potential participants will be identified from the schedule of the sleep labs. Pre-testing screening will be done at least seven days prior to the date of sleep testing by either the study coordinator or one of the investigators. Those patients who appear to satisfy the study inclusion and exclusion criteria will be approached and invited to participate in the study.

STOP-bang score will be obtained prior to the consenting process on the night of the study. Patients with STOP-Bang score of 1-2 will be excluded. Consent will then be obtained by a research certified sleep tech in those who satisfy the study inclusion and exclusion criteria.

2 INTRODUCTION

2.1 STUDY RATIONALE

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

Currently, attended in-lab PSG is the gold standard for diagnosing OSA. However, in-lab PSG needs to be conducted in a sleep lab and scored and analyzed by experienced scoring sleep tech which can be expensive, labor-intensive, and time-consuming. Due to the high prevalence of OSA, there is significant cost associated with evaluating all patients suspected of having OSA with PSG. Further, there also may be limited access to in-lab PSG testing in some areas. Type 3 HSAT, though with limitations, is a commonly used alternative method to diagnose OSA in adults (AASM 2017 guidelines). Therefore, it is of interest to explore potential alternative testing methods that can reliably determine the AHI with other surrogate markers at a lower cost.

Among the different approaches, 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 SpO2 followed by a rise of SpO2 which, in turn, affects the sympathetic and vagal balance resulting in HRV. Therefore, sleep apnea events may be monitored by analyzing parameters derived from SpO2 and HRV. Indeed, clinical research efforts using oximetry have been attempted over the past few years for evaluation of OSA.

Heneghan in 2008 reported the development of an automated algorithm for OSA detection using EKG and oximetry measurements. The algorithm provides (a) epoch-by-epoch estimates of apnea occurrence and (b) estimates of overall per-subject AHI. Using separate thresholds of AHI > or =15 and 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 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 AHI, 85.3% of respiratory events were correctly annotated on an epoch-by-epoch basis. 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 AHI was 0.95 (P <0.001). It was concluded that a combined Holter-oximeter monitoring compares well with

PSG for identifying OSA in an attended setting and is potentially suitable for home-based automated assessment of OSA in a population suspected of having OSA.

In 2012, Poupard reported the development of a new oximetry mathematical analysis, which quantifies amplitude variations of SpO2 and 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). VHI was compared prospectively with standard PSG parameters (AHI and oxygen desaturation index (ODI) in 106 patients suspected of having OSA. The criterion for diagnosis of OSA was AHI >15 of sleep during PSG. They observed a significant correlation between the AHI and VHI ($R = 0.87$, $p < 0.0001$). Using VHI >15 as the criterion for 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 ΔSpO2 and ΔHR show promise as a useful prediction of screening 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 OSA. Among a cohort of 73 patients referred for in-lab evaluation of OSA, 65 were simultaneously monitored with the PPG-based device while undergoing PSG. Of note, 19 had significant cardiopulmonary comorbidities. Using the 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) PSG > 5/h and AHIPSG > 15/h were calculated for the 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 PPG-derived and PSG-derived AHI ($r = 0.81$, $p < 0.001$). For AHIPSG > 5/h, sensitivity was 80%, specificity 86%, PPV 93%, NPV 68%, and +LR was 5.9. For AHIPSG > 15/h, sensitivity was 70%, specificity 91%, PPV 80%, NPV 85%, and +LR was 7.83. The corresponding areas under the receiver operator curves were 0.91 and 0.9. It was concluded that PPG-derived data compare well with simultaneous in-lab PSG in the diagnosis of suspected OSA among patients with and without cardiopulmonary comorbidities.

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

The BLS-100 (Belun Technology Company Limited, Hong Kong) is

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 REM sleep and NREM sleep. Furthermore, ANS activities including SNS and PNS may be measured throughout the monitoring period. Belun Ring measures 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 the interference of the sleep of the testing individuals.

Belun Technology Company has conducted two studies in 2017-201

2.1.1 KNOWN POTENTIAL RISKS

The risk of using Belun Ring is extremely low. In the three studies conducted ir
no device related adverse events was reported. The only reported event was a device clip pressure mark on the skin in the morning that goes away within an hour. No skin burn has been noted thus far.

2.1.2 KNOWN POTENTIAL BENEFITS

There are no immediate potential benefits to study participants since this is an early validation study of a new device. However, if the results of this study are positive, this may revolutionize how OSA is diagnosed and managed in clinical settings. This easy-to-use and relatively inexpensive device may help sleep specialists and non-sleep specialist providers screen, diagnose, or triage patients for further confirmative sleep testing. This may help early diagnosis of OSA and thus improve OSA-associated cardiovascular and metabolic outcomes.

2.1.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There is no immediate potential benefit to the patients participating in this study, however, there is a large potential benefit to individual patients and society as a whole. It is our opinion that the potential benefits outweigh the minimal risks associated with the study intervention and procedures.

3 STUDY OBJECTIVES AND MEASURES

3.1 STUDY OBJECTIVES

Primary objective:

- To determine the overall accuracy, sensitivity, and specificity of the BLS-100 in assessing OSA by comparing to the attended in-lab PSG in individuals referred to the sleep labs with clinical suspicion of OSA and a STOP-Bang score $\geq$ 3.

Secondary objectives:

- To determine the accuracy of BLS-100 sleep stage parameters by comparing to the standard attended in-lab PSG
- To assess the BLS-100 ANS response parameters derived from heart rate variability (HRV), i.e., the sympathetic nervous system response (SNS) from the low frequency component (LF) and the parasympathetic nervous system response (PNS) from the high frequency component (HF) and explore its potential use to explore its potential use

3.2 OUTCOMES MEASURES

Primary endpoints:

- In-lab PSG apnea-hypopnea index using 4% O2 desaturation hypopnea criteria (PSG-AHI4)
- Belun Ring Respiratory event index (bREI)

Secondary endpoints:

- Primary endpoints:
  - In-lab PSG apnea-hypopnea index using 4% O2 desaturation hypopnea criteria (PSG-AHI4)
  - Belun Ring Respiratory event index using improved algorithm (bREI-1)
- Secondary endpoints:
- Primary endpoints:
  - In-lab PSG apnea-hypopnea index using 4% O2 desaturation hypopnea criteria (PSG-AHI4)
  - Belun Ring Respiratory event index using improved algorithm (bREI-1)
- Secondary endpoints:
  - PSG Total sleep Time (PSG-TST), Wake time (PSG-WT), NREM time (PSG-NREM), and REM sleep time (PSG-REM)
  - PSG apnea-hypopnea index using 3% O2 desaturation or arousal hypopnea criteria (PSG-AHI3A), PSG central apnea index (PSG-CAI), O2 desaturation index using 4% criteria (PSG-ODI4), O2 desaturation index using 3% criteria (PSG-ODI3), time with SpO2 < 90% (PSG-T90), periodic limb movement of sleep index (PLMI), PLM-arousal index (PLMAI), and overall arousal index (PSG-AI), Average heart rate, EKG
  - Belun Ring TST (bTST), Wake Time (bWT), NREM time (bNREM), and REM time (bREM)
  - Belun Ring Respiratory event index (bREI-2) using original algorithm
  - Belun Ring time with SpO2 < 90% (bT90)
  - Belun Ring ANS parameters: LF, HF, and LF/HF rati
  - ESS, STOP-Bang, Insomnia Severity Index (ISI)

3.3 BASELINE MEASUREMENTS

- Race
- Age
- Sex
- Height, weight, BMI
- Neck size, Waist size
- Medical history/comorbidities
- Concomitant medications
- Epworth sleepiness score (ESS)
- STOP-bang score

4 STUDY DESIGN

The Belun Ring sensor will be applied to the proximal phalanx of index finger in the non-dominant hand of the participating individuals prior to their sleep onset in the sleep lab and will be removed upon awakening at the end of the sleep period on the following morning. The attended in-lab sleep study will be performed simultaneously in a standard fashion.

4.1 END OF STUDY DEFINITION

The end of a study in a subject is defined as termination of the PSG.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria

1. Provision of signed and dated informed consent form.
2. Age 18-80
3. Clinically assessed and suspicious for OSA with a STOP-Bang score $\geq$ 3

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Full night PAP titration study
2. On home O2, noninvasive ventilator, diaphragmatic pacing, or any form of nerve stimulator
3. Having atrial fibrillation-flutter, pacemaker/defibrillator, LVEF < 55%, left ventricular assist device (LVAD), or status post cardiac transplantation
4. Patients taking narcotics
5. Recent hospitalization or recent surgery in the past 30 days
6. Unstable cardiopulmonary status on the night of the study judged to be unsafe for sleep study by the sleep tech and/or the on-call sleep physician

An individual who meets the above criteria but fails to have at least 4 hours of technically valid sleep based on BLS-100 in a diagnostic study or at least 3 hours of technically valid sleep during the diagnostic portion of a split night study will be excluded from statistical analyses.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We expect to enroll at least 6 participants per week.

To achieve the goal of M:F 1:1 ratio, the study coordinator will monitor recruitment closely and end the recruitment of a specific gender when the number of individuals of the specific gender reaches 50 in UH labs. The recruitment will then be focused on the opposite gender to complete the study.

This study is on a voluntary basis and participants who consent to participate will receive no monetary compensation for this study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION DESCRIPTION

6.2 APPLICATION OF DEVICE

6.3 BLINDING AND OTHER METHODS TO MINIMIZE BIAS

This study has good internal validity as patient will be applied with both the BLS-100 ring and the in-lab PSG on the same night from the beginning to the end of a clinical sleep study. To minimize bias and sustain the external validity, all sites will score the sleep studies based on the latest American Academy of Sleep Medicine (AASM) scoring manual. The research physicians and the sleep lab staff will be blinded to the BLS-100 results until the research data is ready for statistical analysis. The Belun Tech Co. staff involved in the study will be blinded to the attended in-lab PSG scoring results till the time for statistical analysis.

6.4 CONCOMITANT THERAPY

Participants' normal therapies will not be restricted as part of this trial. At the start of each study visit participants will be asked to whether they have taken their maintenance medications where applicable. A current list of the participants currently medications will be recorded during clinic visit.

7 STUDY ASSESSMENTS

7.1 IN-LAB POLYSOMNOGRAPHY

Attended in-lab PSG will be performed in the sleep lab with a montage including EEG leads (O1A2, O2A1, C1A2, C2A1, F1A2, F2A1), REOG, LEOG, chin EMG, and legs EMG (LAT and RAT), EKG, and respiratory status measures by nasal pressure airflow and oro-nasal airflow by thermistor, chest and abdominal respiratory effort (respiratory impedance plethysmographs), body position, and pulse oximetry. Studies will be scored in 30-sec epochs according to the latest AASM scoring manual by a senior scoring tech who will be blinded to the results of the Belun Ring analysis. Likewise, Belun Ring analysis will be conducted without the knowledge of the results of attended in-lab PSG scoring.

An apnea event is defined as a decrease in nasal airflow to < 10% of baseline for ≥ 10 s with continued respiratory effort, and a hypopnea event as decrease in nasal airflow by 30% to 90% of baseline accompanied by oxygen desaturation > 4% for 10 seconds or more. The severity of OSA was defined as follows: "mild" = 5 < AHI < 15, "moderate" 15 < AHI < 30, and "severe" = AHI ≥ 30.

7.2 EPWORTH SLEEPINESS SCORES (ESS)

ESS is a validated, 8-item, patient completed questionnaire with a score of 0-24 that was developed to measure excessive daytime somnolence.

7.3 INSOMNIA SEVERITY INDEX (ISI)

ISI is a validated, standard questionnaire that was designed to assess the severity of both nighttime and daytime components of insomnia and is commonly used for sleep research.

7.4 MEDICAL HISTORY

Relevant medical history, including history of current disease, other pertinent sleep history, and information regarding underlying diseases will be recorded prior to the night of the sleep study.

7.5 CONCOMITANT MEDICATIONS

Current dose, route, unit frequency of administration, and indication for administration will be captured on the night of the sleep study. No medications will be restricted as part of this study.

7.6 ADVERSE EVENTS

7.6.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

7.6.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) 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 adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Any other important medical event that may not result in death, be life-threatening, or require hospitalization 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.

7.6.3 CLASSIFICATION OF AN ADVERSE EVENT

The following guidelines will be used to classify adverse events:

- 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"

7.6.4 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention 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 – Previously known adverse event; or an event that follows a reasonable temporal sequence from administration of the device; that follows a known or expected response pattern to the suspected device; that is confirmed by stopping administration of the device; and that is not explained by any other reasonable hypothesis.
- Probably Related – An event that follows a reasonable temporal sequence from administration of the device; that follows a known or expected response pattern to the suspected device; that is confirmed by stopping the administration of the device; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.

- Potentially Related – An event that follows a reasonable temporal sequence from administration of the device; that follows a known or expected response pattern to that suspected device; but that could readily have been produced by a number of other factors.

- Unlikely to be related – A clinical event whose temporal relationship to the study device makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study device) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Not Related – The AE is completely independent of the study device, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.6.5 EXPECTEDNESS

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.

7.6.6 TIME PERIOD AND FREQUENCY FOR EVENT FOLLOW UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study or immediately after study.

All AEs including local and systemic reactions not meeting the criteria for SAEs 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.

7.6.7 ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB).

7.6.8 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs 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

8 STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE DETERMINATION

Based on previous clinical studies and relevant studies, a mean (μ) and standard deviation (σ) of difference in AHI between Belun Ring and PSG methods are set to 3 events/hr and 9 events/hr. A sample size of 79 will provide 85% power to detect a maximum allowed difference 26 events/hr with significant level of 0.05. Because some recruited patients may fail to complete the study for needed technically valid sleep duration, we believe there is a need to collect data from at least 100 patients.

8.2 STATISTICAL ANALYSIS

Bland-Altman plots analyses will be generated to demonstrate the agreement in AHI between Belun Ring and PSG methods. Pearson correlation and regression analysis will be used to evaluate the association between Ring-REI and PSG-AHI. Sensitivity (the proportion of patients correctly diagnosed with OSA) and specificity (the proportion of patients correctly rejected as having OSA) values and 95% CIs of Ring-REI will be computed, and the area under the receiving operating characteristic (ROC) curve will also be calculated at PSG cutoffs of 5, 10, 15, 20, and 30. Paired t-tests will be used to assess the accuracy of BLS-100 sleep stage parameters by comparing to the standard attended in-lab PSG. Additional data such as ANS parameters will be reported as descriptive analyses.

9 SUPPORTING

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

The following consent materials are submitted with this protocol. Please see the attachment.

9.1.1.2 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 Institutional Review Board (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 carefully review the written consent form 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. The participant will sign the informed consent document prior to any procedures being done specifically for the study. 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.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (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
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

9.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of

biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, 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 Institutional Review Board (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.

The 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, which is for purposes of statistical analysis and scientific reporting, will be stored on an electronic database. 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 research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

9.1.4 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

will conduct the UH on-site comprehensive monitoring (100% data verification of endpoint, safety and other key data variables) at one week, two weeks and then monthly until the end of this study. The monitoring report will be distributed to the research teams, the statisticians, as well as Belun Technology Company.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial 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 electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into ıill allow the safe, secure storage of all your research data, including the storage of PHI (Protected Health Information) HIPAA identifier fields for you ,rotocols.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (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.

9.1.6 PUBLICATION POLICY

Data obtained from the current study will be submitted for publication to an international peer reviewed journal.

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