Official Title:

Validation of a novel device for screening patients with symptoms of obstructive sleep apnea

Study ID# PR 2018-259

NCT number: NCT04121923

COMMERCIAL SPONSOR:
Belun Technology Company Ltd.

Document Ownership:

Document Approver:

Revision History:

Revision	Date	Revision Description
Version 1	02/01/18	Original issue
Version 2	02/27/18	Incorporated

Author:

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ETHICS COMMITTEE REVIEW:

STUDY PROCEDURE:

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COMMERCIAL SPONSOR:

PRINCIPAL INVESTIGATOR:

SUB-INVESTIGATORS

MEDICAL OVERSIGHT:

STUDY SITE:

CONFIDENTIALITY:

Validation of a novel device for screening patients with symptoms of obstructive sleep apnea
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Synopsis

Objectives of the Clinical Investigation Plan

The purpose of this study is to evaluate the sensitivity and specificity of the Belun Ring Pulse Oximetry system for screening of obstructive sleep apnea (OSA) in adults during standard polysomnography sleep study conditions. The primary outcome metric is the Apnea-Hypopnea Index (AHI).

The goal, in its entirety, is to evaluate the performance of the Belun Ring Pulse Oximeter during a standard polysomnography sleep study and its ability to compare to the determined Apnea-Hypopnea Index (AHI) of the subjects. It is expected that the Belun Ring Pulse Oximeter will adequately record SpO2, pulse rate, body position and heart rate variability throughout the duration of the study.

Background

Obstructive sleep apnea (OSA) is one of the most common disorders affecting sleep. Severe OSA is usually associated with significant morbidity and mortality of cardiovascular and pulmonary diseases. Polysomnography (PSG) is the current gold standard for diagnosing OSA. The Apnea-Hypopnea Index (AHI) derived from PSG monitoring is used to indicate the severity of OSA. The AHI values for adults are categorized as: AHI<5 = Normal, 5≤AHI<15 = Mild sleep apnea, 15≤AHI<30 = Moderate sleep apnea, and AHI≥30 = Severe sleep apnea.

PSG results need to be conducted and analyzed by an experienced sleep technologist in a sleep lab which is expensive and time consuming. Therefore, it is of interest to explore potential alternative methods which can reliably determine the AHI with other surrogate markers at a lower cost. Among different approaches, OSA severity 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, affecting the sympathetic and vagal balance resulting in tachycardia. Therefore, sleep apnea events can be monitored by analyzing parameters derived from SpO2 and HRV.

In this study, the Belun ring pulse oximeter will be evaluated for home-based OSA screening.

Summary Overview

The overall accuracy performance of the Belun Ring Pulse Oximeter will be evaluated during sleep study conditions and compared to the standard PSG study data including electroencephalography (EEG), bilateral electrooculography (EOG), submental electromyography (EMG) and electrocardiography (ECG), nasal flow (thermistor), thoracic and abdominal movements and body position, oxygen saturation by traditional pulse oximetry and snoring by a surface microphone attached above the sternal notch. A minimum of 50 healthy adult subjects, ranging in age from 18 to 90 years will be enrolled in the study. It is expected that approximately10 subjects will have an AHI index <5, ten will have an AHI index between 5 and 15, ten between 15 and 30 and ten >30.

The data analysis will compare the results of the PSG study to those collected by the Belun ring as reflected by the AHI score.

Subject Inclusion to the study will be a minimum of 50 adult subjects, ranging in age form 18-90 years of age to meet the study design requirements.

Subject exclusion to the study include: patients requiring oxygen therapy or noninvasive ventilation, a diagnosis of chronic obstructive pulmonary disease, neuromuscular disease, periodic limb movement, or narcolepsy, patients on medication known to interfere with heart rate, such as beta-blockers, digoxin or calcium receptor antagonists.

It is expected that the data collection will take 2 to 4 months to complete. Follow-up to the subject will be conducted immediately following the study procedure.

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Identification and Description of the Investigational Device

Investigational Device: Belun Ring Oximeter

All appropriate testing will be performed and will demonstrate safety and efficacy for use in human studies prior tc . Such documentation will reside in the design history documentation at Testing of these devices will include: patient leakage, dielectric strength,

surface temperatures and biocompatibility testing. The sensors are the components expected to come in contact with the subjects.

The staff is familiar with the use of pulse oximetry monitors and the application of sensors. Additional training will be provided by the sponsor.

Risks and Benefits of the Investigational Device and Clinical Investigation:

Currently the FDA defines pulse oximeters as Class II devices which transmit radiation at a known wavelength(s) through blood and to measure the blood oxygen saturation based on the amount of reflected or scattered radiation and may be used alone or in conjunction with a fiberoptic oximeter catheter. All oximeters being used in this study work by transmittance of radiation at known wavelength(s) through tissue to measure blood oxygen saturation based on the amount of reflected and scattered radiation. **The devices under test in this study are thereby considered non-significant risk devices.**

For the purpose of this study:

- It is not intended as an implant.
    - Pulse oximetry sensors are applied to the surface of the site (such as forehead, ears and fingers) and is removed following data collection typically less than 1 day.
    - Sensors may be warm to the touch but are not expected to overheat during normal operations
    - Clip on sensors, the forehead headband may exert a small amount of pressure with mild discomfort
    - Adhesives may cause some skin irritations.
- It is not purported or represented to be for use in supporting or sustaining human life, nor does it present a potential for serious risk to the health, safety, or welfare of a subject.
    - Pulse oximeters are monitors and are not used to support or sustain human life.
- It is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
    - Pulse oximeters are Class II devices used to measure the blood oxygen saturation. They are not used to diagnose, cure mitigate or treat disease. These devices are typically labeled with a general indication for non-invasive measurement of blood oxygen saturation.
- The device as used in this investigation does not present a serious risk to the health, safety, or welfare of a subject.
    - See below for discussion of risk associated with the device and use of the device.

Pulse Oximetry Sensor

Pulse Oximetry Sensor placement involves positioning pulse oximetry sensors on the volunteer subject in the same manner that is used on hospitalized patients. The sensors may be warm to the touch. Under normal operating conditions, (no fault conditions), the sensors are not expected to overheat. If the sensors are too warm, they will be removed immediately. Clip on sensors exert a minimal amount of pressure. They should not cause discomfort. Sensor retention headband for the forehead sensor exert a minimal amount of pressure and may cause a headache if on for extended periods of time. If the sensors are too uncomfortable, they will be removed immediately. Adhesive sensors or tape may cause some irritations to the skin in some subjects.

Every effort will be made to minimize products with natural rubber or latex. Products containing natural rubber or latex will be identified. The risk in the use of pulse oximetry sensors is believed to be minimal

ECG Electrodes

Materials (such as the adhesive and/or gel contact) used in the electrodes may cause some skin irritations in some subjects. Typical skin irritations present with redness of skin and in some cases of sensitivity is an allergic reaction. Because the adhesive is aggressive on the ECG pads, it may cause pulling of the skin or hair upon removal. Biocompatibility testing for surface contact electrodes is a requirement of the International Standards Organization (ISO) 10993 – Biological Evaluation of Medical Devices. The risk in the use of ECG electrodes is believed to be minimal.

Benefits

The benefits to the study are to the advancement of non-invasive medical monitoring of patients by improving accuracy and performance of pulse oximeters. There are no direct benefits to the subjects participating in this study other than being a paid volunteer. The only alternative to this study is to NOT participate.

Design of the Clinical Investigation

Method

This study is a comparative, non-randomized study in a minimum of 50 subjects. Each subject test is expected to take up to 10 hours. The overall data collection process is expected to be completed in 2 - 4 months.

Subjects will be provided an IRB approved Informed Consent. As applicable, subjects will be told about any new information that might change their decision to participate. Subjects who have completed the informed consent and meet inclusion criteria and none of the exclusion criteria will be enrolled in the study.

Subjects will sleep for the duration of the study.

To avoid bias in the data collection, the ring size that best fits the subject will be selected.

Endpoint / Comparator

The primary objective of this study is to evaluate the ability of the Belun ring pulse oximeter to correctly gauge the Apnea-Hypopnea Index (AHI). Traditional PSG data will be used as the basis for comparison for the Belun ring pulse oximeter. The study population will include a minimum of fifty (50) subjects. All data will be used for the analysis unless identified as unstable. Data that is found to be unstable will be removed prior to the comparative analysis. For the statistical analysis, A Pearson's correlation will be used to determine the accuracy performance of the sleep score generated by the Belun Ring Oximeter to the AHI score generated from the PSG data. The sensitivity and specificity values of the Belun sleep scores will be computed respectively in the three levels of sleep apnea severity (mild AHI ≥ 5, moderate AHI ≥ 15, and severe ≥ 30). The area under the receiver operating characteristic (ROC) curve will also be calculated.

There are no deviations expected from this investigation plan, Should deviations be needed, discussions will be conducted with the Sponsoring company, Principal investigator and reported to the IRB as appropriate.

Study Population

The study population will include a minimum of 50 competent adults, ages 18 to 90 years. The subject selection will be a mix of males and females including approximately10 subjects with an AHI index <5, ten with an AHI index between 5 and 15, ten between 15 and 30 and ten >30.

The subjects must understand the study and consent to participate by signing the Informed Consent Form.

Subject enrollment is based on meeting the inclusion criteria and none of the exclusion criteria and the subject and data demographics needed for the study.

Inclusion Criteria

- Subject must have the ability to understand and provide written informed consent
- Subject is 18 to 90 years of age
- Subject must be willing and able to comply with study procedures and duration
- Male or female of any race

Exclusion Criteria

- Subject requires oxygen therapy or noninvasive ventilation
- Subject has a current diagnosis of chronic obstructive pulmonary disorder (COPD), neuromuscular disease, periodic limb movement, or narcolepsy.
- Compromised circulation, injury, or physical malformation of fingers, toes, hands, ears or forehead/skull or other sensor sites which would limit the ability to test sites needed for the study. (Note: Certain malformations may still allow subjects to participate if the condition is noted and would not affect the particular sites utilized.)
- Subject is on medication known to interfere with heart rate, such as beta blockers, digoxin, or calcium receptor agonists.
- Subjects with severe contact allergies to standard adhesives, latex or other materials found in pulse oximetry sensors, ECG electrodes, respiration monitor electrodes or other medical sensors (self-reported)
- Unwillingness or inability to remove colored nail polish from test digits.
- Other known health condition, which should be considered

Duration of Clinical Investigation

Each subject, and therefore use of the device, is expected to take 5-8 hours. The study is expected to take 2 - 4 months to complete for this subject population.

Participation in the study is voluntary. Subjects may choose to withdraw from the study at any point.

Procedure

1. Complete Equipment checkout list prior to starting study.
2. Set the clocks to sync data collection for the Belun ring pulse oximeter.
3. Explain the procedure to the subject. Have them read the Informed Consent Form, and review the information answering all questions. Once all questions have been answered, have the subject sign the form. Each subject will be given a copy of the consent form prior to release.

4. Based on the responses record accepted or declined from the study. Continue if accepted into the study.
5. Record subject information. Subject number and demographics information for subject description.
6. Apply all polysomnography equipment as is appropriate for the prescribed polysomnography study.
7. Measure both index fingers to find the correct ring size.
8. Apply the correct size Belun Ring Oximeter (device under test).
9. Conduct the polysomnography study as prescribed by the patient's physician while recording information from the Belun Ring Oximeter (device under test).
10. The clinician will review any final questions with the subject and ask if there were any effects from the study. The subject will be provided with phone numbers for questions pertaining to participation in this study or research-related injury or reaction post the study. The subject will be informed of the follow up procedure post the study.

The test sensor(s) will be placed on fingers, rotating sites where appropriate.

Monitoring Arrangements

Monitoring Plan:

Statistical Analysis

A Pearson's correlation between sleep score generated by the Belun software and AHI generated by the PSG analysis will be calculated. The Belun sleep score will be tested separately against three AHI cut-off points representing three levels of sleep apnea severity (mild AHI ≥ 5, moderate AHI ≥ 15, and severe ≥ 30). The sensitivity and specificity values of the sleep scores will be computed respectively against the three AHI thresholds listed above. The area under the receiver operating characteristic (ROC) curve will also be calculated. Data analysis & demographics will be presented in final report

Deviations from the Statistical Plan

Any deviations from this statistical plan will be described and justified in the final report.

Data and Quality Management / Confidentiality

Study Documentation / Case Report Forms

Study procedure

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Amendments to the Clinical Investigation Plan

Deviations from the Clinical Investigation Plan

Device Accountability

Packaging and Labeling

Storage and Accountability

Statement of Compliance

Informed Consent Process

- The Principal Investigator or his / her designee conducts the informed consent process
- Verify that the subject acknowledges ability to read English
- Instruct the subject to ask questions at any time during this process, especially about things they do not understand.
- Allow subject ample time to read the entire form and ask questions.
- Give a thorough description of the study and the subject's involvement – especially explain that they may withdraw from the study at any time.
- After the subject has read the form ask if they understand everything
- Ask if they would like to take part in the study and if so explain that they may sign and date the form.
- Once the subject has signed and dated the informed consent, the principal investigator or authorized designee will sign and date the form.
- Give a copy of the informed consent to the subject.
- No procedure may be performed before the informed consent is signed by the subject

Safety

Investigators

All experimenters must review the protocol prior to test and sign that they read and understood the contents.

Subject

Equipment is checked out for proper functionality prior to being placed on the subject.

The subject will review and sign the informed consent following a discussion of the test procedure and when all questions regarding the study have been answered and prior to start of any study procedures. The subject may withdraw from the study at any time. The subject may be withdrawn per the Procedure section below.

A clinician will be present to monitor the subject at all times.

Adverse Event Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, unanticipated adverse device effect, and their classifications are provided below (ISO 14155, 21 CFR 812.3).

- **Adverse Device Effect (ADE):** Adverse event related to the use of an investigational medical device resulting from insufficiencies or inadequacies in the instructions for use, the deployment, installation, the operation, or any malfunction of the investigational medical device or from error use.

- **Adverse Event (AE):** Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device or investigational procedure

- **Anticipated Serious Adverse Device Effects (ASADE):** ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

- **Mild:** a mild adverse event is one in which the subject is aware of the event, but it is easily tolerated without intervention.

- **Moderate:** a moderate adverse event is one that causes sufficient discomfort to interfere with usual activities.

- **Serious Adverse Device Effect (SADE):** adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

- **Serious Adverse Event (SAE):** a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.

- **Severe:** a severe adverse event is one that results in the inability to perform usual activities.

- **Unanticipated Adverse Device Effect (UADE):** serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Management of Adverse Event Reporting

Should the subject experience an adverse or non-typical event, assessment of the situation is first initiated and a determination will be made of appropriate actions. The Medical Director and Principle Investigator will be contacted as appropriate. Adverse Events are reported through standard Procedures.

Adverse events will be recorded in the Case Report Form
The following information will be obtained:

- Type of effect (ADE, AE. ASADE, SADE, SAE, UADE)
- Date of onset and resolution
- Intensity (mild, moderate, severe)
- Serious (yes/no)
- Relationship to device (unknown, not related, possibly related, probably related, definitely related)
- Anticipated (yes/no)
- Treatment given and / or action taken (procedure stopped, withdrawn from study, no action)

Reporting of Serious Adverse Events and / or UADE

All SAE's, SADE, ASADE and UADE will be reported in writing to the Principal Investigator, Medical Director, Sponsor and IRB within 72 hrs of knowledge of the event.

If the event resulted in death of a subject, the event shall be reported to the Principal Investigator, Medical Director, Sponsor and IRB within 24hrs of knowledge of the event.

Sponsor Records and Reports

Records 21 CFR 812.140 (b) 4,5

The following records shall be consolidated in one location and available for FDA inspection and copying:

- The name and intended use of the device and the objectives of the investigation;
- A brief explanation of why the device is not a significant risk device:
- The name and address of each investigator:
- The name and address of each IRB that has reviewed the investigation:
- A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and
- Any other information required by FDA.
- Records concerning adverse device effects (whether anticipated or unanticipated) and complaints

Reporting 21 CFR 812.150 (b) 1,2,3,5,6,7,8,9,10:

The sponsor shall prepare and submit the following complete, accurate, and timely reports:

Unanticipated Adverse Device Effect

A sponsor shall immediately conduct an evaluation of an unanticipated adverse device effect. The results of such evaluation shall be reported to the FDA, IRB and participating investigators within 10 days after the sponsor first receives notice of the effect.

Withdrawal of IRB approval

Withdrawal of IRB approval shall be reported to the FDA, IRB and the investigator within 5 working days after receipt of the withdrawal approval by the sponsor.

Withdrawal of FDA approval

Withdrawal of FDA approval of an investigation shall be reported by the sponsor to the IRB and the investigator within 5 working days after receipt of notice the withdrawal approval.

Progress Reports

The sponsor shall submit progress reports to the IRB at least yearly.

Recall and device

The sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

Informed consent

The sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

Significant risk device determinations

If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

Other

A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Investigators Records and Reporting

Records 21 CFR 812.140 (a)(3)(i)

The investigator maintains records of each subject's case history and exposure to the device and supporting data including signed and dated consent forms, and progress notes during the study. Records should show evidence that informed consent was signed and dated prior to the subject participating in the study.

Reports 21 CFR 812.150 (a) 1,2,5,7

The investigator shall prepare and submit the following complete, accurate, and timely reports:

Unanticipated adverse device effects.

The investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Withdrawal of IRB approval.
The investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

Informed consent.
If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

Other.
The investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Withdrawal, Early Termination or Suspension of the Investigation

Participation in the study is voluntary. Subjects may choose to withdraw from the study at any point. If a subject officially withdraws from the study, the laboratory staff will document the reason for withdrawal in the Case Report Form.

Participation in the study may also be stopped at any time by the principal investigator or by the Sub-investigators or sponsor.

- The subject's failure to cooperate fully (as determined by the investigator in his or her sole discretion) with the required conduct of this study.
- The subject's development of an illness as determined by the investigator in his or her sole discretion.
- A determination by ε representative (in his or her sole discretion), for whatever cause, that the study should be discontinued.
- A determination by the sponsor (in his or her sole discretion), for whatever cause, that the study should be discontinued

The collection of data for study subjects will cease in the following cases:

- Subject completes all study requirements
- Subject withdraws consent
- Investigator's decision that it is in subject's best interest to be discontinued from the study
- Subject death
- Adverse event other than death requiring withdrawal of the subject from the study
- Determination that the subject was ineligible for the study.

There will not be any follow-up procedures for withdrawn or discontinued subjects required, unless a follow-up is required at the Investigator's discretion.

Consideration for early termination or suspension of the investigation is tied to unanticipated equipment failure or a decision by the sponsor or the site. Both ·eserve the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of, but not limited to, inadequate data collection, low subject enrollment, or non-compliance with the protocol or other research requirements.

Early termination results when the study is closed prior to the end of the study. A study suspension is a temporary postponement of the study activities related to enrollment. Both are possible for the study.

If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol.

If the study is terminated prematurely or suspended by the sponsor/investigator, the sponsor /investigator will promptly inform the regulatory authorities (if required) of the termination and the reason(s). IRB/IECs will also be promptly informed and provided with the reason(s) for termination or suspension by the sponsor/ investigator. The investigator will promptly inform the subjects and assure appropriate follow-up for the subject.

If the investigator (or IRB/IEC) terminates or suspends the investigation the investigator will promptly inform the institution (if required) and the IRB/IEC, and provide a detailed written explanation of the termination or suspension. The investigator will promptly inform the subjects and assure appropriate therapy and follow-up for the subjects. The sponsor will inform the regulatory authorities (if required).

Withdrawal of IRB approval shall be reported to the sponsor by the investigator within 2 working days.

In case of early termination of the study, all study subjects should be followed until the resolution of any pending adverse event(s).

Publication Policy

Attachment A - Protocol Signature Page